CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

18-553/S013

Trade Name: Inderal LA

Generic Name: Propranolol Hydrochloride

Sponsor: Ayerst Laboratories

Approval Date: March 18, 1987

Indications: The treatment of hypertension.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-553/S013

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	X
Approvable Letter	X
Labeling	X
Summary Review	
Officer/Employee List	
Office Director Memo	X
Cross Discipline Team Leader Review	
Medical Review(s)	X
Chemistry Review(s)	X
Environmental Assessment	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-553/S013

APPROVAL LETTER

NDA 18-553/S-013 MAR 18 1987

Ayerst Laboratories
Attention: John R. Rapoza
685 Third Avenue
New York, NY 10017-4071

Dear Mr. Rapoza:

Please refer to your December 30, 1985 supplemental new drug application submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Inderal LA (long acting propranolol hydrochloride) Capsules.

We also acknowledge receipt of your amendment dated February 9, 1987.

The supplemental application provides for a new 60 mg dosage strength.

We have completed the review of this supplemental application including the submitted draft labeling and it is approved effective on the date of this letter. The labeling, however, must be revised to include the word "fatigue" immediately after the word "formulations" in the last sentence of the Central Nervous System subsection of the ADVERSE REACTION section. See enclosed copy.

These revisions are terms of the supplemental NDA approval. Marketing the dosage strength before making the revisions, exactly as requested, in the product's final printed labeling (FPL) may render the product misbranded and an unapproved dosage strength.

When available, please submit twelve copies of the FPL, seven of which are mounted on heavy weight paper or similar material. For administrative purposes, the submission of FPL should be designated an "FPL Supplement amendment" to the approved NDA 18-553/S-013. Approval of the final printed labeling by FDA is not required before the labeling is used.

Our letter of April 19, 1983 detailed the conditions relating to the approval of this application.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Ms. Constance Burner Henry
Consumer Safety Officer
(301) 443-4730

Sincerely yours,

RJL 3/13/87

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Research and Review
Center for Drugs and Biologics

Enclosure

cc:
Original NDA
HFN-110
HFN-110/CSO
HFN-713/GChi
HFN-80/DDIR
HFN-232 (with labeling)
HFN-110/CHenry/2/27/87
sb/3/3/87;3/11/87/5124s
R/D: JShort/3/5/87
RWolters/3/9/87
KKnudsen
CResnick/3/10/87

CBHenry 3/13/87
3/16/87

APPROVAL

RWolters 3/17/87

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-553/S013

APPROVABLE LETTER

34.1

FEB 4 1987

NDA 18-553/S-013

Ayerst Laboratories
Attention: Mr. John R. Rapoza
685 Third Avenue
New York, NY 10017-4071

Dear Mr. Rapoza:

Please refer to your December 30, 1985 supplemental new drug application submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Inderal LA (long acting propranolol hydrochloride) Capsules.

We also acknowledge receipt of your amendments dated March 27, April 3 and 17, July 15, December 22, 1986 and January 15, 1987.

The supplemental application provides for a new dosage strength - 60 mg.

We have completed the review of this supplemental application as submitted with draft labeling. Before this supplement may be approved, however, it will be necessary for you to submit final printed labeling. The package insert should be identical in content to the submitted draft except that we ask you add the statement "Protect from light and moisture" to the end of the How Supplied section. In addition, all previous revisions as reflected in the most recently approved package insert must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

If additional information relating to the safety or effectiveness of this drug becomes available before we receive the final printed labeling, revision of that labeling may be required.

Please submit twelve copies of the printed package inserts seven of which are individually mounted on heavy weight paper or similar material.

Within 10 days after the date of this letter, you are required to amend this supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action, FDA may take action to withdraw this supplemental application.

This dosage strength may not be legally marketed until you have been notified in writing that this supplemental application is approved.

Should you have any questions, please contact:

Ms. Constance Burner Henry
Consumer Safety Officer
Telephone: (301) 443-4730

Sincerely yours,

RJL 2/3/87

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Research and Review
Center for Drugs and Biologics

cc:
Original NDA
HFN-110
HFN-110/CSO
HFN-713/GChi
HFN-83
HFN-110/CHenry/1/23/87;1/27/87
sb/1/27/87;2/2/87/4903s
R/D: JShort/1/28/87
CResnick/1/29/87
NMorgenstern/1/30/87 /2/4/87
RLipicky/2/2/87

CBHenry 2/2/87

APPROVABLE

2/3/87

2/3/87

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-553/S013

LABELING

Ayerst

INDERAL® LA

Brand of

PROPRANOLOL HYDROCHLORIDE

(Long Acting Capsules)

[redacted]

470, 471, 473, 479

314

[redacted]

CAUTION: Federal law prohibits dispensing without prescription.

DESCRIPTION

INDERAL (propranolol hydrochloride) is a synthetic beta-adrenergic receptor-blocking agent chemically described as 1-(Isopropylamino)-3-(1-naphthyloxy) -2-propanol hydrochloride. Its structural formula is

Propranolol hydrochloride is a stable, white, crystalline solid which is readily soluble in water and ethanol. Its molecular weight is 295.81.

INDERAL LA is formulated to provide a sustained release of propranolol hydrochloride. INDERAL LA is available as 60 mg, 80 mg, 120 mg, and 160 mg capsules.

INDERAL LA contains the following inactive ingredients: ethylcellulose, gelatin capsules, hydroxypropyl methylcellulose, microcrystalline cellulose, and titanium dioxide. In addition, INDERAL LA 60 mg Capsules contain FD&C Blue No. 1 and FD&C Red No. 3; INDERAL LA 80 mg and 120 mg Capsules contain FD&C Blue No. 1, FD&C Red No. 3, and D&C Red No. 28; INDERAL LA 160 mg Capsules contain FD&C Blue No. 1.

CLINICAL PHARMACOLOGY

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

INDERAL LA Capsules (60, 80, 120, and 160 mg) release propranolol HCl at a controlled and predictable rate. Peak blood levels following dosing with INDERAL LA occur at about 6 hours, and the apparent plasma half-life is about 10 hours. When measured at steady state over a 24-hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60% to 65% of the AUCs for a comparable divided daily dose of INDERAL Tablets. The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol, resulting from the slower rate of absorption of propranolol. Over a twenty-four (24) hour period, blood levels are fairly constant for about twelve (12) hours, then decline exponentially.

INDERAL LA should not be considered a simple mg-for-mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose. When changing to INDERAL LA from conventional propranolol, a possible need for retitration upwards should be considered, especially to maintain effectiveness at the end of the dosing interval. In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, INDERAL LA has been therapeutically equivalent to the same mg dose of conventional INDERAL as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure, and rate pressure product. INDERAL LA can provide effective beta blockade for a 24-hour period.

The mechanism of the antihypertensive effect of INDERAL has not been established. Among the factors that may be involved in contributing to the antihypertensive action 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. Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with chronic

ing dose of conventional INDERAL as assessed by 24-hour effects on blood pressure and on 24 hour exercise responses of heart rate, systolic pressure, and rate pressure product. INDERAL LA can provide effective beta blockade for a 24-hour period.

The mechanism of the antihypertensive effect of INDERAL has not been established. Among the factors that may be involved in contributing to the antihypertensive action 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. Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with chronic use. Effects on plasma volume appear to be minor and somewhat variable. INDERAL has been shown to cause a small increase in serum potassium concentration when used in the treatment of hypertensive patients.

In angina pectoris, propranolol generally reduces the oxygen requirement of the heart at any given level of effort by blocking the catecholamine-induced increases in the heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. Propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure, and systolic ejection period. The net physiologic effect of beta-adrenergic blockade is usually advantageous and is manifested during exercise by delayed onset of pain and increased work capacity.

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential. The significance of the membrane action in the treatment of arrhythmias is uncertain.

The mechanism of the antimigraine effect of propranolol has not been established. Beta-adrenergic receptors have been demonstrated in the pial vessels of the brain.

Beta-receptor blockade can be useful in conditions in which, because of pathologic or functional changes, sympathetic activity is 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, greater than first degree, 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.

Propranolol is not significantly dialyzable.

INDICATIONS AND USAGE

Hypertension

INDERAL LA is indicated in the management of hypertension; it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. INDERAL LA is not indicated in the management of hypertensive emergencies.

Angina Pectoris Due to Coronary Atherosclerosis

INDERAL LA is indicated for the long-term management of patients with angina pectoris.

Migraine

INDERAL LA is indicated for the prophylaxis of common migraine headache. The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use.

Hypertrophic Subaortic Stenosis

INDERAL LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL LA also improves exercise performance. The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient, which is exacerbated by beta-receptor stimulation. Clinical improvement may be temporary.

CONTRAINDICATIONS

INDERAL is contraindicated in 1) cardiogenic shock; 2) sinus bradycardia and greater than first-degree block; 3) bronchial asthma; 4) congestive heart failure (see WARNINGS), unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.

WARNINGS

CARDIAC FAILURE: Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following *abrupt* discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned, the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL 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 athero-

results in bronchial constriction by interfering with adrenergic bronchodilator activity, which should be preserved in patients subject to bronchospasm.

Propranolol is not significantly dialyzable.

INDICATIONS AND USAGE

Hypertension

INDERAL LA is indicated in the management of hypertension; it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. INDERAL LA is not indicated in the management of hypertensive emergencies.

Angina Pectoris Due to Coronary Atherosclerosis

INDERAL LA is indicated for the long-term management of patients with angina pectoris.

Migraine

INDERAL LA is indicated for the prophylaxis of common migraine headache. The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use.

Hypertrophic Subaortic Stenosis

INDERAL LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL LA also improves exercise performance. The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient, which is exacerbated by beta-receptor stimulation. Clinical improvement may be temporary.

CONTRAINDICATIONS

INDERAL is contraindicated in 1) cardiogenic shock; 2) sinus bradycardia and greater than first-degree block; 3) bronchial asthma; 4) congestive heart failure (see WARNINGS), unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.

WARNINGS

CARDIAC FAILURE: Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following *abrupt* discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned, the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL 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.

Nonallergic Bronchospasm (eg, chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, eg, dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA: Beta blockers should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. Following insulin-induced hypoglycemia, propranolol may cause a delay in the recovery of blood glucose to normal levels.

THYROTOXICOSIS: Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol may change thyroid function tests, increasing T_4 and reverse T_3, and decreasing T_3.

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.

PRECAUTIONS

GENERAL: Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta-adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

CLINICAL LABORATORY TESTS: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS: Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Caution should be exercised when patients receiving a beta blocker are administered a calcium-channel-blocking drug, especially intravenous verapamil, for both agents may depress myocardial contractility or atrioventricular conduction. On rare occasions, the concomitant intravenous use of a beta blocker and verapamil has resulted in serious adverse reactions, especially in patients with severe cardiomyopathy, congestive heart failure or recent myocardial infarction.

Aluminum hydroxide gel greatly reduces intestinal absorption of propranolol.

Ethanol slows the rate of absorption of propranolol.

Phenytoin, phenobarbitone, and *rifampin* accelerate propranolol clearance.

Chlorpromazine, when used concomitantly with propranolol, results in increased plasma levels of both drugs.

Antipyrine and *lidocaine* have reduced clearance when used concomitantly with propranolol.

Thyroxine may result in a lower than expected T_3 concentration when used concomitantly with propranolol.

Cimetidine decreases the hepatic metabolism of propranolol, delaying elimination and increasing blood levels.

Theophylline clearance is reduced when used concomitantly with propranolol.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies, in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

PREGNANCY: Pregnancy Category C: INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose.

There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS: INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

PEDIATRIC USE: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: Bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; thrombocytopenic purpura; arterial insufficiency, usually of the Raynaud type.

Central Nervous System: Light-headedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; vivid dreams; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics. For immediate formulations lethargy and vivid dreams appear dose related.

ADVERSE REACTIONS

Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: Bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; thrombocytopenic purpura; arterial insufficiency, usually of the Raynaud type.

Central Nervous System: Light-headedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; vivid dreams; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics. For immediate formulations, lethargy and vivid dreams appear dose related. Fatigue

Gastrointestinal: Nausea, vomiting, epigastic 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.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: Alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes, and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

DOSAGE AND ADMINISTRATION

INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily. If patients are switched from INDERAL Tablets to INDERAL LA Capsules, care should be taken to assure that the desired therapeutic effect is maintained. INDERAL LA should not be considered a simple mg-for-mg substitute for INDERAL. INDERAL LA has different kinetics and produces lower blood levels. Retitration may be necessary, especially to maintain effectiveness at the end of the 24-hour dosing interval.

HYPERTENSION—*Dosage must be individualized.* The usual initial dosage is 80 mg INDERAL LA once daily, whether used alone or added to a diuretic. The dosage may be increased to 120 mg once daily or higher until adequate blood-pressure control is achieved. The usual maintenance dosage is 120 to 160 mg once daily. In some instances a dosage of 640 mg may be required. The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks.

ANGINA PECTORIS—*Dosage must be individualized.* Starting with 80 mg INDERAL LA once daily, dosage should be gradually increased at three- to seven-day intervals until optimal response is obtained. Although individual patients may respond at any dosage level, the average optimal dosage appears to be 160 mg once daily. In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established.

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS).

MIGRAINE—*Dosage must be individualized.* The initial oral dose is 80 mg INDERAL LA once daily. The usual effective dose range is 160-240 mg once daily. The dosage may be increased gradually to achieve optimal migraine prophylaxis. If a satisfactory response is not obtained within four to six weeks after reaching the maximal dose, INDERAL LA therapy should be discontinued. It may be advisable to withdraw the drug gradually over a period of several weeks.

HYPERTROPHIC SUBAORTIC STENOSIS—80 160 mg INDERAL LA once daily.

PEDIATRIC DOSAGE

At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

OVERDOSAGE

INDERAL is not significantly dialyzable. In the event of overdosage or exaggerated response, 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, eg, LEVARTERENOL OR EPINEPHRINE (THERE IS EVIDENCE THAT EPINEPHRINE IS THE DRUG OF CHOICE).

BRONCHOSPASM—ADMINISTER ISOPROTERENOL AND AMINOPHYLLINE.

HOW SUPPLIED

INDERAL® LA CAPSULES
(propranolol hydrochloride)

—Each white/light-blue capsule, identified by 3 narrow bands, 1 wide band, and "INDERAL LA 60," contains 60 mg of propranolol hydrochloride in bottles of 100 (NDC 0046-0470-81) and 1,000 (NDC 0046-0470-91). Also available in a Unit Dose package of 100 (NDC 0046-0470-99).

—Each light-blue capsule, identified by 3 narrow bands, 1 wide band, and "INDERAL LA 80," contains 80 mg of propranolol hydrochloride in bottles of 100 (NDC 0046-0471-81) and 1,000 (NDC 0046-0471-91). Also available in a Unit Dose package of 100 (NDC 0046-0471-99).

—Each light-blue/dark-blue capsule, identified by 3 narrow bands, 1 wide band, and "INDERAL LA 120," contains 120 mg of propranolol hydrochloride in bottles of 100 (NDC 0046-0473-81) and 1,000 (NDC 0046-0473-91). Also available in a Unit Dose package of 100 (NDC 0046-0473-99).

—Each dark-blue capsule, identified by 3 narrow bands, 1 wide band, and "INDERAL LA 160," contains 160 mg of propranolol hydrochloride in bot-

INDERAL is not significantly dialyzable. In the event of overdosage or exaggerated response, 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, eg, LEVARTERENOL OR EPINEPHRINE (THERE IS EVIDENCE THAT EPINEPHRINE IS THE DRUG OF CHOICE).

BRONCHOSPASM—ADMINISTER ISOPROTERENOL AND AMINOPHYLLINE.

HOW SUPPLIED

INDERAL® LA CAPSULES
(propranolol hydrochloride)

—Each white/light-blue capsule, identified by 3 narrow bands, 1 wide band, and "INDERAL LA 60," contains 60 mg of propranolol hydrochloride in bottles of 100 (NDC 0046-0470-81) and 1,000 (NDC 0046-0470-91). Also available in a Unit Dose package of 100 (NDC 0046-0470-99).

—Each light-blue capsule, identified by 3 narrow bands, 1 wide band, and "INDERAL LA 80," contains 80 mg of propranolol hydrochloride in bottles of 100 (NDC 0046-0471-81) and 1,000 (NDC 0046-0471-91). Also available in a Unit Dose package of 100 (NDC 0046-0471-99).

—Each light-blue/dark-blue capsule, identified by 3 narrow bands, 1 wide band, and "INDERAL LA 120," contains 120 mg of propranolol hydrochloride in bottles of 100 (NDC 0046-0473-81) and 1,000 (NDC 0046-0473-91). Also available in a Unit Dose package of 100 (NDC 0046-0473-99).

—Each dark-blue capsule, identified by 3 narrow bands, 1 wide band, and "INDERAL LA 160," contains 160 mg of propranolol hydrochloride in bottles of 100 (NDC 0046-0479-81) and 1,000 (NDC 0046-0479-91). Also available in a Unit Dose package of 100 (NDC 0046-0479-99).

The appearance of these capsules is a registered trademark of Ayerst Laboratories.

Store at room temperature (approximately 25° C). Protect from light and moisture.

AYERST LABORATORIES INC.
NEW YORK, NY 10017

Revised December 1986. 314 Printed in U.S.A.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-553/S013

MEDICAL REVIEW(S)

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

NDA #: 18-553/S-013 REVIEWER: Robert E. Keenan, M.D.

M.O. REVIEW #: A

SPONSOR: Ayerst Laboratories

DRUG: Inderal LA, 60 mg Capsule

DATE OF CORRESPONDENCE: December 30, 1985

DATE RECEIVED BY REVIEWER: February 7, 1985

DATE REVIEW COMPLETED: July 26, 1985

Resume:

The Japanese clinical trials submitted supporting the efficacy of Inderal LA, 60 mg, are not of the quality expected in an original NDA. Propranolol and propranolol long-acting formulations are not, however, original, by any definition. Just the opposite: both propranolol tablets (immediate release) and propranolol long-acting capsules (sustained release), in a variety of dosage strengths, are already approved for the treatment of hypertension and angina pectoris. This NDA supplement provides evidence which simply extends the approvals already granted--that is, a lower (60 mg) long-acting dosage strength which behaves kinetically the same as the higher doses (80 mg, 120 mg and 160 mg) already approved. It almost goes without saying, therefore, that the lower, 60 mg INDERAL-LA, dosage will be as effective as the 80 mg dosage in some patients (50-60 Kg body weight range) suffering mild/moderate hypertension or stable angina pectoris. On its face, then, given the biopharm review and conclusions, INDERAL-LA, 60 mg, is medically approvable (prima facie) and the following discussion is likely redundant.

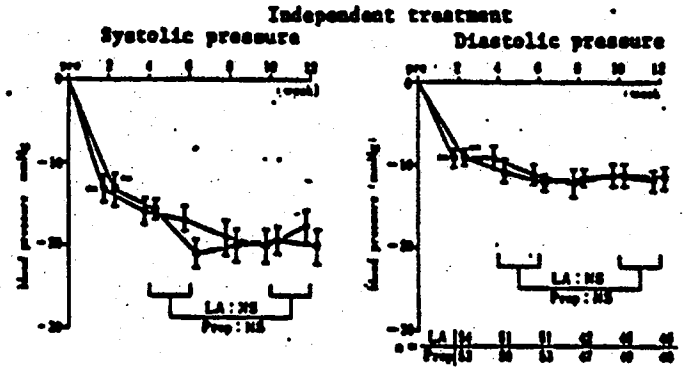
Inderal-LA, 60 mg, was systematically studied in controlled and in open clinical trials which support its use for 2 indications: mild/moderate hypertension and angina pectoris.

I. Altogether, 8 published clinical trials examining the anti-hypertensive effectiveness of Inderal-LA, 60 mg once daily, are submitted in support of this NDA supplement. A combined total of 773 patients were included in these (8) studies; 56 patients received the drug for 6 months or longer. Two of the clinical trials (described below) are representative and provide the necessary safety and efficacy data; the other six are consistent and supportive.

In the first of the two representative trials, 351 mild/moderately hypertensive patients were enrolled in a multi-center, double-blind study comparing

Inderal-LA, 60 mg, once daily, to conventional propranolol 20 mg T.I.D. Trough blood pressure measurements established the equivalence of once-daily 60 mg LA with propranolol, 20 mg T.I.D. in 94 patients (Figure 1).

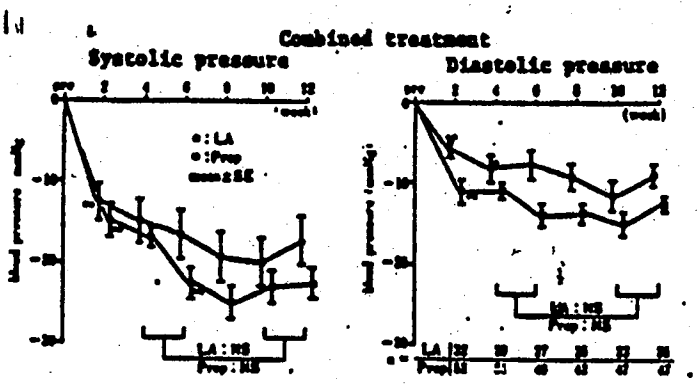
Figure 1



[t-tests were performed for degree of decrease from the previous week. *: $p < 0.05$; **: $p < 0.01$; no symbol: NS.

The low-dose, LA-60 mg once daily, or regular propranolol, 20 mg, T.I.D., required added hydrochlorthiazide in 73 patients (26 Inderal-LA and 47 propranolol T.I.D.). Again the long-acting formulation, in combination with HCTZ, given once daily, is shown to be equivalent to the same total daily dose of regular propranolol divided into 3 separate doses, in combination with HCTZ (Figure 2).

Figure 2

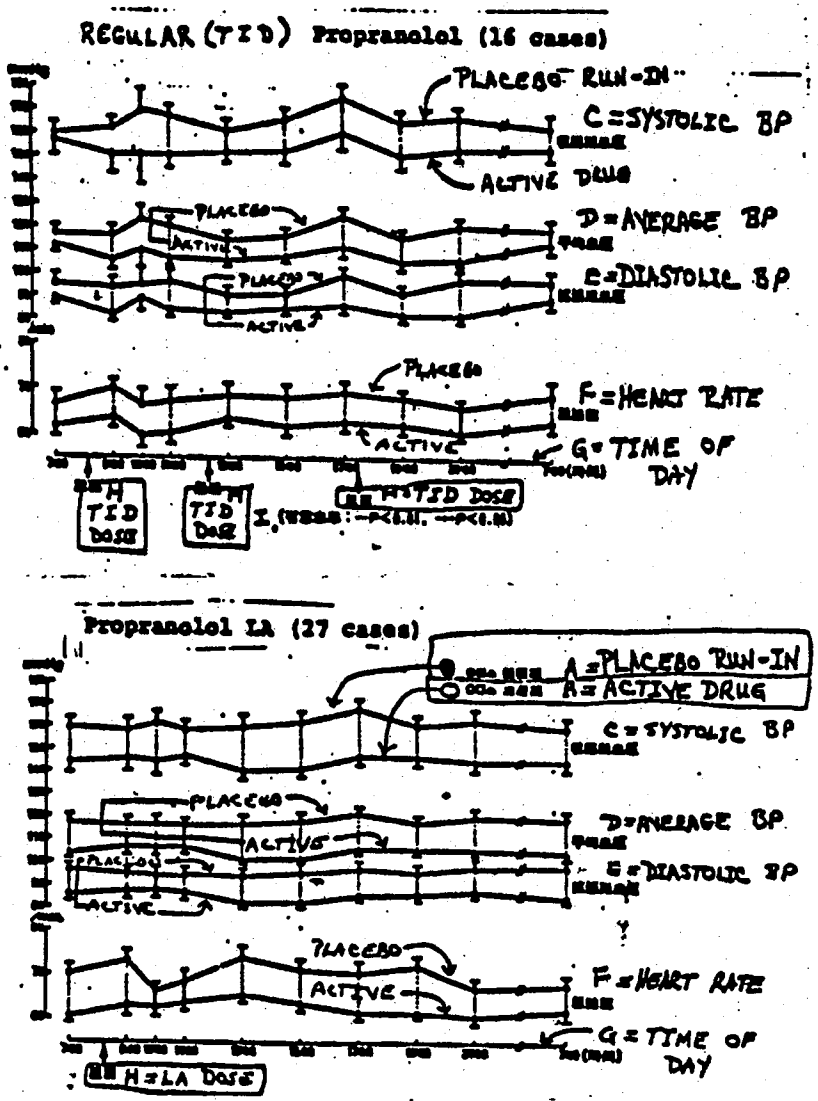


[t-tests were performed for degree of decrease from the previous week. *: $p < 0.05$; **: $p < 0.01$; no symbol: NS.

The remaining 184 patients (of the original 351) either failed the entry criteria or, eventually, required propranolol doses above 60 mg/day.

In the second of the two representative clinical trials, blood pressures of 36 hypertensive patients were performed throughout a 24-hour period on the day of completion of a one-week in-patient treatment period (which followed a one-week in-patient no-treatment period). Blood pressure measurements were recorded with an automatic blood pressure meter ——————— at 7:00 a.m. (trough), 9:00 a.m., 10:00 a.m., 11:00 a.m., 1:00 p.m., 3:00 p.m., 5:00 p.m., 7:00 p.m., 9:00 p.m., and again the next morning at 7:00 a.m. The end-of-treatment blood pressures were then compared to the control 24-hour blood pressures that were recorded in the same manner but after one-week in-patient no-treatment period. Results are displayed in Figure 3.

Figure 3: 24 hours blood pressure and pulse beat



As is obvious in Figure 3, Inderal-LA, 60 mg once daily, produced a sustained, 24-hour, blood pressure-lowering effect equivalent to that seen with regular propranolol, 20 mg T.I.D.

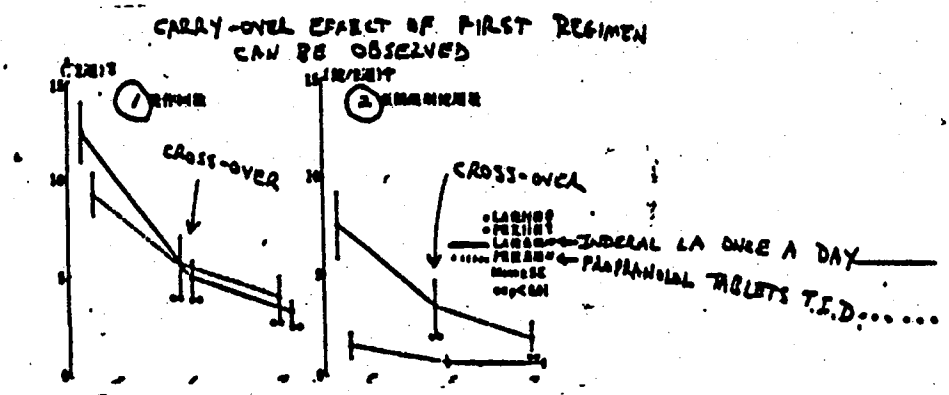
In all 8 anti-hypertensive trials, drug safety parameters were measured regularly. Laboratory and clinical adverse experiences were consistent with the current propranolol labelling. No unexpected events occurred.

II. Altogether, 5 published clinical trials examining the anti-anginal effectiveness of Inderal-LA, 60 mg once daily, are submitted in support of this supplement. A combined total of 166 patients were included in these (5) separate trials. Two representative studies provide the necessary safety and efficacy data; the other 3 are consistent and supportive.

In the first of the 2 representative trials, 69 patients were enrolled in a double-blind crossover study comparing Inderal-LA, 60 mg once daily, with regular propranolol tablets, 20 mg T.I.D and placebo. After a 2-week single-blind placebo lead-in period, patients were randomized to one of the 2 propranolol treatments, which was administered for 2 weeks, after which each patient was crossed over to the alternative regimen for a second 2-week treatment period. Trough exercise testing (modified Bruce protocol) was performed at baseline and again at the end of each of the 3 two-week treatments (placebo, Inderal-LA, 60 mg once daily, propranolol, 20 mg T.I.D.). End-points included time to ST depressions of $<.5$, $\leq.5$, and $\geq.5$ to 1.0 mm, depending upon patient characteristics. There was a "period" effect (i.e., carryover from the drug regimen received first in the crossover design) observed and considered appropriately in the data analysis. Treadmill time to the specified (ST segment) end-point improved 46.9% (average) in the patients when they received Inderal-LA, 60 mg once daily and an average of 39.1% when they took regular propranolol tablets, 20 mg T.I.D. for 2 weeks. Statistically these were significantly superior to placebo but not different from each other.

The use of nitroglycerin sublingual tablets was also determined as a measure of treatment effectiveness and the results of this evaluation was consistent with and supportive of the treadmill stress tests (see Figure 4).

Figure 4



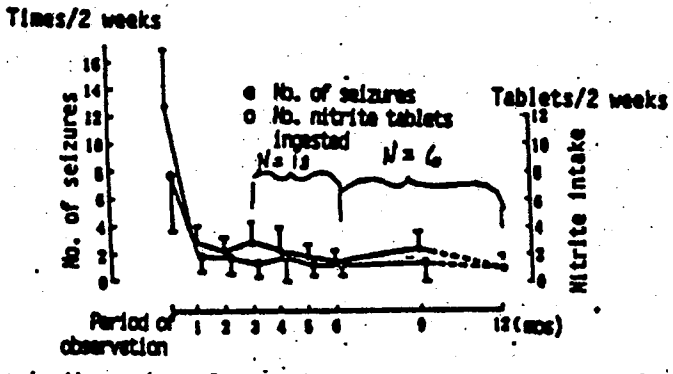
In the second of the 2 representative trials, long-term efficacy and safety was assessed after completion of a 4-week double-blind multi-center (21 centers) trial of 50 patients with exertional or mixed angina pectoris. Only sublingual nitroglycerin was allowed during a 2-week run-in period establishing an ETT baseline. Patients were then randomized to receive either Inderal-LA, 60 mg once daily or regular propranolol, 20 mg T.I.D. for 2 weeks double-blind. After 2 weeks, investigators had the option of continuing 60 mg/day or increasing the blinded dose to 120 mg/day (40 mg tablets T.I.D. or 120 mg LA once daily). Two patients had their dose increased and ten other patients were excluded from the final analysis for a variety of (but legitimate) reasons. Exertional angina was diagnosed in 29 of the 40 patients (29 males and 11 females) analyzed and mixed angina in the remaining 11 patients.

Trough exercise tolerance tests revealed significant improvement in both groups of patients at the end of the double-blind (4 weeks) period. Eighteen patients were then placed on long-term Inderal-LA, 60 mg once daily, treatment (open). Exercise tolerance tests were performed again upon "completion" of long-term (3-12 months) Inderal-LA treatment revealed. Half (50%) of the long-term patients retained a significant ETT improvement throughout the 3-12 month period. The others (mostly "mixed" angina which included unstable patients) were also numerically (but not statistically) improved by ETT evaluation, probably because their disease process continued to worsen over the long-term follow-up.

In a more practical vein, both the short-term (double-blind) and long-term (open) patients had an improved quality of life, at least from the point-of-view of numbers of anginal episodes. A decrease in both the incidence of anginal "seizures" and the consumption of sublingual nitroglycerin tablets was sustained throughout the various (per patient) treatment periods (see Figure 5).

Figure 5

A



Changes in the number of anginal seizures and nitrite intake (mean ± S.E.)

B

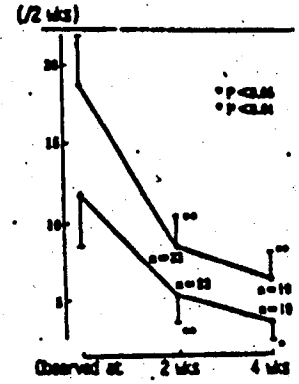


Fig. 5 Change in incidence of attack (o) and in the amount of nitrite taken (●)

Safety was assessed by the usual clinical and laboratory observations. The well-known, predictable propranolol ADR profile emerged. However, the incidence of the most common troublesome problems appeared to occur less often than was expected.

In summary, the published Japanese literature provided in this supplement support the biopharm review and simply extend and confirm the already known factual clinical data relevant to the 3 already-approved dosage strengths of Inderal-LA. From the preceding discussion, it is apparent that Inderal-LA, 60 mg once a day, will not control all patients suffering with stable or mixed angina pectoris or mild/moderate hyptertension. As expected apriori, however, substantial numbers of patients having these afflictions, particularly patients in the 50-60 Kg weight range, can be adequately controlled with the lower dose (60 mg) of long-acting propranolol. And this is clearly enunciated in the "dosage and administration" section of the proposed revised labeling. In keeping with the supportive data submitted and the wisdom of using the lowest effective drug dose then, the new formulation of Inderal-LA, 60 mg once daily, fulfills a medical need. Therefore, approval of NDA 18-553, Supplement S-013 is enthusiastically recommended and endorsed.

Robert E Keenan, MD

Robert E. Keenan, M.D.

cc: Orig. NDA
HFN-110
HFN-110/CSO
HFN-110/RKeenan:10/15/86
ef:10/15/86/10/16/86:#0657g

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-553/S013

CHEMISTRY REVIEW(S)

34.1

CHEMIST'S REVIEW
(If necessary, continue any item on 8" x 10½" paper. Key continuation to item by number.)

1. ORGANIZATION	2. NDA NUMBER
HFN-110	18-553

3. NAME AND ADDRESS OF APPLICANT *(City and State)*
Ayerst Laboratories
New York, New York

FEB 19 1987

4. AF NUMBER
19-003

5. SUPPLEMENT (S)

NUMBER(S)	DATE(S)
S013	12/20/85

6. NAME OF DRUG	7. NONPROPRIETARY NAME
Inderal LA	Propranolol Hydrochloride

8. SUPPLEMENT(S) PROVIDES FOR:
manufacture of a 60 mg capsule. This amendment provides for FPL for the PI.

9. AMENDMENTS AND OTHER *(Reports, etc.)* **DATES**
2/9/87

10. PHARMACOLOGICAL CATEGORY	11. HOW DISPENSED	12. RELATED IND/NDA/DMF(S)
Antihypertensive, Antianginal	☐ RX ☐ OTC	

13. DOSAGE FORM (S)	14. POTENCY *(Iea)*
CHG	80, 120, 160 mg

15. CHEMICAL NAME AND STRUCTURE

16. RECORDS AND REPORTS
CURRENT ☐ YES ☐ NO
REVIEWED ☐ YES ☐ NO

17. COMMENTS
The "How Supplied" section has been modified to include the statement "Protect from light and moisture" as I recommended in my review of their 12/22/86 amendment.

18. CONCLUSIONS AND RECOMMENDATIONS
The PI is now approvable as far as the technical aspects are concerned.

19. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
James H. Short	James H. Short	FEB 18 1987

DISTRIBUTION ■ ORIGINAL JACKET ☐ REVIEWER ☐ DIVISION FILE

FORM FDH 2266 (7/75) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED. 1

HFN-110/CSO

34.1

CHEMIST'S REVIEW
(If necessary, continue any item on 8" x 10½" paper. Key continuation to item by number.)

	1. ORGANIZATION: HFN-110	2. NDA NUMBER: 18-553
3. NAME AND ADDRESS OF APPLICANT *(City and State)*: Ayerst Laboratories, New York, New York FEB 3		4. AF NUMBER: 19-003
		5. SUPPLEMENT (S) NUMBER(S): S013 DATE(S): 12/30/85
6. NAME OF DRUG: Inderal LA	7. NONPROPRIETARY NAME: Propranolol Hydrochloride	
8. SUPPLEMENT(S) PROVIDES FOR: manufacture of a 60 mg dosage form. This amendment provides for inclusion of a new statement under the Adverse Reactions section.		9. AMENDMENTS AND OTHER *(Reports, etc.)* DATES: 1/15/87
10. PHARMACOLOGICAL CATEGORY: Antihypertensive	11. HOW DISPENSED: ☒ RX ☐ OTC	12. RELATED IND/NDA/DMF(S)
13. DOSAGE FORM (S): CHG	14. POTENCY *(tea)*: 80, 120, 160 mg	
15. CHEMICAL NAME AND STRUCTURE		16. RECORDS AND REPORTS: CURRENT ☐ YES ☐ NO; REVIEWED ☐ YES ☐ NO

17. COMMENTS

The change provided for in this amendment does not effect the technical aspects of the labeling.

18. CONCLUSIONS AND RECOMMENDATIONS

The supplement is approvable as far as the manufacturing and controls portion is concerned when some questions raised in my review of 1/13/87 (amendment S013, 12/22/87) have been satisfactorily resolved.

19. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
James H. Short	James H. Short	FEB 2 1987

DISTRIBUTION ■ ORIGINAL JACKET ☐ REVIEWER ☐ DIVISION FILE

FORM FDH 2266 (7/75) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED.

JHS 2/2/87

HFN-110/CSO

34.1

CHEMIST'S REVIEW
(If necessary, continue any item on 8" x 10½" paper. Key continuation to item by number.)

1. ORGANIZATION	2. NDA NUMBER
HFN-110	18-553

3. NAME AND ADDRESS OF APPLICANT *(City and State)*
Ayerst Laboratories
New York, New York

JAN 13 1987

4. AF NUMBER
19-003

5. SUPPLEMENT (S)

NUMBER(S)	DATE(S)
S013	12/30/85

6. NAME OF DRUG	7. NONPROPRIETARY NAME
Inderal LA	Propranolol Hydrochloride

8. SUPPLEMENT(S) PROVIDES FOR:
manufacture of a 60 mg capsule. The amendment provides thefinal printed labeling.

9. AMENDMENTS AND OTHER *(Reports, etc.)* DATES
12/22/86

10. PHARMACOLOGICAL CATEGORY	11. HOW DISPENSED	12. RELATED IND/NDA/DMF(S)
Antihypertensive, Antianginal	☒ RX ☐ OTC	

13. DOSAGE FORM (S)	14. POTENCY *(tea)*
CHG	80, 120, 160 mg

15. CHEMICAL NAME AND STRUCTURE

16. RECORDS AND REPORTS
CURRENT ☐ YES ☐ NO
REVIEWED ☐ YES ☐ NO

17. COMMENTS
see attachment

18. CONCLUSIONS AND RECOMMENDATIONS
Labeling will be approvable, as far as the technical aspects are concerned, when the deficiencies noted are corrected.

19. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
James H. Short	James H. Short	JAN 9 1987

DISTRIBUTION ■ ORIGINAL JACKET ☐ REVIEWER ☐ DIVISION FILE

FORM FDH 2266 (7/75) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED.

HFN-110/CSO

1. In the "How Supplied" section of the PI the following statement should appear after "Store at room temperature, etc.," "Protect from light and moisture."

2. The bottle labels should contain the statement "Dispense in tight, light-resistant container (USP)," to bring these labels into conformance with those for the approved dosage forms.

3. We should confirm that the lot number and expiration date will appear, on the bottle labels, in the blank space on the right hand side of these labels.

It is my understanding that the one label containing "Exp" and "Lot" will be attached to each unit dose capsule. This should be confirmed.

It is not clear how the expiration date and lot number will be handled for the promotional blisters.

33.1

CHEMIST'S REVIEW
(If necessary, continue any item on 8" x 10½" paper. Key continuation to item by number.)

1. ORGANIZATION	2. NDA NUMBER
HFN-110	18-553

3. NAME AND ADDRESS OF APPLICANT *(City and State)*
Ayerst Laboratories
New York, New York
JUL 30 1986

4. AF NUMBER
19-003

5. SUPPLEMENT (S)

NUMBER(S)	DATE(S)
S013	12/30/85

6. NAME OF DRUG	7. NONPROPRIETARY NAME
Inderal LA	Propranolol Hydrochloride

8. SUPPLEMENT(S) PROVIDES FOR:
updated manufacturing and controls data to provide for a 60 mg capsule. The amendments already reviewed provide for correction of errors, stability data, comparative dissolution data, answers to questions raised in the review of the original submission, and extension of the expiration date. (cont)

9. AMENDMENTS AND OTHER *(Reports, etc.)* DATES
7/15/86

10. PHARMACOLOGICAL CATEGORY	11. HOW DISPENSED	12. RELATED IND/NDA/DMF(S)
Antihypertensive/Antianginal	☒ RX ☐ OTC	

13. DOSAGE FORM (S)	14. POTENCY *(ies)*
CHG	60, 80, 120, 160 mg

15. CHEMICAL NAME AND STRUCTURE

16. RECORDS AND REPORTS
CURRENT ☐ YES ☐ NO
REVIEWED ☐ YES ☐ NO

17. COMMENTS
This amendment contains no new information.

18. CONCLUSIONS AND RECOMMENDATIONS
No reply is deemed necessary.

19. REVIEWER NAME	SIGNATURE	DATE COMPLETED
James H. Short	James H. Short	JUL 30 1986

DISTRIBUTION ■ ORIGINAL JACKET ☐ REVIEWER ☐ DIVISION FILE

FORM FDH 2266 (7/75) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED.

8. SUPPLEMENT PROVIDES FOR:

The amendment of 7/15/86 consists of report No. 85-56, "Analysis of Propranolol in Plasma Using HPLC." It was provided at the request of Dr. Donald Heald, HFN-225. This procedure was referenced in the original submission. This amendment contains no new information.

32.1

CHEMIST'S REVIEW
(If necessary, continue any item on 8" x 10½" paper. Key continuation to item by number.)

1. ORGANIZATION	2. NDA NUMBER
HFN-110	18-553

3. NAME AND ADDRESS OF APPLICANT *(City and State)*
Ayerst Laboratories
New York, New York
MAY 6 1986

4. AF NUMBER
19-003

5. SUPPLEMENT (S)

NUMBER(S)	DATE(S)
S013	12/30/85

6. NAME OF DRUG	7. NONPROPRIETARY NAME
Inderal LA	Propranolol Hydrochloride

8. SUPPLEMENT(S) PROVIDES FOR:
see attachment

9. AMENDMENTS AND OTHER *(Reports, etc.)* DATES
3/27/86
4/3/86
4/17/86

10. PHARMACOLOGICAL CATEGORY	11. HOW DISPENSED	12. RELATED IND/NDA/DMF(S)
Antihypertensive/Antiangina	[X] RX [ ] OTC	NDA 16-418

13. DOSAGE FORM (S)	14. POTENCY *(ies)*
CHG	60, 80, 120, 160 mg

15. CHEMICAL NAME AND STRUCTURE

16. RECORDS AND REPORTS
CURRENT [X] YES [ ] NO
REVIEWED [X] YES [ ] NO

17. COMMENTS
see attachment

18. CONCLUSIONS AND RECOMMENDATIONS
This supplement is approvable as far as the manufacturing and controls portion is concerned, including the extension of the expiration date from 24 to 36 months. The labeling is satisfactory as far as the technical aspects are concerned. The supplement has not yet been reviewed by the Biopharmaceutics Division.

19. REVIEWER NAME	SIGNATURE	DATE COMPLETED
James H. Short	James H. Short	MAY 2 1986

DISTRIBUTION ■ ORIGINAL JACKET [ ] REVIEWER [ ] DIVISION FILE

FORM FDH 2266 (7/75) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED.

pw 5/6/86

3 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

CHEMIST'S REVIEW
(If necessary, continue any item on 8" x 10½" paper. Key continuation to item by number.)

1. ORGANIZATION	2. NDA NUMBER
HFN-110	18-553

3. NAME AND ADDRESS OF APPLICANT *(City and State)*

Ayerst Laboratories
New York, NY

MAR 4 1986

4. AF NUMBER: 19-003

5. SUPPLEMENT (S)

NUMBER(S)	DATE(S)
S012	12/30/85
S013	12/30/85

6. NAME OF DRUG: Inderal LA

7. NONPROPRIETARY NAME: Propranolol Hydrochloride

8. SUPPLEMENT(S) PROVIDES FOR:

S012 provides for the use of a new stability indicating assay utilizing HPLC.

S013 provides for a new dosage strength, a 60 mg capsule.

9. AMENDMENTS AND OTHER (Reports, etc.) DATES

10. PHARMACOLOGICAL CATEGORY: Antihypertensive Antianginal

11. HOW DISPENSED: ☒ RX ☐ OTC

12. RELATED IND/NDA/DMF(S)

13. DOSAGE FORM (S): CHG

14. POTENCY *(Ies)*: 60, 80, 120, 160, mg

15. CHEMICAL NAME AND STRUCTURE

16. RECORDS AND REPORTS

CURRENT: ☒ YES ☐ NO

REVIEWED: ☒ YES ☐ NO

17. COMMENTS

SEE ATTACHMENT

18. CONCLUSIONS AND RECOMMENDATIONS

S012 is approvable. Additional information is needed before S013 can be approved. The applicant should state if the packaging materials have been approved previously, and if not suitable information should be provided. A review by the Biopharmaceutics Division is needed. The labeling is satisfactory as far as the technical aspects are concerned except that the applicant should affirm that the labels will contain lot numbers and expiration dates as appropriate.

10 Lbs 3/31/86

19. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
James H Short	James H Short	FEB 6, 1986

DISTRIBUTION: ☒ ORIGINAL JACKET ☐ REVIEWER ☐ DIVISION FILE CSO

FORM FDH 2266 (7/75) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED.

5 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-553/S013

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

JUL 2 1987

NDA 18-553/S-013

Ayerst Laboratories
Attention: John R. Rapoza
685 Third Avenue
New York, NY 10017-4071

Dear Mr. Rapoza:

We acknowledge the receipt of your May 11, 1987 submission containing final printed labeling in response to our March 18, 1987 letter approving your new drug application for Inderal LA (long acting propranolol hydrochloride) Capsules.

We have reviewed the labeling that you have submitted in accordance with our March 18, 1987 letter, and we find it acceptable.

Sincerely yours,

RK 7/1/87

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Research and Review
Center for Drugs and Biologics

cc:
Original NDA
~~HFN-110~~
HFN-110/CSO
HFN-80/DDIR
HFN-232 (with labeling)
HFN-110/CHenry/6/17/87
sb/6/19/87/5780s

ACKNOWLEDGE AND RETAIN

CBHenry 6/22/87
6/22/87
7/1/87

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-553/S013

OFFICE DIRECTOR MEMO

FEB 5 1987

Department of Health and Human Services
Public Health Service
Food and Drug Administration

Memorandum

Date:

To: File

From: Director
Division of Cardio-Renal Drug Products, HFN-110

Subject: NDA 18-553/S-013 60 mg Inderal LA

Although clinical trials were conducted for 60 mg Inderal LA, these were not necessary for approval.

The disclosable reviews constitute the summary basis of approval.

Raymond J. Lipicky, M.D.

cc
Orig.
HFN-110
HFN-110/CHenry
sb/2/2/87/4945s