CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

75-663

Generic Name: Sotalol Hydrochloride Tablets, 80 mg, 120 mg, 160 mg, and 240 mg

Sponsor: IMPAX Laboratories, Inc.

Approval Dates: November 7, 2000

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
75-663

CONTENTS

Reviews / Information Included in this ANDA Review.	
Approval Letter	X
Tentative Approval Letter	
ANDAs	
Approvable Letter	
Final Printed Labeling	X
Medical Review(s)	
Chemistry Review(s)	X
EA/FONSI	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology & Biopharmaceutics Reviews	
Bioequivalence Review(s)	X
Administrative Document(s)	X
Correspondence	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-663

APPROVAL LETTER

ANDA 75-663

NOV 7 2000

IMPAX Laboratories, Inc.
Attention: Mark C. Shaw
30831 Huntwood Avenue
Hayward, CA 94544

Dear Sir:

This is in reference to your abbreviated new drug application dated June 30, 1999, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Sotalol Hydrochloride Tablets, 80 mg, 120 mg, 160 mg and 240 mg.

Reference is also made to your amendments dated September 14, and October 8, 1999; and September 18, September 26, and October 19, 2000.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Sotalol Hydrochloride Tablets, 80 mg, 120 mg, 160 mg, and 240 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Betapace® Tablets, 80 mg, 120 mg, 160 mg and 240 mg, respectively, of Berlex Laboratories, Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

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

We request that you submit, in duplicate, any proposed advertising or promotional copy that you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

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

Validation of the regulatory methods has not been completed. It is the policy of the Office not to withhold approval until the validation is complete. We acknowledge your commitment to satisfactorily resolve any deficiencies that may be identified.

Sincerely yours,

/S/

Gary Buehler 11/7/00
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-663

Final Printed Labeling

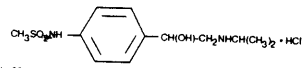
Sotalol Hydrochloride Tablets, 80 mg, 120 mg, 160 mg, and 240 mg

Rx only

To minimize the risk of induced arrhythmia, patients initiated on and re-initiated on sotalol should be placed for a minimum of three days (on their maintenance dose) in a facility that can provide cardiac resuscitation and continuous electrocardiographic monitoring. Calculations of creatinine clearance should be calculated prior to dosing. For detailed instructions regarding dose selection and special cautions for people with renal impairment, see **DOSAGE AND ADMINISTRATION**. Sotalol is also indicated for the maintenance to normal sinus rhythm [delay in time to recurrence of atrial fibrillation/atrial flutter (AFIB/AFL)] in patients with symptomatic AFIB/AFL who are currently in sinus rhythm and is marketed under the brand name BETAPACE AF. Sotalol is not approved for the AFIB/AFL indication and should not be substituted for BETAPACE AF because only BETAPACE AF is distributed with a patient package insert that is appropriate for patients with AFIB/AFL.

DESCRIPTION

Sotalol hydrochloride is an antiarrhythmic drug with Class II (beta-adrenoreceptor blocking) and Class III (cardiac action potential duration prolongation) properties. It is supplied as a light blue, capsule-shaped tablet for oral administration. Sotalol hydrochloride is a white, crystalline solid with a molecular weight of 308.8. It is hydrophilic, soluble in water, propylene glycol and ethanol, but only slightly soluble in chloroform. Chemically, sotalol hydrochloride is d,l-N-[4-[1-hydroxy-2-[(1-methylethyl)amino] ethyl]phenyl]methane-sulfonamide monohydrochloride. The molecular formula is $C_{12}H_{20}N_2O_3S{\cdot}HCl$ and is represented by the following structural formula:



Sotalol hydrochloride tablets contain 80 mg, 120 mg, 160 mg, or 240 mg sotalol hydrochloride. In addition, each tablet contains the following inactive ingredients: anhydrous lactose NF, colloidal silicon dioxide NF, corn starch NF, FD&C blue #2 HT Aluminum Lake, magnesium stearate NF, and microcrystalline cellulose NF.

CLINICAL PHARMACOLOGY

Mechanism of Action: Sotalol has both beta-adrenoreceptor blocking (Vaughan Williams Class II) and cardiac action potential duration prolongation (Vaughan Williams Class III) antiarrhythmic properties. Sotalol is a racemic mixture of d- and l-sotalol. Both isomers have similar Class III antiarrhythmic effects, while the l-isomer is responsible for virtually all the beta-blocking activity. The beta-blocking effect of sotalol is non-cardioselective, half maximal at about 80 mg/day and maximal at doses between 320 and 640 mg/day. Sotalol does not have partial agonist or membrane stabilizing activity. Although significant beta-blockage occurs at oral doses as low as 25 mg, significant Class III effects are seen only at daily doses of 160 mg and above.

Electrophysiology: Sotalol prolongs the plateau phase of the cardiac action potential in the isolated myocyte, as well as in isolated tissue preparations of ventricular or atrial muscle (Class III activity). In intact animals it slows heart rate, decreases AV nodal conduction and increases the refractory periods of atrial and ventricular muscle and conduction tissue.

In man, the Class II (beta-blockade) electrophysiological effects of sotalol are manifested by increased sinus cycle length (slowed heart rate), decreased AV nodal conduction and increased AV nodal refractoriness. The Class III electrophysiological effects in man include prolongation of the atrial and ventricular monophasic action potentials, and effective refractory period prolongation of atrial muscle, ventricular muscle, and atrio-ventricular accessory pathways (where present) in both the anterograde and retrograde directions. With oral doses of 160 to 640 mg/day, the surface ECG shows dose-related mean increases of 40 – 100 msec in QT and 10 – 40 msec in QT_C. (See **WARNINGS** for description of relationship between QT_C and torsade de pointes type arrhythmias). No significant alteration in QRS interval is observed.

In a small study (n = 25) of patients with implanted defibrillators treated concurrently with sotalol, the average defibrillatory threshold was 6 joules (range 2 – 15 joules) compared to a mean of 16 joules for a non-randomized comparative group primarily receiving amiodarone.

Hemodynamics: In a study of systemic hemodynamic function measured invasively in 12 patients with a mean LV ejection fraction of 37% and ventricular tachycardia (9 sustained and 3 non-sustained), a median dose of 160 mg twice daily of sotalol produced a 28% reduction in heart rate and a 24% decrease in cardiac index at 2 hours post dosing at steady-state. Concurrently, systemic vascular resistance and stroke volume showed non-significant increases of 25% and 8%, respectively. Pulmonary capillary wedge pressure increased significantly from 6.4 mmHg to 11.8 mmHg in the 11 patients who completed the study. One patient was discontinued because of worsening congestive heart failure. Mean arterial pressure, mean pulmonary artery pressure and stroke work index did not significantly change. Exercise and isoproterenol induced tachycardia are antagonized by sotalol, and total peripheral resistance increases by a small amount.

In hypertensive patients, sotalol produces significant reductions in both systolic and diastolic blood pressures. Although sotalol is usually well-tolerated hemodynamically, caution should be exercised in patients with marginal cardiac compensation as deterioration in cardiac performance may occur. (See **WARNINGS: Congestive Heart Failure.**)

Clinical Actions: Sotalol has been studied in life-threatening and less severe arrhythmias. In patients with frequent premature ventricular complexes (VPC), sotalol was significantly superior to placebo in reducing VPC's, paired VPC's and non-sustained ventricular tachycardia (NSVT); the response was dose-related through 640 mg/day with 80 – 85% of patients having at least a 75% reduction of VPC's. Sotalol was also superior, at the doses evaluated, to propranolol (40 – 80 mg TID) and similar to quinidine (200 – 400 mg QID) in reducing VPC's. In patients with life-threatening arrhythmias [sustained ventricular tachycardia/fibrillation (VT/VF)], sotalol was studied acutely [by suppression of programmed electrical stimulation (PES) induced VT and by suppression of Holter monitor evidence of sustained VT] and, in acute responders, chronically.

In a double-blind, randomized comparison of sotalol and procainamide given intravenously (total of 2 mg/kg sotalol hydrochloride vs. 19 mg/kg procainamide over 90 minutes), sotalol suppressed PES induction in 30% of patients vs. 20% for procainamide (p=0.2).

In a randomized clinical trial [Electrophysiologic Study Versus Electrocardiographic Monitoring (ESVEM) Trial] comparing choice of antiarrhythmic therapy by PES suppression vs. Holter monitor selection (in each case followed by treadmill exercise testing) in patients with a history of sustained VT/VF who are also inducible by PES, the effectiveness acutely and chronically of sotalol was compared with 6 other drugs (procainamide, quinidine, mexiletine, propafenone, imipramine and pirmenol). Overall response, limited to first randomized drug, was 39% for sotalol and 30% for the pooled other drugs. Acute response rate for first drug randomized using suppression of PES induction was 36% for sotalol vs. a mean of 13% for the other drugs. Using the Holter monitoring endpoint (complete suppression of sustained VT, 90% suppression of NSVT, 80% suppression of VPC pairs, and at least 70% suppression of VPCs), sotalol yielded 41% response vs. 45% for the other drugs combined. Among responders placed on long-term therapy identified acutely as effective (by either PES or Holter), sotalol, when compared to the pool of other drugs, has the lowest two-year mortality (13% vs. 22%), the lowest two-year VT recurrence rate (30% vs. 60%), and the lowest withdrawal rate (38% vs. about 75 – 80%). The most commonly used doses of sotalol hydrochloride in this trial were 320 to 480 mg/day (66% of patients), with 16% receiving 240 mg/day or less and 18% receiving 640 mg or more.

It cannot be determined, however, in the absence of a controlled comparison of sotalol vs. no pharmacologic treatment (e.g., in patients with implanted defibrillators) whether sotalol response causes improved survival or identifies a population with a good prognosis.

In a large, double-blind, placebo controlled secondary prevention (post-infarction) trial (n=1456), sotalol hydrochloride was given as a non-titrated initial dose of 320 mg once daily. Sotalol did not produce a significant increase in survival (7.3% mortality on sotalol vs. 8.9% on placebo; p=0.3), but overall did not suggest an adverse effect on survival. There was, however, a suggestion of an early (i.e., first 10 days) excess mortality (3% on sotalol vs. 2% on placebo). In a second small trial (n=17 randomized to sotalol) where sotalol was administered at high doses (e.g., 320 mg twice daily) to high-risk post-infarction patients (ejection fraction < 40% and either > 10 VPC/hr or VT on Holter), there were 4 fatalities and 3 serious hemodynamic/electrical adverse events within two weeks of initiating sotalol.

Pharmacokinetics: In healthy subjects, the oral bioavailability of sotalol hydrochloride is 90 – 100%. After oral administration, peak plasma concentrations are reached in 2.5 to 4 hours, and steady-state plasma concentrations are attained within 2 – 3 days (i.e., after 5 – 6 doses when administered twice daily). Over the dosage range 160 to 640 mg/day sotalol hydrochloride displays dose proportionality with respect to plasma concentrations. Distribution occurs to a central (plasma) and to a peripheral compartment, with a mean elimination half-life of 12 hours. Dosing every 12 hours results in trough plasma concentrations which are approximately one-half of those at peak.

Sotalol does not bind to plasma proteins and is not metabolized. Sotalol shows very little intersubject variability in plasma levels. The pharmacokinetics of the d and l enantiomers of sotalol are essentially identical. Sotalol crosses the blood brain barrier poorly. Excretion is predominantly via the kidney in the unchanged form, and therefore lower doses are necessary in conditions of renal impairment (see **DOSAGE AND ADMINISTRATION**). Age per se does not significantly alter the pharmacokinetics of sotalol, but impaired renal function in geriatric patients can increase the terminal elimination half-life, resulting in increased drug accumulation. The absorption of sotalol was reduced by approximately 20% compared to fasting when it was administered with a standard meal. Since sotalol is not subject to first-pass metabolism, patients with hepatic impairment show no alteration in clearance of sotalol.

INDICATIONS AND USAGE

Oral sotalol hydrochloride is indicated for the treatment of documented ventricular arrhythmias, such as sustained ventricular tachycardia, that in the judgement of the physician are life-threatening. Because of the proarrhythmic effects of sotalol (See **WARNINGS**), including a 1.5 to 2% rate of torsade de pointes or new VT/VF in patients with either NSVT or supraventricular arrhythmias, its use in patients with less severe arrhythmias, even if the patients are symptomatic, is generally not recommended. Treatment of patients with asymptomatic ventricular premature contractions should be avoided.

Initiation of sotalol treatment or increasing doses, as with other antiarrhythmic agents used to treat life-threatening arrhythmias, should be carried out in the hospital. The response to treatment should then be evaluated by a suitable method (e.g., PES or Holter monitoring) prior to continuing the patient on chronic therapy. Various approaches have been used to determine the response by antiarrhythmic therapy, including sotalol.

In the ESVEM Trial, response to Holter monitoring was tentatively defined as 100% suppression of ventricular tachycardia, 90% suppression of non-sustained VT, 80% suppression of paired VPCs, and 75% suppression of total VPCs in patients who had at least 10 VPCs/hour at baseline; this tentative response was confirmed if VT lasting 5 or more beats was not observed during treadmill exercise testing using a standard Bruce protocol. The PES protocol utilized a maximum of three extrastimuli at three pacing cycle lengths and two right ventricular pacing sites. Response by PES was defined as prevention of induction of the following: 1) monomorphic VT lasting over 15 seconds; 2) non-sustained polymorphic VT containing more than 15 beats of monomorphic VT in patients with a history of monomorphic VT; 3) polymorphic VT or VF greater than 15 beats in patients with VF or a history of aborted sudden death without monomorphic VT; and 4) two episodes of polymorphic VT or VF of greater than 15 beats in a patient presenting with monomorphic VT. Sustained VT or NSVT producing hypotension during the final treadmill test was considered a drug failure.

In a multicenter open-label long-term study of sotalol in patients with life-threatening ventricular arrhythmias which have proven refractory to other antiarrhythmic medications, response by Holter monitoring was defined as in ESVEM. Response by PES was defined as noninducibility of sustained VT by at least double extrastimuli delivered at a pacing cycle length of 400 msec. Overall survival and arrhythmia recurrence rates in this study were similar to those seen in ESVEM, although there was no comparative group to allow a definitive assessment of outcome.

Antiarrhythmic drugs have not been shown to enhance survival in patients with ventricular arrhythmias.

Sotalol is also indicated for the maintenance of normal sinus rhythm [delay in time to recurrence of atrial fibrillation/atrial flutter (AFIB/AFL)] in patients with symptomatic AFIB/AFL who are currently in sinus rhythm and is marketed under the brand name BETAPACE AF. Sotalol is not approved for the AFIB/AFL indication and should not be substituted for BETAPACE AF because only BETAPACE AF is distributed with a patient package insert that is appropriate for patients with AFIB/AFL.

CONTRAINDICATIONS

Sotalol hydrochloride is contraindicated in patients with bronchial asthma, sinus bradycardia, second and third degree AV block, unless a functioning pacemaker is present, congenital or acquired long QT syndromes, cardiogenic shock, uncontrolled congestive heart failure, and previous evidence of hypersensitivity to sotalol.

WARNINGS

Mortality: The National Heart, Lung, and Blood Institute's Cardiac Arrhythmia Suppression Trial I (CAST I) was a long-term, multi-center, double-blind study in patients with asymptomatic, non-life-threatening ventricular arrhythmias, 1 to 103 weeks after acute myocardial infarction. Patients in CAST I were randomized to receive placebo or individually optimized doses of encainide, flecainide, or moricizine. The Cardiac Arrhythmia Suppression Trial II (CAST II) was similar, except that the recruited patients had had their index infarction 4 to 90 days before randomization, patients with left ventricular ejection fractions greater than 40% were not admitted, and the randomized regimens were limited to placebo and moricizine.

CAST I was discontinued after an average time-on-treatment of 10 months, and CAST II was discontinued after an average time-on-treatment of 18 months. As compared to placebo treatment, all three active therapies were associated with increases in short term (14-day) mortality, and encainide and flecainide were associated with significant increases in longer-term mortality as well. The longer-term mortality rate associated with moricizine treatment could not be statistically distinguished from that associated with placebo.

The applicability of these results to other populations (e.g., those without recent myocardial infarction) and to other than Class I antiarrhythmic agents is uncertain. Sotalol is devoid of Class I effects, and in a large (n=1,456) controlled trial in patients with a recent myocardial infarction, who did not necessarily have ventricular arrhythmias, sotalol did not produce increased mortality at doses up to 320 mg/day (See **Clinical Actions**). On the other hand, in the large post-infarction study using a non-titrated initial dose of 320 mg once daily and in a second small randomized trial in high-risk post-infarction patients treated with high doses (320 mg BID), there have been suggestions of an excess of early sudden deaths.

Proarrhythmia: Like other antiarrhythmic agents, sotalol can provoke new or worsened ventricular arrhythmias in some patients, including sustained ventricular tachycardia or ventricular fibrillation, with potentially fatal consequences. Because of its effect on cardiac repolarization (QT_C interval prolongation), torsade de pointes, a polymorphic ventricular tachycardia with prolongation of the QT interval and a shifting electrical axis is the most common form of proarrhythmia associated with sotalol, occurring in about 4% of high risk (history of sustained VT/VF) patients. The risk of torsade de pointes progressively increases with prolongation of the QT interval, and is worsened also by reduction in heart rate and reduction in serum potassium (See **Electrolyte Disturbances**).

Because of the variable temporal recurrence of arrhythmias, it is not always possible to distinguish between a new or aggravated arrhythmic event and the patients underlying rhythm disorder. (Note, however, that torsade de pointes is usually a drug-induced arrhythmia in people with an initially normal QT_C.) Thus, the incidence of drug-related events cannot be precisely determined, so that the occurrence rates provided must be considered approximations. Note also that drug-induced arrhythmias may often not be identified, particularly if they occur long after starting the drug, due to less frequent monitoring. It is clear from the NIH-sponsored CAST (see **WARNINGS: Mortality**) that some antiarrhythmic drugs can cause increased sudden death mortality, presumably due to new arrhythmias or asystole, that do not appear early in treatment but that represent a sustained increased risk.

Overall, in clinical trials with sotalol, 4.3% of 3257 patients experienced a new or worsened ventricular arrhythmia. Of this 4.3%, there was new or worsened sustained ventricular tachycardia in approximately 1% of patients and torsade de pointes in 2.4%. Additionally, in approximately 1% of patients, deaths were considered possibly drug-related; such cases, although difficult to evaluate, may have been associated with proarrhythmic events. **In patients with a history of sustained ventricular tachycardia, the incidence of torsade de pointes was 4% and worsened VT in about 1%; in patients with other, less serious, ventricular arrhythmias and supraventricular arrhythmias, the incidence of torsade de pointes was 1% and 1.4%, respectively.**

Torsade de pointes arrhythmias were dose related, as in the prolongation of QT (QT_C) interval, as shown in the table below:

Percent Incidence of Torsade de Pointes and Mean QT_C Interval by Dose For Patients With Sustained VT/VF

Daily Dose (mg)	Incidence of Torsade de pointes	Mean QT_C* (msec)
80	0 (69)	463 (17)
160	0.5 (832)	467 (181)
320	1.6 (835)	473 (344)
480	4.4 (459)	483 (234)
640	3.7 (324)	490 (185)
>640	5.8 (103)	512 (62)

() Number of patients assessed

*Highest on-therapy value

In addition to dose and presence of sustained VT, other risk factors for torsade de pointes were gender (females) had a higher incidence, excessive prolongation of the QT_C interval (see table below) and history of cardiomegaly or congestive heart failure. Patients with sustained ventricular tachycardia and a history of congestive heart failure appear to have the highest risk for serious proarrhythmia (7%). Of the patients experiencing torsade de pointes, approximately two-thirds spontaneously reverted to their baseline rhythm. The others were either converted electrically (D/C cardioversion or overdrive pacing) or treated with other drugs (see **OVERDOSAGE**). It is not possible to determine whether some sudden deaths represented episodes of torsades de pointes, but in some instances sudden death did follow a documented episode of torsade de pointes. Although sotalol therapy was discontinued in most patients experiencing torsade de pointes, 17% were continued on a lower dose. Nonetheless, sotalol should be used with particular caution if the QT_C is greater than 500 msec on-therapy and serious consideration should be given to reducing the dose or discontinuing therapy when the QT_C exceeds 550 msec. Due to the multiple risk-factors associated with torsade de pointes, however, caution should be exercised regardless of the QT_C interval. The table below relates the incidence of torsade de pointes to on-therapy QT_C and change in QT_C from baseline. It should be noted, however, that the highest on-therapy QT_C was in many cases the one obtained at the time of the torsade de pointes event, so that the table overstates the predictive value of a high QT_C.

Relationship Between QT_C Interval Prolongation and Torsades de Pointes

On-Therapy QT_C Interval (msec)	Incidence of Torsade de Pointes
less than 500	1.3% (1787)
500 – 525	3.4% (236)
525 – 550	5.6% (125)
>550	10.8% (157)

Change in QT_C Interval From Baseline (msec)	Incidence of Torsade de Pointes
less than 65	1.6% (1516)
65 – 80	3.2% (158)
80 – 100	4.1% (146)
100 – 130	5.2% (115)
>130	7.1% (99)

() Number of patients assessed

Proarrhythmic events must be anticipated not only on initiating therapy, but with every upward dose adjustment. Proarrhythmic events most often occur within 7 days of initiating therapy or of an increase in dose; 75% of serious proarrhythmic (torsade de pointes and worsened VT) occurred within 7 days of initiating sotalol therapy, while 60% of such events occurred within 3 days of initiation or a dosage change. Initiating therapy at 80 mg BID with gradual upward dose titration and appropriate evaluations for efficacy (e.g., PES or Holter) and safety (e.g., QT interval, heart rate and electrolytes) prior to dose escalation, should reduce the risk of proarrhythmia. Avoiding excessive accumulation of sotalol in patients with diminished renal function, by appropriate dose reduction, should also reduce the risk of proarrhythmia (see **DOSAGE AND ADMINISTRATION**).

Congestive Heart Failure: Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta-blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In patients who have congestive heart failure controlled by digitalis and/or diuretics, sotalol should be administered cautiously. Both digitalis and sotalol slow AV conduction. As with all beta-blockers, caution is advised when initiating therapy in patients with any evidence of left ventricular dysfunction. In premarketing studies, new or worsened congestive heart failure (CHF) occurred in 3.3% (n=3257) of patients and led to discontinuation in approximately 1% of patients receiving sotalol. The incidence was higher in patients presenting with sustained ventricular tachycardia/fibrillation (4.6%, n=1363), or a prior history of heart failure (7.3%, n=696). Based on a life-table analysis, the one-year incidence of new or worsened CHF was 3% in patients without a prior history and 10% in patients with a prior history of CHF. NYHA Classification was also closely associated to the incidence of new or worsened heart failure while receiving sotalol (1.8% in 1395 Class I patients, 4.9% in 1254 Class II patients and 6.1% in 278 Class III or IV patients).

Electrolyte Disturbances: Sotalol should not be used in patients with hypokalemia or hypomagnesemia prior to correction of imbalance, as these conditions can exaggerate the degree of QT prolongation, and increase the potential for torsade de pointes. Special attention should be given to electrolyte and acid-base balance in patients experiencing severe or prolonged diarrhea or patients receiving concomitant diuretic drugs.

Conduction Disturbances: Excessive prolongation of the QT interval (>550 msec) can promote serious arrhythmias and should be avoided (see **Proarrhythmias** above). Sinus bradycardia (heart rate less than 50 bpm) occurred in 13% of patients receiving sotalol in clinical trials, and led to discontinuation in about 3% of patients. Bradycardia itself increases the risk of torsade de pointes. Sinus pause, sinus arrest and sinus node dysfunction occur in less than 1% of patients. The incidence of 2nd- or 3rd-degree AV block is approximately 1%.

Recent Acute MI: Sotalol can be used safely and effectively in the long-term treatment of life-threatening ventricular arrhythmias following a myocardial infarction. However, experience in the use of sotalol to treat cardiac arrhythmias in the early phase of recovery from acute MI is limited and at least at high initial doses is not reassuring. (See **WARNINGS: Mortality**.) In the first 2 weeks post-MI caution is advised and careful dose titration is especially important, particularly in patients with markedly impaired ventricular function.

The following warnings are related to the beta-blocking activity of sotalol.

Abrupt Withdrawal: Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy. Occasional cases of exacerbation of angina pectoris, arrhythmias and, in some cases, myocardial infarction have been reported after abrupt discontinuation of beta-blocker therapy. Therefore, it is prudent when discontinuing chronically administered sotalol, particularly in patients with ischemic heart disease, to carefully monitor the patient and consider the temporary use of an alternative beta-blocker if appropriate. If possible, the dosage of sotalol should be gradually reduced over a period of one to two weeks. If angina or acute coronary insufficiency develops, appropriate therapy should be instituted promptly. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized in patients receiving sotalol, abrupt discontinuation in patients with arrhythmias may unmask latent coronary insufficiency.

Non-Allergic Bronchospasm (e.g., chronic bronchitis and emphysema): **PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS.** It is prudent, if sotalol is to be administered, to use the smallest effective dose, so that inhibition of bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors may be minimized.

Anaphylaxis: While taking beta-blockers, patients with a history of anaphylactic reaction to a variety of allergens may have

more severe reaction on repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual dose of epinephrine used to treat the allergic reaction.

Anesthesia: The management of patients undergoing major surgery who are being treated with beta-blockers is controversial. Protracted severe hypotension and difficulty in restoring and maintaining normal cardiac rhythm after anesthesia have been reported in patients receiving beta-blockers.

Diabetes: In patients with diabetes (especially labile diabetes) or with a history of episodes of spontaneous hypoglycemia, sotalol should be given with caution since beta-blockade may mask some important premonitory signs of acute hypoglycemia; e.g., tachycardia.

Sick Sinus Syndrome: Sotalol should be used only with extreme caution in patients with sick sinus syndrome associated with symptomatic arrhythmias, because it may cause sinus bradycardia, sinus pauses or sinus arrest.

Thyrotoxicosis: Beta-blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-blockade which might be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm.

PRECAUTIONS

Renal Impairment: Sotalol is mainly eliminated via the kidneys through glomerular filtration and to a small degree by tubular secretion. There is a direct relationship between renal function, as measured by serum creatinine or creatinine clearance, and the elimination rate of sotalol. Guidance for dosing in conditions of renal impairment can be found under "DOSAGE AND ADMINISTRATION."

Drug Interactions

Drugs undergoing CYP450 metabolism: Sotalol is primarily eliminated by renal excretion; therefore, drugs that are metabolized by CYP450 are not expected to alter the pharmacokinetics of sotalol. Sotalol is not expected to inhibit or induce any CYP450 enzymes, therefore, it is not expected to alter the PK of drugs that are metabolized by these enzymes.

Antiarrhythmics: Class Ia antiarrhythmic drugs, such as disopyramide, quinidine and procainamide and other Class III drugs (e.g., amiodarone) are not recommended as concomitant therapy with sotalol, because of their potential to prolong refractoriness (see **WARNINGS**). There is only limited experience with the concomitant use of Class Ib or Ic antiarrhythmics. Additive Class II effects would also be anticipated with the use of other beta-blocking agents concomitantly with sotalol.

Digoxin: Single and multiple doses of sotalol do not substantially affect serum digoxin levels. Proarrhythmic events were more common in sotalol treated patients also receiving digoxin; it is not clear whether this represents an interaction or is related to the presence of CHF, a known risk factor for proarrhythmia, in patients receiving digoxin.

Calcium blocking drugs: Sotalol should be administered with caution in conjunction with calcium blocking drugs because of possible additive effects on atrioventricular conduction or ventricular function. Additionally, concomitant use of these drugs may have additive effects on blood pressure, possibly leading to hypotension.

Catecholamine-depleting agents: Concomitant use of catecholamine-depleting drugs, such as reserpine and guanethidine, with a beta-blocker may produce an excessive reduction of resting sympathetic nervous tone. Patients treated with sotalol plus a catecholamine depletor should therefore be closely monitored for evidence of hypotension and or marked bradycardia which may produce syncope.

Insulin and oral antidiabetics: Hyperglycemia may occur, and the dosage of insulin or antidiabetic drugs may require adjustment. Symptoms of hypoglycemia may be masked.

Beta-2-receptor stimulants: Beta-agonists such as salbutamol, terbutaline and isoprenaline may have to be administered in increased dosages when used concomitantly with sotalol.

Clonidine: Beta-blocking drugs may potentiate the rebound hypertension sometimes observed after discontinuation of clonidine; therefore, caution is advised when discontinuing clonidine in patients receiving sotalol.

Other: No pharmacokinetic interactions were observed with hydrochlorothiazide or warfarin.

Antacids: Administration of sotalol within 2 hours of antacids containing aluminum oxide and magnesium hydroxide should be avoided because it may result in a reduction in C_{max} and AUC of 26% and 20%, respectively and consequently in a 25% reduction in the bradycardic effect at rest. Administration of the antacid two hours after sotalol has no effect on the pharmacokinetics or pharmacodynamics of sotalol.

Drugs prolonging the QT interval: Sotalol should be administered with caution in conjunction with other drugs known to prolong the QT interval such as Class I and Class III antiarrhythmic agents, phenothiazines, tricyclic antidepressants, astemizole, bepridil, certain oral macrolides, and certain quinolone antibiotics (see **WARNINGS**).

DRUG/Laboratory Test Interactions

The presence of sotalol in the urine may result in falsely elevated levels of urinary metanephrine when measured by fluorometric or photometric methods. In screening patients suspected of having a pheochromocytoma and being treated with sotalol, a specific method, such as a high performance liquid chromatographic assay with solid phase extraction (e.g., J. Chrmatogr. 385:241, 1987) should be employed in determining levels of catecholamines.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No evidence of carcinogenic potential was observed in rats during a 24-month study at 137 to 275 mg/kg/day (approximately 30 times the maximum recommended human oral dose (MRHD) as mg/kg or 5 times the MRHD as mg/m^2) or in mice, during a 24-month study at 4141 to 7122 mg/kg/day (approximately 450 – 750 times the MRHD as mg/kg or 36 – 63 times the MRHD as mg/m^2).

Sotalol has not been evaluated in any specific assay of mutagenicity or clastogenicity.

No significant reduction in fertility occurred in rats at oral doses of 1000 mg/kg/day (approximately 100 times the MRHD as mg/kg or 9 times the MRHD as mg/m^2) prior to mating, except for a small reduction in the number of offspring per litter.

Pregnancy: *Teratogenic Effects:* Pregnancy Category B: Reproduction studies in rats and rabbits during organogenesis at 100 and 22 times the MRHD as mg/kg (9 and 7 times the MRHD as mg/m2), respectively, did not reveal any teratogenic potential associated with sotalol. In rabbits, a high dose of sotalol (160 mg/kg/day) at 16 times the MRHD as mg/kg (6 times the MRHD as mg/m^2) produced a slight increase in fetal death likely due to maternal toxicity. Eight times the maximum dose (80 mg/kg/day or 3 times the MRHD as mg/m2) did not result in an increased incidence of fetal deaths. In rats, 1000 mg/kg/day sotalol, 100 times the MRHD (18 times the MRHD as mg/m^2), increased the number of early resorptions, while at 14 times the maximum dose (2.5 times the MRHD as mg/m2), no increase in early resorptions was noted. However, animal reproduction studies are not always predictive of human response.

Although there are no adequate and well-controlled studies in pregnant women, sotalol has been shown to cross the placenta, and is found in amniotic fluid. There has been a report of subnormal birth weight with sotalol. Therefore, sotalol should be used during pregnancy only if the potential benefit outweighs the potential risk.

Nursing Mothers: Sotalol is excreted in the milk of laboratory animals and has been reported to be present in human milk. Because of the potential for adverse reactions in nursing infants from sotalol, a decision should be made whether to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: The safety and effectiveness of sotalol in pediatric patients have not been established.

ADVERSE REACTIONS

During premarketing trials, 3186 patients with cardiac arrhythmias (1363 with sustained ventricular tachycardia) received oral sotalol, of whom 2451 received the drug for at least two weeks. The most important adverse effects are torsade de pointes and other serious new ventricular arrhythmias (see **WARNINGS**), occurring at rates of almost 4% and 1%, respectively, in the VT/VF population. Overall, discontinuation because of unacceptable side-effects was necessary in 17% of all patients in clinical trials, and in 13% of patients treated for at least two-weeks. The most common adverse reactions leading to discontinuation of sotalol are as follows: fatigue 4%, bradycardia (less than 50 bpm) 3%, dyspnea 3%, proarrhythmia 3%, asthenia 2%, and dizziness 2%. Occasional reports of elevated serum liver enzymes have occurred with sotalol therapy but no cause and effect relationship has been established. One case of peripheral neuropathy which resolved on discontinuation of sotalol and recurred when the patient was rechallenged with the drug was reported in an early dose tolerance study. Elevated blood glucose levels and increased insulin requirements can occur in diabetic patients.

The following table lists as a function of dosage the most common (incidence of 2% or greater) adverse events, regardless of relationship to therapy and the percent of patients discontinued due to the event, as collected from clinical trials involving 1292 patients with sustained VT/VF.

Incidence (%) of Adverse Events and Discontinuations

	DAILY DOSE						
Body System	**160mg (n=832)**	**240mg (n=263)**	**320mg (n=836)**	**480mg (n=458)**	**640mg (n=324)**	**Any Dose* (n=1292)**	**Discontinued (n=1292)**
Body as a whole							
infection	1	2	2	2	3	4	<1
fever	1	2	3	2	2	4	<1
localized pain	1	1	2	2	2	3	<1
Cardiovascular							
dyspnea	5	8	11	15	15	21	2
bradycardia	8	8	9	7	5	16	2
chest pain	4	3	10	10	14	16	<1
palpitation	3	3	8	9	12	14	<1
edema	2	2	5	3	5	8	1
ECG abnormal	4	2	4	2	2	7	1
hypotension	3	4	3	2	3	6	2
proarrhythmia	<1	<1	2	4	5	5	3
syncope	1	1	3	2	5	5	1
heart failure	2	3	2	2	2	5	1
presyncope	1	2	2	4	3	4	<1
peripheral vascular disorder	1	2	1	1	2	3	<1
cardiovascular disorder	1	<1	2	2	2	3	<1
vasodilation	1	<1	1	2	1	3	<1
AICD Discharge	<1	2	2	2	2	3	<1
hypertension	<1	1	1	1	2	2	<1
Nervous							
fatigue	5	8	12	12	13	20	2
dizziness	7	6	11	11	14	20	1
asthenia	4	5	7	8	10	13	1
light-headed	4	3	6	6	9	12	1
headache	3	2	4	4	4	8	<1
sleep problem	1	1	5	5	6	8	<1
perspiration	1	2	3	4	5	6	<1
altered consciousness	2	3	1	2	3	4	<1
depression	1	2	2	2	3	4	<1
paresthesia	1	1	2	3	2	4	<1
anxiety	2	2	2	3	2	4	<1
mood change	<1	<1	1	3	2	3	<1
appetite disorder	1	2	2	1	3	3	<1
stroke	<1	<1	1	1	<1	1	<1
Digestive							
nausea/vomiting	5	4	4	6	6	10	1
diarrhea	2	3	3	3	5	7	<1
dyspepsia	2	3	3	3	3	6	<1
abdominal pain	<1	<1	2	2	2	3	<1
colon problem	2	1	1	<1	2	3	<1
flatulence	1	<1	1	1	2	2	<1
Respiratory							
pulmonary problems	3	3	5	3	4	8	<1
upper respiratory tract problem	1	1	3	4	3	5	<1
asthma	1	<1	1	1	1	2	<1
Urogenital							
genitourinary disorder	1	0	1	1	2	3	<1
sexual dysfunction	<1	1	1	1	3	2	<1
Metabolic							
abnormal lab value	1	2	3	2	1	4	<1
weight change	1	1	1	<1	2	2	<1
Musculoskeletal							
extremity pain	2	2	4	5	3	7	<1
back pain	1	<1	2	2	2	3	<1
Skin and Appendages							
rash	2	3	2	3	4	5	<1
Hematologic							
bleeding	1	<1	1	<1	2	2	<1
Special Senses							
visual problem	1	1	2	4	5	5	<1

*Because patients are counted at each dose level tested, the Any Dose column cannot be determined by adding across the doses.

Potential Adverse Effects: Foreign marketing experience with sotalol shows an adverse experience profile similar to that described above from clinical trials. Voluntary reports since introduction include rare reports (less than one report per 10,000 patients) of: emotional lability, slightly clouded sensorium, incoordination, vertigo, paralysis, thrombocytopenia, eosinophilia, leukopenia, photosensitivity reaction, fever, pulmonary edema, hyperlipidemia, myalgia, pruritus, alopecia.

The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been associated with sotalol during investigational use and foreign marketing experience.

OVERDOSAGE

Intentional or accidental overdosage with sotalol has rarely resulted in death.

Symptoms and Treatment of Overdosage: The most common signs to be expected are bradycardia, congestive heart failure, hypotension, bronchospasm and hypoglycemia. In cases of massive intentional overdosage (2 to 16 grams) of sotalol the following clinical findings were seen: hypotension, bradycardia, cardiac asystole, prolongation of QT interval, torsade de pointes, ventricular tachycardia, and premature ventricular complexes. If overdosage occurs, therapy with sotalol should be discontinued and the patient observed closely. Because of the lack of protein binding, hemodialysis is useful for reducing sotalol plasma concentrations. Patients should be carefully observed until QT intervals are normalized and the heart rate returns to levels >50 bpm. The occurrence of hypotension following an overdose may be associated with an initial slow drug elimination phase (half life of 30 hours) thought to be due to a temporary reduction of renal function caused by hypotension. In addition, if required, the following therapeutic measures are suggested:

Bradycardia or cardiac asystole: Atropine, another anticholinergic drug, a beta-adrenergic agonist or transvenous cardiac pacing.

Heart Block: (second and third degree) transvenous cardiac pacemaker.

Hypotension: (depending on associated factors) epinephrine rather than isoproterenol or norepinephrine may be useful.

Bronchospasm: Aminophylline or aerosol beta-2-receptor stimulant.

Torsade de pointes: DC cardioversion, transvenous cardiac pacing, epinephrine, magnesium sulfate.

DOSAGE AND ADMINISTRATION

As with other antiarrhythmic agents, sotalol should be initiated and doses increased in a hospital with facilities for cardiac rhythm monitoring and assessment (see **INDICATIONS AND USAGE**). Sotalol should be administered only after appropriate clinical assessment (see **INDICATIONS AND USAGE**), and the dosage of sotalol must be individualized for each patient on the basis of therapeutic response and tolerance. Proarrhythmic events can occur not only at initiation of therapy, but also with each upward dosage adjustment.

Dosage of sotalol should be adjusted gradually, allowing 3 days between dosing increments in order to attain steady-state plasma concentrations, and to allow monitoring of QT intervals. Graded dose adjustment will help prevent the usage of doses which are higher than necessary to control the arrhythmia. The recommended initial dose is 80 mg twice daily. This dose may be increased, if necessary, after appropriate evaluation to 240 or 320 mg/day (120 to 160 mg twice daily). In most patients, a therapeutic response is obtained at a total daily dose of 160 to 320 mg/day, given in two or three divided doses. Some patients with life-threatening refractory ventricular arrhythmias may require doses as high as 480 to 640 mg/day; however, these doses should only be prescribed when the potential benefit outweighs the increased risk of adverse events, in particular proarrhythmia. Because of the long terminal elimination half-life of sotalol, dosing on more than a BID regimen is usually not necessary.

DOSAGE IN RENAL IMPAIRMENT

Because sotalol is excreted predominantly in urine and its terminal elimination half-life is prolonged in conditions of renal impairment, the dosing interval (time between divided doses) of sotalol should be modified (when creatinine clearance is lower than 60 mL per minute) according to the following table.

Creatinine Clearance mL/min	Dosing* Interval (hours)
>60	12
30 – 59	24
10 – 29	36 – 48
<10	Dose should be individualized

*The initial dose of 80 mg and subsequent doses should be administered at these intervals. See following paragraph for dosage escalations.

Since the terminal elimination half-life of sotalol is increased in patients with renal impairment, a longer duration of dosing is required to reach steady-state. Dose escalation in renal impairment should be done after administration of at least 5 – 6 doses at appropriate intervals (see table above).

Extreme caution should be exercised in the use of sotalol in patients with renal failure undergoing hemodialysis. The half-life of sotalol is prolonged (up to 69 hours) in anuric patients. Sotalol, however, can be partly removed by dialysis with subsequent partial rebound in concentrations when dialysis is completed. Both safety (heart rate, QT interval) and efficacy (arrhythmia control) must be closely monitored.

Transfer to Sotalol

Before starting sotalol, previous antiarrhythmic therapy should generally be withdrawn under careful monitoring for a minimum of 2 – 3 plasma half-lives if the patient's clinical condition permits (see **PRECAUTIONS, Drug Interactions**). Treatment has been initiated in some patients receiving I.V. lidocaine without ill effect. After discontinuation of amiodarone, sotalol should not be initiated until the QT interval is normalized (see **WARNINGS**).

Transfer to BETAPACE AF from Sotalol

Patients with a history of symptomatic AFIB/AFL who are currently receiving sotalol for the maintenance of normal sinus rhythm should be transferred to BETAPACE AF because of the significant differences in labeling (i.e., patient package insert for BETAPACE AF, dosing administration and safety information).

HOW SUPPLIED

Sotalol hydrochloride; capsule-shaped light-blue scored tablets

Tablets 80 mg—(imprinted "G" on one side and 2711 on the other side)
Bottles of 100 ..... NDC 0115-2711-01
Bottles of 500 ..... NDC 0115-2711-02
Bottles of 1000 ..... NDC 0115-2711-03

Tablets 120 mg—(imprinted "G" on one side and 2722 on the other side)
Bottles of 100 ..... NDC 0115-2722-01
Bottles of 500 ..... NDC 0115-2722-02
Bottles of 1000 ..... NDC 0115-2722-03

Tablets 160 mg—(imprinted "G" on one side and 2733 on the other side)
Bottles of 100 ..... NDC 0115-2733-01
Bottles of 500 ..... NDC 0115-2733-02
Bottles of 1000 ..... NDC 0115-2733-03

Tablets 240 mg—(imprinted "G" on one side and 2744 on the other side)
Bottles of 100 ..... NDC 0115-2744-01
Bottles of 500 ..... NDC 0115-2744-02
Bottles of 1000 ..... NDC 0115-2744-03

Store at controlled room temperature 15° to 30°C (59° to 86°F) (see USP).
Dispense in tightly-closed, light-resistant containers with safety closures (USP).

Mfg. by: IMPAX Laboratories, Inc.
Hayward, California 94544

Dist. by: Global Pharmaceuticals
Division of IMPAX Laboratories, Inc.
Philadelphia, PA 19124
Rev. 08/00
144-02

GLOBAL®

NDC 0115-2711-03

SOTALOL HCl

Tablets

80 mg

Rx only

1000 TABLETS

USUAL DOSAGE: See accompanying outsert for complete prescribing information. Dispense in tightly-closed, light-resistant containers with safety closures.

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

Keep this and all medication out of reach of children.

Dist. by:
Global Pharmaceuticals
Division of IMPAX Laboratories, Inc.
Philadelphia, PA 19124

Rev. 2/00
138-01

Lot No.:

NOV 7 2000
APPROVED

Exp. Date

GLOBAL®

NDC 0115-2711-01

SOTALOL HCl

Tablets

80 mg

Rx only

100 TABLETS

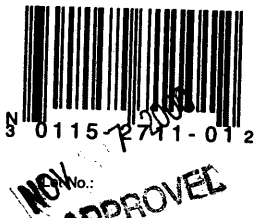
USUAL DOSAGE: See accompanying outsert for complete prescribing information. Dispense in tightly-closed, light-resistant containers with safety closures.

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

Keep this and all medication out of reach of children.

Dist. by:
Global Pharmaceuticals
Division of IMPAX Laboratories, Inc.
Philadelphia, PA 19124

Rev. 2/00
137-01



Lot No.:

NOV
APPROVED

Exp. Date

GLOBAL®

NDC 0115-2711-02

SOTALOL HCl

Tablets

80 mg

Rx only

500 TABLETS

USUAL DOSAGE: See accompanying outsert for complete prescribing information. Dispense in tightly-closed, light-resistant containers with safety closures.

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

Keep this and all medication out of reach of children.

Dist. by:
Global Pharmaceuticals
Division of IMPAX Laboratories, Inc.
Philadelphia, PA 19124

Rev. 2/00
170-01

Lot No.:

NOV
APPROVED

Exp. Date

GLOBAL®

NDC 0115-2722-02

SOTALOL HCl
Tablets
120 mg

Rx only

500 TABLETS

USUAL DOSAGE: See accompanying outsert for complete prescribing information. Dispense in tightly-closed, light-resistant containers with safety closures.

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

Keep this and all medication out of reach of children.

Dist. by:
Global Pharmaceuticals
Division of IMPAX Laboratories, Inc.
Philadelphia, PA 19124

Rev. 2/00
171-01

3 0115-2722-02 5

Lot No.:

APPROVED
NOV 17 2000

Exp. Date

GLOBAL®

NDC 0115-2722-03

SOTALOL HCl
Tablets
120 mg

Rx only

1000 TABLETS

APPROVED

USUAL DOSAGE: See accompanying outsert for complete prescribing information. Dispense in tightly-closed, light-resistant containers with safety closures.

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

Keep this and all medication out of reach of children.

Dist. by:
Global Pharmaceuticals
Division of IMPAX Laboratories, Inc.
Philadelphia, PA 19124

Rev. 2/00
140-01

3 0115-2722-03 2

Lot No.:

NOV 17 2000

Exp. Date

GLOBAL®

NDC 0115-2722-01

SOTALOL HCl
Tablets
120 mg

Rx only

100 TABLETS

USUAL DOSAGE: See accompanying outsert for complete prescribing information. Dispense in tightly-closed, light-resistant containers with safety closures.

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

Keep this and all medication out of reach of children.

Dist. by:
Global Pharmaceuticals
Division of IMPAX Laboratories, Inc.
Philadelphia, PA 19124

Rev. 2/00
139-01

0115-2722-01 8

Lot No.:

APPROVED
NOV 17 2000

Exp. Date

GLOBAL®

NDC 0115-2733-02

SOTALOL HCl
Tablets
160 mg

Rx only

DOSAGE: See accompanying outsert
plete prescribing information. Dispense
y-closed, light-resistant containers with
losures.

t controlled room temperature, 15°-30°C
F). (See USP).

ls and all medication out of reach of
n.

harmaceuticals
of IMPAX Laboratories, Inc.
lphia, PA 19124

Rev. 2/00
172-01

Lot No.:

7 2000

APPROVED

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-663

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 1

2. ANDA # 75-663

3. NAME AND ADDRESS OF APPLICANT
IMPAX Pharmaceuticals, Inc.
Attention: Mark C. Shaw
30831 Huntwood Avenue
Hayward, CA 94544

4. LEGAL BASIS FOR SUBMISSION
The listed drug is BETAPACE® Tablets, 80 mg, 120 mg, 160, mg and 240 mg of Berlex Laboratories. The applicant certified that in their opinion and to the best of their knowledge patent information has not been filed with the FDA.

The exclusivity for BETAPACE® Tablets expires October 30, 1999 and the applicant states that to the best of their knowledge no exclusivity has been registered.

See pp. 11 and 12 for patent and exclusivity statements.

5. SUPPLEMENT(s): N/A

6. PROPRIETARY NAME: N/A

7. NONPROPRIETARY NAME: Sotalol Tablets

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

9. AMENDMENTS AND OTHER DATES:
Firm:
Submitted: June 30, 1999
Amendment: September 14, 1999
Amendment: October 8, 1999
New Correspondence: July 26, 1999

FDA:
Acknowledgement: August 3, 1999
Bio letter: November 2,1999

10. PHARMACOLOGICAL CATEGORY
Antiarrhythmic

11. Rx or OTC
Rx

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

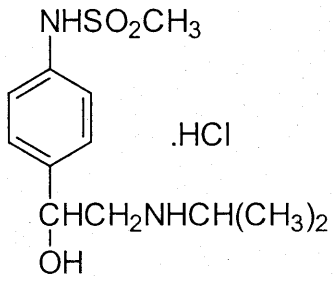
DMF —

13. DOSAGE FORM
Tablets

14. POTENCIES: 80 mg, 120 mg, 160 mg and 240 mg

15: CHEMICAL NAME AND STRUCTURE

Sotalol Hydrochloride
$C_{12}H_{20}N_2O_3S.HCl$;M.W.=308.8



SOTALOL HYDROCHLORIDE

4'-[1-Hydroxy-2-(isopropylamino)ethyl]methanesulfonanilide monohydrochloride. CAS [959-24-0]

16. RECORDS AND REPORTS: N/A

17. COMMENTS

[redacted]

18. CONCLUSIONS AND RECOMMENDATIONS

This ANDA is NOT APPROVABLE. The amendment will be MAJOR.

19. REVIEWER: Sema Basaran , Ph.D.
DATE COMPLETED: December 16, 1999

Redacted 25

pages of trade secret and/or confidential commercial information

D.1

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 75-663

3. NAME AND ADDRESS OF APPLICANT
IMPAX Laboratories, Inc.
Attention: Mark C. Shaw
30831 Huntwood Avenue
Hayward, CA 94544

4. LEGAL BASIS FOR SUBMISSION
The listed drug is BETAPACE® Tablets, 80 mg, 120 mg, 160, mg and 240 mg of Berlex Laboratories. The applicant certified that in their opinion and to the best of their knowledge patent information has not been filed with the FDA.

The exclusivity for BETAPACE® Tablets expires October 30, 1999 and the applicant states that to the best of their knowledge no exclusivity has been registered.

See pp. 11 and 12 for patent and exclusivity statements.

5. SUPPLEMENT(s): N/A

6. PROPRIETARY NAME: N/A

7. NONPROPRIETARY NAME: Sotalol Hydrochloride Tablets

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

9. AMENDMENTS AND OTHER DATES:
Firm:
Submitted: June 30, 1999
Amendment: September 14, 1999
Amendment: October 8, 1999
New Correspondence: July 26, 1999
Amendment: March 20, 2000

FDA:
Acknowledgement: August 3, 1999
Bio letter: November 2,1999
Deficiency letter: Jan 27, 2000

10. PHARMACOLOGICAL CATEGORY
Antiarrhythmic

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]

DMF
DMF

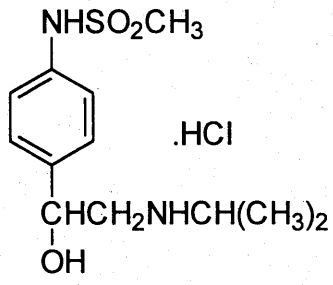
DMF

13. DOSAGE FORM
Tablets

14. POTENCIES: 80 mg, 120 mg, 160 mg and 240 mg

15: CHEMICAL NAME AND STRUCTURE

Sotalol Hydrochloride
$C_{12}H_{20}N_2O_3S.HCl$;M.W.=308.82



SOTALOL HYDROCHLORIDE

4'-[1-Hydroxy-2-(isopropylamino)ethyl]methanesulfonanilide monohydrochloride. CAS [959-24-0]

16. RECORDS AND REPORTS: N/A

17. COMMENTS

18. CONCLUSIONS AND RECOMMENDATIONS

This ANDA is NOT APPROVABLE. The amendment will be Facsimile.

19. REVIEWER: Sema Basaran , Ph.D.
DATE COMPLETED: August 11, 2000

Redacted 29

pages of trade secret and/or confidential commercial information

1. CHEMISTRY REVIEW NO. 3

2. ANDA # 75-663

3. NAME AND ADDRESS OF APPLICANT
IMPAX Laboratories, Inc.
Attention: Mark C. Shaw
30831 Huntwood Avenue
Hayward, CA 94544

4. LEGAL BASIS FOR SUBMISSION
The listed drug is BETAPACE® Tablets, 80 mg, 120 mg, 160, mg and 240 mg of Berlex Laboratories. The applicant certified that in their opinion and to the best of their knowledge patent information has not been filed with the FDA.

The exclusivity for BETAPACE® Tablets expires October 30, 1999 and the applicant states that to the best of their knowledge no exclusivity has been registered.

See pp. 11 and 12 for patent and exclusivity statements.

5. SUPPLEMENT(s): N/A

6. PROPRIETARY NAME: N/A

7. NONPROPRIETARY NAME: Sotalol Hydrochloride Tablets

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

9. AMENDMENTS AND OTHER DATES:
Firm:
Submitted: June 30, 1999
Amendment: September 14, 1999
Amendment: October 8, 1999
New Correspondence: July 26, 1999
Amendment: March 20, 2000
Fax amendment: September 18, 2000

FDA:
Acknowledgement: August 3, 1999
Bio letter: November 2,1999
Deficiency letter: Jan 27, 2000
Labeling deficiencies: July 19, 2000
Facsimile deficiencies: August 29, 2000

10. PHARMACOLOGICAL CATEGORY
Antiarrhythmic

11. Rx or OTC
Rx

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

DMF —
DMF —
DMF —
DMF —
DMF —

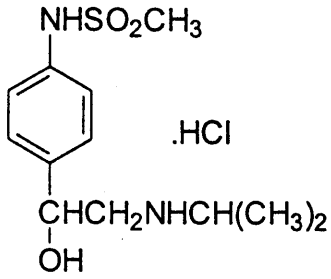
DMF —

13. DOSAGE FORM
Tablets

14. POTENCIES: 80 mg, 120 mg, 160 mg and 240 mg

15: CHEMICAL NAME AND STRUCTURE:

$C_{12}H_{20}N_2O_3S.HCl$; M.W.=308.8



SOTALOL HYDROCHLORIDE

4'-[1-Hydroxy-2- isopropylamino)ethyl]methanesulfonanilide monohydrochloride. CAS [959-24-0]

16. RECORDS AND REPORTS: N/A

17. COMMENTS

18. CONCLUSIONS AND RECOMMENDATIONS

This ANDA can be approved based on acceptable ~~EER~~, MV ~~and labeling~~.

EER ac. 10/9/2000

19. REVIEWER: DATE COMPLETED:
Sema Basaran, Ph.D. October 1, 2000

Redacted 29

pages of trade secret and/or confidential commercial information

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-663

BIOEQUIVALENCE REVIEW

Sotalol Tablets
80, 120, 160 and 240 mg
ANDA 75-663
Reviewer: Nhan L. Tran
v:\new\firmsam\Impax\ltrs&rev\75663sdw.699

Impax Pharmaceuticals, Inc.
Huntwood Avenue, Hayward, CA.
Submission Dated:
June 30, 1999
September 14, 1999
October 8, 1999.

Review of Bioequivalence Studies Dissolution Data and Waiver Requests

Background
Indication: Antiarrhythmic
Type of Submission: Original ANDA
Contents of Submission:
160 mg Sotalol hydrochloride tablets: Bioequivalence studies under fasting and fed conditions and in vivo dissolution data.
80 mg, 120 mg, and 240 mg Sotalol hydrochloride tablets: Dissolution data and waiver request.

RLD: Betapace® tablets, 160 mg (**Jan-May 98 Supl., and Current Edition of the "Orange Book"**), manufactured by Berlex Laboratories.
Noted that the 240 mg tablet strength was listed as a RLD in editions of the Orange Book earlier than the current edition. Since the May 1998 Supplement of the Orange Book, the FDA changed the RLD designation to the 160 mg tablet strength, presumably due to safety concerns associated with dosing healthy normal subjects with 240 mg strength. Accordingly, since the studies were conducted in December 1998, the selection of 160 mg as a RLD is deemed appropriate.

Summary Background Information (from the PDR):

Sotalol hydrochloride has both β adrenoreceptor blocking (Class II) and cardiac action potential duration prolongation (Class III) properties. Betapace® is a racemic mixture of d and l sotalol. It is indicated for the treatment of documented ventricular arrhythmias such as sustained ventricular tachycardia that is life threatening. Although significant β blockade occurs at oral doses as low as 25 mg, Class III effects are seen only at daily doses of 160 mg and above. Pharmacokinetics of d and l enantiomers are identical. After oral administration, bioavailability of Sotalol hydrochloride is 90-100% in healthy subjects with peak plasma concentrations occurring within 2.5 to 4 hours and elimination half life of 12 hours. Food decreases bioavailability of sotalol by 20%. Sotalol is not metabolized, and excretion is predominantly via kidney in the unchanged form.

In-Vivo Bioequivalence Fasting Study----Protocol No.: 9834612

Study Information	
Clinical Facility:	[redacted]
Principal Investigator:	[redacted]
Clinical Study Dates;	Period I: 12/05/98, Period II: 12/12/98
Analytical Director:	[redacted]
Analytical Facility:	[redacted]
Analytical Study Dates:	12/31/98 to 01/22/99

Drug Information		
Treatment ID:	A (Test)	B (Reference)
Product Name:	Sotalol hydrochloride	Betapace®
Manufacturer:	Impax Pharmaceuticals, Inc.	Berlex Laboratories..
Manufacture Date:	11/13/98	N/A
Expiration Date:	10/2000 (tentative)	05/2002
ANDA Batch Size:	[redacted]	N/A
Batch/Lot No.:	R98028-100	W80099
Potency:	[redacted]	[redacted]
Content Uniformity: (mean, %cv, range, n)	98.4 (95.6 – 101) %CV: 1.94%, N=12	97.1 (95.8 – 98.9 0 %CV: 0.99% (N=12)
Strength:	160 mg (1 tablet)	160 mg (1 tablet)
Dosage Form:	Tablet	Tablet

Study Design Information			
Randomized:	Y	Design Type: Single dose, Crossover	Y
No. of sequences:	2	No. of periods:	2
No. of treatments:	2	Washout Period:	1 week
Randomization Scheme:	AB BA	**2,4,5,8,9,11,13,16,17,19,22,23,26,28,29,32** **1,3,6,7,10,12,14,15,18,20,21,24,25,27,30,31**	32 subjects

Treatment Information			
Study Condition	Fasting	IRB approval:	Y
Length of Fasting	10 hrs	Informed consent obtained:	Y
Volume of liquid intake:	240 ml	No. of subjects enrolled:	32
Dose of administration:	160 mg	No. of subjects completing:	30
Sampling Schedule:	Over 48 hrs	0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 30, 36 and 48 hours	19 samples
Samples collected		Stored at –20°C until processing	1
No. of adverse reaction events:	68	Adverse events (in 24 subjects) were the same for the test and reference products, and were mild in intensity. No treatments were required	24 subjects
No. of dropouts:	2	Subj. #10 was dropped prior to Per. 2 due to increased QT. Subj. #30 was dropped prior to Per. 2 due to positive alcohol test.	

Formulation: Table 1.

Study Results

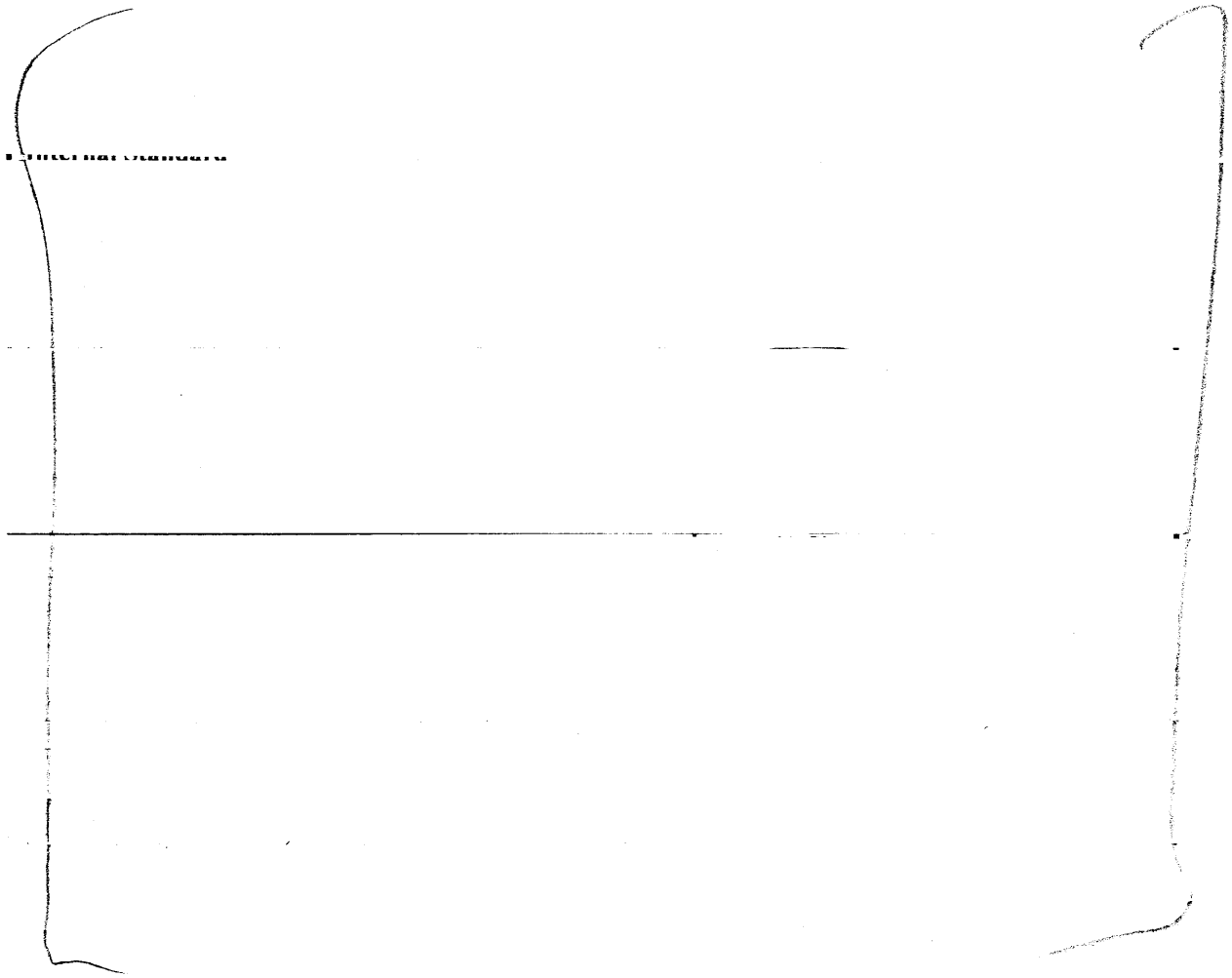
1) Clinical

Adverse Events: Twenty-four subjects reported 68 adverse events, which were distributed about the same between the test and reference products. Symptoms of adverse events were varied such as headache, decreased heart rate, increased QTC interval, 1^{o} AV block, cold, lethargy and lightheadedness. All the events were mild, probably or possibly drug related and were resolved without medical intervention (details in vol. 1.3, Table C3, pg.653).

Protocol Deviations: Minor deviations with respect to recording of vital signs in 1 subject (#12).

Dropouts: 2 subjects before period II due to a) positive alcohol screen (#30), or b) due to increased QT intervals (#10).

2) Analytical



Conclusion: Analytical method is acceptable.

3) Pharmacokinetic

Mean Plasma concentrations: Table 2 and Figure 1
Pharmacokinetic Parameters: Table 3
90% Confidence Intervals: Table 3

Comments:

1) The 90% confidence intervals re-calculated by the reviewer are in good agreement with the values determined by the firm. There were no statistically significant period, sequence or group effects for any of these parameters.

2) The 90% confidence intervals for ln-transformed AUCT, AUCi and Cmax ratios are within acceptable limits of 80-125%.

Conclusion: The fasting single dose bioequivalence study is acceptable.

Protocol No: 9834613, *In-Vivo* Food Effects Bioequivalence Study

Study Information	
Clinical Facility:	
Principal Investigator:	
Clinical Study Dates:	**Period I: 2/13/99, Period II: 2/27/99, Period III: 3/13/99**
Analytical Director:	
Analytical Facility:	
Analytical Study Dates:	03/23/99 to 4/19/99

Drug Information		
Treatment ID:	A (Test)	B (Reference)
Product Name:	Sotalol hydrochloride	Betapace®
Manufacturer:	Impax Pharmaceuticals, Inc.	Berlex Laboratories..
Manufacture Date:	11/13/98	N/A
Expiration Date:	10/2000 (tentative)	05/2002
ANDA Batch Size:		N/A
Batch/Lot No.:	R98028-100	W80099
Potency:		
Content Uniformity: (mean, %CV, range, n)	98.4 (95.6 – 101) %CV: 1.94%, N=12	97.1 (95.8 – 98.9 0 %CV: 0.99% (N=12)
Strength:	160 mg (1 tablet)	160 mg (1 tablet)
Dosage Form:	Tablet	Tablet

Study Design Information			
Randomized:	Y	Single dose, 3-way Crossover	Y
No. of sequences:	6	No. of periods:	3
No. of treatments:	3	Washout Period:	1 week
Randomization Scheme: **Treatments were:** **A: TEST, FED** **B: TEST, FAST** **C: REFERENCE, FED**	ABC BAC CAB ACB BCA CBA	2, 3, 5, 11, 20 1, 15, 17, 22, 23 10, 12, 16, 26, 27 6, 9, 18, 25, 29 7, 14, 19, 24 4, 8, 13, 21, 30	29 subjects enrolled 21 completed. No subject was assigned to # 28

Treatment Information			
Study Condition	Fasting & fed	IRB approval:	Y
Length of Fasting	10 hrs	Informed consent obtained:	Y
Volume of liquid intake:	240 ml	No. of subjects enrolled:	29
Dose of administration:	160 mg	No. of subjects completing:	21
Sampling Schedule:	Over 48 hrs	0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 30, 36 and 48 hours	19 samples per subject
Samples collected		Stored at –20°C until processing	
No. of adverse reaction events:	85	Adverse events (in 23 subjects) were the same for the test and reference products, and were mild (except Subj. #2) in intensity. No treatments were required.	23 subjects. Adverse event distribution: A (T, fed): 19; B (T, fast): 41; C (Ref., fed): 25
No. of dropouts:	8 subjects.	Subj. #2,4,13, were withdrawn prior to Per. 3, and # 14, 15, 22 were withdrawn prior to Period 1 due to adverse events. Subj. # 23, 29 were withdrawn prior to Per. 1 due to personal reasons.	Subject # 2, 4, 13, 14, 15, 22, 23, and 29

Study Results

1) Clinical

Adverse Events: Twenty-three subjects reported 85 adverse events, which were distributed about the same between the test and reference products. Symptoms of adverse events were varied such as bradycardia, headache, decreased heart rate, increased QTC interval, 1° AV block and lightheadedness. All the events were mild, except 1 subject (Subject #2), probably or possibly drug related and were resolved without medical intervention (details in vol. 1.9, Table C3, pg.2809).

Protocol Deviations: Minor deviations with respect to recording of vital signs in 9 subjects (#2, 5, 13, 21, 24, 25, 26, 27, and 30), 2 subjects were late for checking in (# 4, and 24), and 1 subject was under (#29) and 1 over (#26) 15% weight criteria.

Dropouts: 8 subjects. Subj. # 2, 4, 13, were withdrawn prior to Period 3, and # 14, 15, 22 were withdrawn prior to Period 1 due to adverse events. Subj. # 23, 29 were withdrawn prior to Period 1 due to personal reasons. No subject was assigned to #28.

2) Analytical:

[redacted]

3) Pharmacokinetic:

Mean Plasma concentrations: Table 4 and Figure 2.
Pharmacokinetic Parameters and Means ratios: Table 5.

Comments:

1) The pharmacokinetic parameter ratios re-calculated by the reviewer are in good agreement with the values determined by the firm.

2) The test/reference ratios were within the acceptable range of 0.80-1.25.

3) There were no statistically significant period, sequence or group effects for lnAUCt, lnAUCi or lnCmax parameters.

Conclusion: The single dose post prandial bioequivalence study is acceptable.

Dissolution Data and Waiver Request

Applicant is requesting a waiver of in vivo bioequivalence testing for the 80, 120 and 240 mg dosage strengths. Comparative dissolution profiles were provided for the reference (Berlex's Betapace®) and test (Impax's Sotalol) tablets, 80, 120, 160 and 240 mg strengths. A full list of components in Impax's Sotalol tablets is provided for all the strengths in Table 1 below.

Table 1: Formulation: (Not to be released under FOI).

The composition of the **Sotalol hydrochloride tablets** is as follows:

Ingredient	Amount (mg) Per Dosage Unit Strength			
	80 mg	**120 mg**	**160 mg**	**240 mg**
Sotalol HCl	80.00	120.00	160.00	240.00
Microcrystalline Cellulose, NF	[redacted]			
[redacted]				
Corn Starch NF				
Colloidal Silicon Dioxide, NF				
FD&C Blue #2 Alumunium Lake				
Magnesium Stearate, NF				
Total Tablet Wt.	200	300	400	600

Product Specifications:

Reference Product: **80 mg**: Capsule shaped, light blue, scored tablet, imprinted "80mg" on 1 side and "BETAPACE" on the other side.

Test Product: **80 mg:** Capsule shaped, light blue, scored tablet, imprinted [redacted] on 1 side, and [redacted] on the other side.

Reference Product: **120 mg** Capsule shaped, light blue, scored tablet, imprinted "120mg" on 1 side and "BETAPACE" on the other side.

Test Product: **120 mg** Capsule shaped, light blue, scored tablet, imprinted [redacted] on 1 side, and [redacted] on the other side.

Reference Product: **160 mg** Capsule shaped, light blue, scored tablet, imprinted "160mg" on 1 side and "BETAPACE" on the other side.

Test Product: **160 mg** Capsule shaped, light blue, scored tablet, imprinted [redacted] on 1 side, and [redacted] on the other side.

Reference Product: **240 mg** Capsule shaped, light blue, scored tablet, imprinted "240mg" on 1 side and "BETAPACE" on the other side.

Test Product: **240 mg** Capsule shaped, light blue, scored tablet, imprinted [redacted] on 1 side, and [redacted] on the other side.

IN VITRO DISSOLUTION TESTING

Test Drug: Sotalol Hydrochloride Tablets — Impax Pharmaceuticals Inc.
Reference Drug: Betapace® tablets — Berlex Laboratories.

I. Conditions for Dissolution Testing:

Apparatus: Paddle Method — Speed: 50 RPM — Medium: Water
Volume: 900mL — No. Units Tested: 12 — Assay Method: [redacted]
Tolerances: Firm proposed: NLT [redacted] in 45 minutes
FDA Recommendation: NLT [redacted], in 30 minutes.

II. Results of *In Vitro* Dissolution Testing:

80 mg strength

Sampling Times (min)	Test Product Lot No.: R99009			Reference Product Lot No.: W70245		
	Mean %	Range	% CV	Mean %	Range	% CV
10	48.4	[redacted]	9.9	61.3	[redacted]	6.87
20	78.7	[redacted]	5.56	93.3	[redacted]	1.44
30	89.0	[redacted]	3.59	95.1	[redacted]	0.88

F2 = 42.7

120 mg strength

Sampling Times (min)	Test Product Lot No.: R98031			Reference Product Lot No.: W50123		
	Mean %	Range	% CV	Mean %	Range	% CV
10	53.5	[redacted]	12.1	48.1	[redacted]	15.9
20	87.0	[redacted]	6.07	89.9	[redacted]	3.35
30	91.0	[redacted]	3.75	94.2	[redacted]	1.59

F2 = 73.6

160 mg strength

Sampling Times (min)	Test Product Lot No.: R98028			Reference Product Lot No.: W80099		
	Mean %	Range	% CV	Mean %	Range	% CV
10	59.5	[redacted]	9.99	51.8	[redacted]	15.5
20	85.9	[redacted]	5.47	92.0	[redacted]	3.48
30	89.9	[redacted]	3.64	94.7	[redacted]	1.92

F2 = 57.1

240 mg strength

Sampling Times (min)	Test Product Lot No.: R99010			Reference Product Lot No.: W70141		
	Mean %	Range	% CV	Mean %	Range	% CV
10	40.6	[redacted]	12.9	47.2	[redacted]	11.3
20	74.3	[redacted]	5.43	86.3	[redacted]	3.41
30	85.1	[redacted]	1.37	91.4	[redacted]	2.24

F2 = 49.4

Comments:

1) The formulations of Sotalol hydrochloride, 80, 120, 160 and 240 mg tablets by Impax Pharmaceuticals, Inc. are exactly proportional with respect to active and all inactive ingredients. The total tablet weight is proportional with respect to 80, 120, 160 and 240 mg strengths.

2) Dissolution testing was carried out in water (900 mL) using USP 23 paddle apparatus at 50 RPM, as recommended by FDA/OGD/Div. of Bioequivalence.

Recommendations:

1) The bioequivalence fasting and nonfasting studies, conducted by Impax Pharmaceuticals Inc., on its Sotalol Hydrochloride tablets, 160 mg, Lot # Lot No. R98028, comparing it to Betapace® 160 mg tablets manufactured by Berlex Laboratories, Lot # W80099 have been found acceptable by the Division of Bioequivalence. The studies demonstrate that Impax's Sotalol Hydrochloride tablets, 160 mg strength, are bioequivalent to Berlex's Betapace® tablets, 160 mg strength.

2) In vitro dissolution testing conducted by Impax pharmaceuticals Inc., on its Sotalol Hydrochloride tablets, 80, 120, 160 and 240 mg is acceptable.
The dissolution testing should be incorporated into the firm's manufacturing controls and stability programs. Dissolution testing should be conducted in 900 mL of water at 37°C using USP 23 apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications:

Not less than — (Q) of the labeled amount of the drug in the dosage form is dissolved in 30 min.

3) The formulations for the 80, 120 and 240 mg strengths are proportional to the 160 mg strength, which underwent bioequivalence testing. Waiver of in vivo bioequivalence testing requirements for the 80, 120 and 240 mg strengths is granted. Impax's Sotalol Hydrochloride tablets, 80, 120, and 240 mg, manufactured by Impax Pharmaceuticals Inc., are bioequivalent to Betapace® tablets, 80, 120, and 240 mg, manufactured by Berlex Laboratories.

/S/ 10/19/99
Nhan L. Tran, Ph.D.
Review Branch II
Division of Bioequivalence

/S/ 10/19/1999
RD INITIALED SNERURKAR
FT INITIALED SNERURKAR

Concur: /S/ Date 11/2/99
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

cc: ANDA# 75-663 (original, duplicate), HFD-655 (Tran, Nerurkar), Drug File, Division File

Table 2

Mean Plasma Concentrations of Sotalol following an oral dose of 160 mg, under fasting conditions

Time (hours)	Mean N= 30 (%CV) Plasma Concentrations (ng/ml)				Ratio
	Treatment A (test)		Treatment B (Ref.)		A/B
0	0.00	-------	0.00	-------	0.00
0.5	255.09	69.91%	221.34	87.19%	1.15
1	645.47	55.79	577.00	51.93	1.01
1.5	779.13	41.49	801.93	43.13	0.97
2	939.00	38.71	933.43	39.30	1.00
2.5	1110.97	33.72	1021.90	33.95	1.00
3	1129.50	30.74	1917.83	31.03	1.09
3.5	1125.40	29.09	1025.27	31.64	1.09
4	1091.37	28.80	958.73	28.76	1.13
5	939.67	25.19	882.20	27.02	1.06
6	836.70	23.19	764.27	27.01	1.09
8	677.03	21.19	626.87	21.71	1.08
10	586.53	19.96	537.87	24.18	1.09
12	480.40	20.73	442.50	21.23	1.08
16	340.27	19.59	320.87	22.39	1.06
24	198.30	21.11	192.00	23.07	1.03
30	128.50	26.29	126.68	25.84	1.01
36	81.41	28.78	83.44	29.78	0.97
48	35.53	44.56	38.98	44.81	0.91

Table 3

Pharmacokinetic Parameters

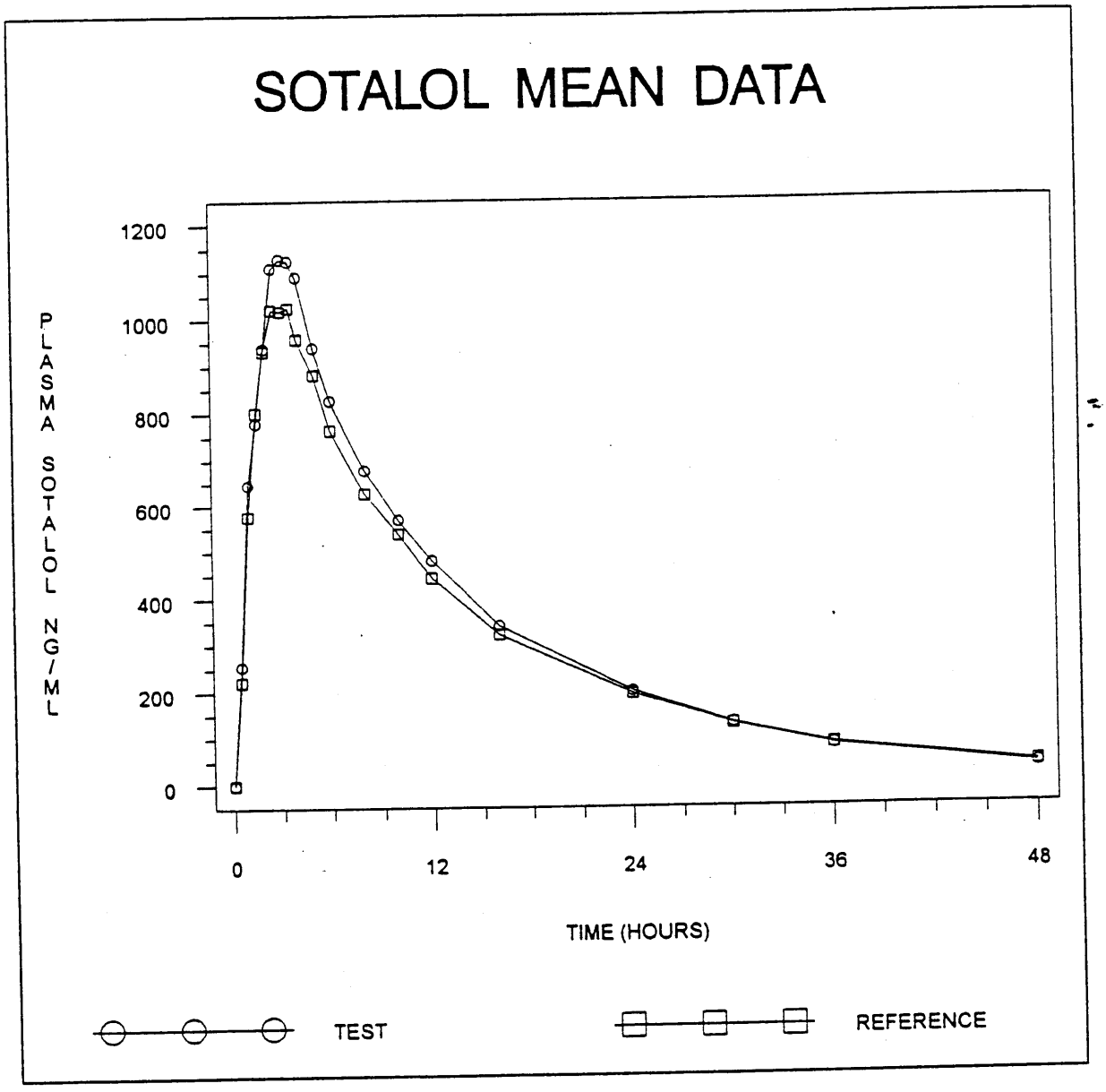
Parameter	Cmax (ng/ml)		AUCt (ng/ml-hours)		AUCi (ng/ml-hours)	
Treatment	A (Test)	B (Ref.)	A (Test)	B (Ref.)	A (Test)	B (Ref.)
MEAN	1347.73	1202.27	15064.06	14217.57	15613.78	14852.88
CV%	27.13	27.84	18.66	21.64	18.27	21.20
N	30	30	30	30	30	30

Parameter	T1/2 (hours)		Tmax (hours)		Kel (1/hours)	
Treatment	A (Test)	B (Ref.)	A (Test)	B (Ref.)	A (Test)	B (Ref.)
MEAN	9.73	10.34	2.83	3.02	0.074	0.07
CV%	19.51	20.52	29.43	37.82	20.34	20.12
N	30	30	30	30	30	30

Parameter	90% C.I.
ln AUCt (ng·hr/mL)	101 – 113
ln AUCi (ng·hr/mL)	100 – 112
LnCmax (ng·hr/mL)	102 – 121

SOTALOL HC1 160 MG TABLET FASTING STUDY
IMPAX 9834612

Linear Plot of Mean Plasma Sotalol Concentrations *vs* Time



SOTALOL HC1 160 MG TABLET FASTING STUDY
IMPAX 9834612

Semi-logarithmic Plot of Mean Plasma Sotalol Concentrations *vs* Time

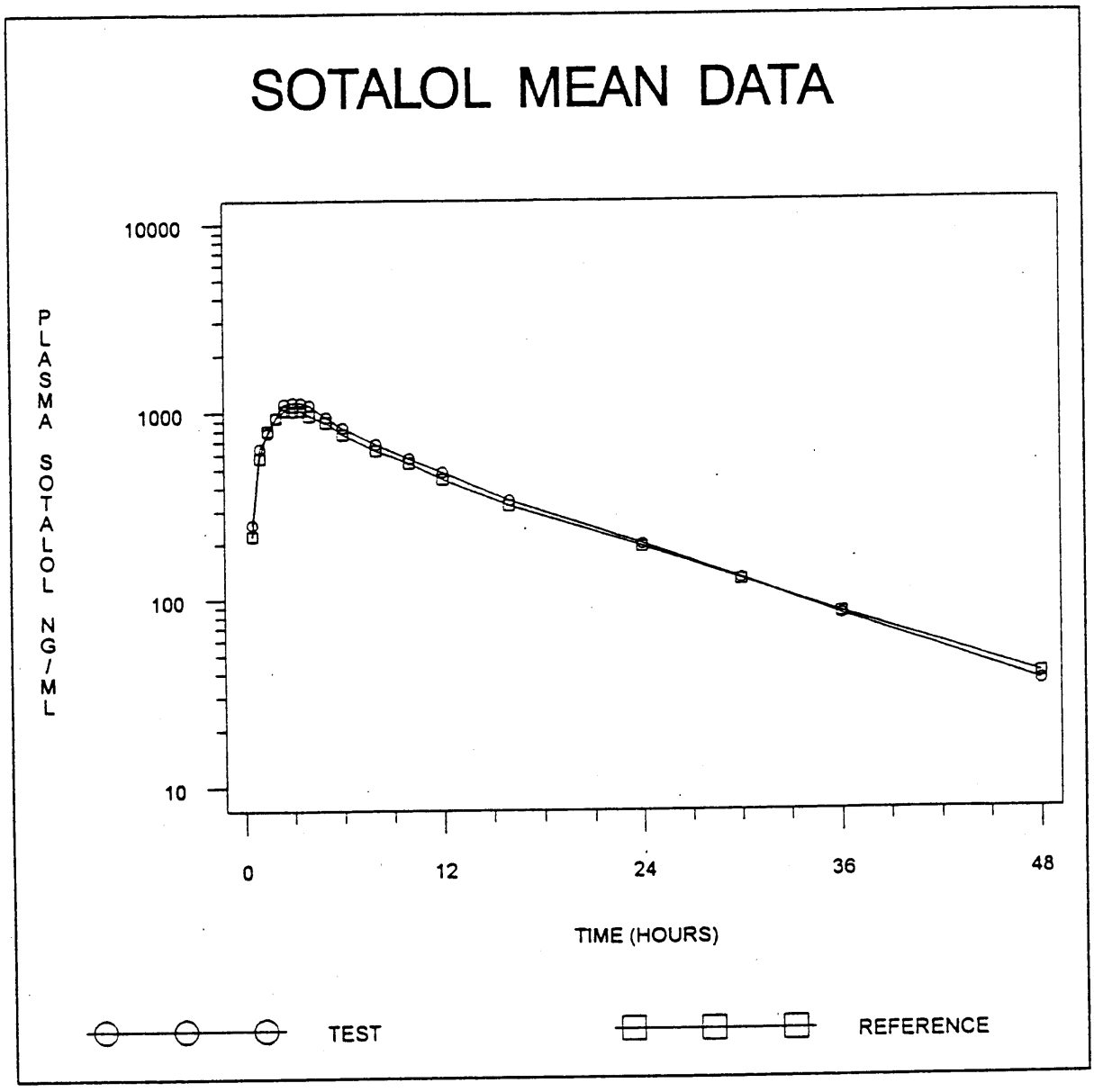


Table 4

Mean Plasma Concentrations after an oral dose of 160 mg Sotalol under fasting/fed conditions

Time (hours)	Mean (N=21) Plasma Concentration (ng/ml), and %CV.							
	Trt A (Test, fed)		Trt B (Test fast)		Trt C (Ref. Fed)		A/C	A/B
0	0		0		0			
1	658.88	61.75	670.11	61.25	591.93	49.89	1.11	0.98
1.5	1007.83	47.75	924.37	57.53	996.29	36.16	1.01	1.09
2	1079.71	35.76	1053.03	48.77	1141.33	31.27	0.95	1.02
2.5	1144.62	27.53	1204.42	47.18	1175.33	24.67	0.97	0.95
3	1152.52	23.47	1295.58	38.82	1177.95	21.02	0.98	0.89
3.5	1124.09	21.85	1300.78	36.38	1144.57	19.08	0.98	0.86
4	1082.52	21.73	1208.98	34.39	1102.38	20.98	0.98	0.98
4.5	1043.67	22.16	1150.50	32.64	1083.72	22.32	0.96	0.91
5	1019.23	20.50	1109.93	32.69	1031.57	20.95	0.99	0.92
6	896.14	19.78	954.77	33.02	897.62	18.85	1.0	0.94
8	722.05	18.51	770.80	31.29	726.19	18.81	0.99	0.94
10	590.62	16.42	621.54	29.63	583.52	17.56	1.01	0.95
12	500.48	15.57	524.16	30.14	504.57	17.73	0.99	0.95
16	359.76	15.06	359.88	29.10	365.52	17.47	0.98	1.0
24	217.67	17.72	211.56	28.86	219.81	22.32	0.99	1.02
30	149.24	23.97	131.68	31.33	148.29	25.82	1.00	1.13
36	104.52	31.83	84.65	37.14	101.91	32.82	1.02	1.23
48	55.30	49.18	40.30	46.89	53.06	46.64	1.04	1.37

Table 5

Sotalol Pharmacokinetic Parameters

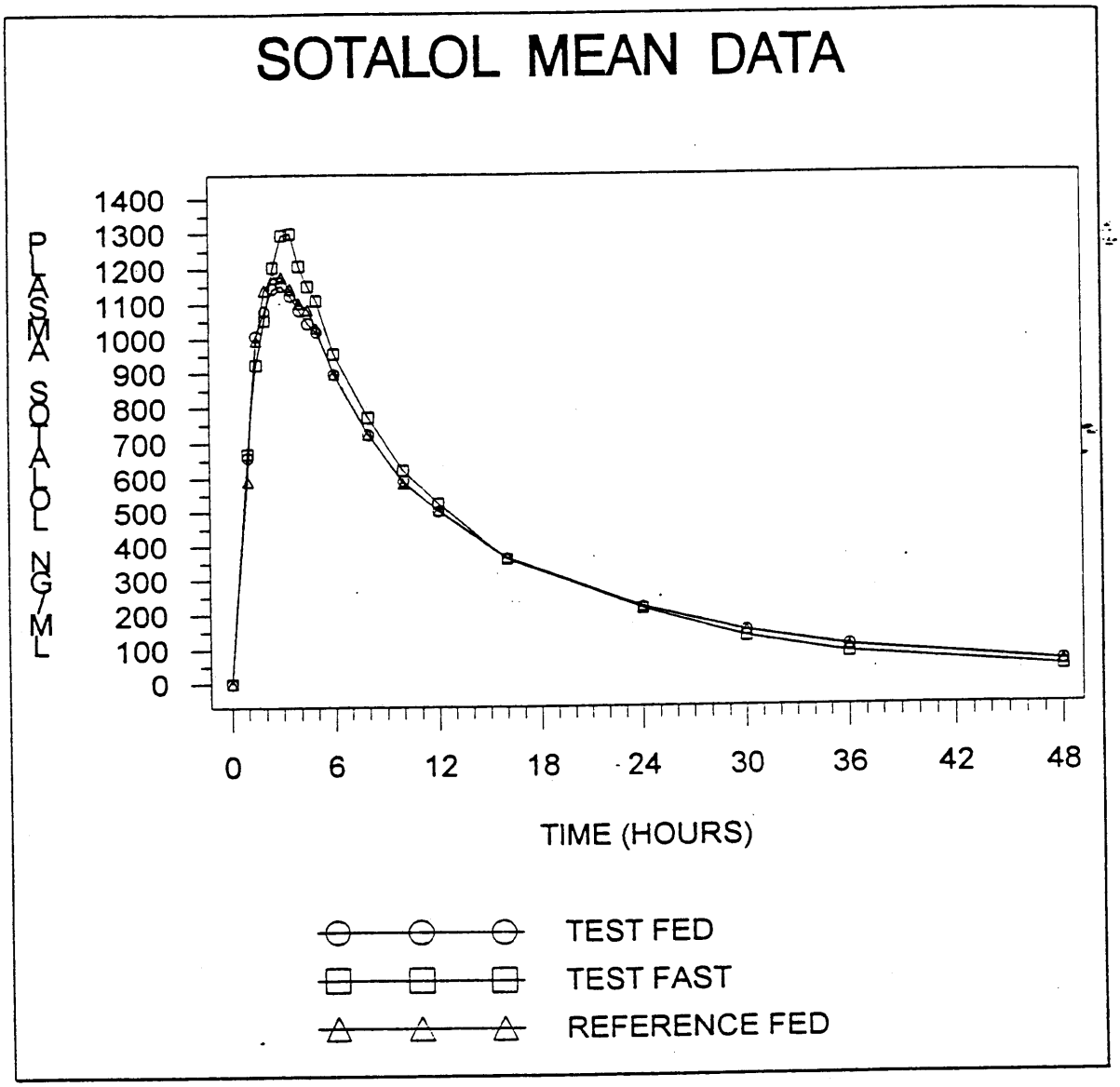
Parameters	Cmax (ng/ml)			AUCt (ng/ml-hours)			AUCi (ng/ml-hours)		
Treatment	A(T,Fed)	B(T,Fast)	C(R,fed)	A	B	C	A	B	C
MEAN	1292	1509.77	1297.76	16398	16601.84	16470.31	17441.83	17248.32	17349.36
CV%	22.51	38.17	19.27	13.92	30.09	15.60	14.04	29.46	16.16

Parameters	T1/2 (hours)			Tmax (hours)			Kel (1/hours)		
Treatment	A	B	C	A	B	C	A	B	C
MEAN	11.54	10.14	11.41	2.62	3.07	2.86	0.063	0.071	0.064
CV%	29.97	21.62	26.56	45.14	29.70	30.38	19.61	16.12	21.94

PK Parameter	LS Mean Ratio
	A (Test, fed)/ C (Ref., fed)
AUCt	0.99
AUCi	1.0
Cmax	0.99

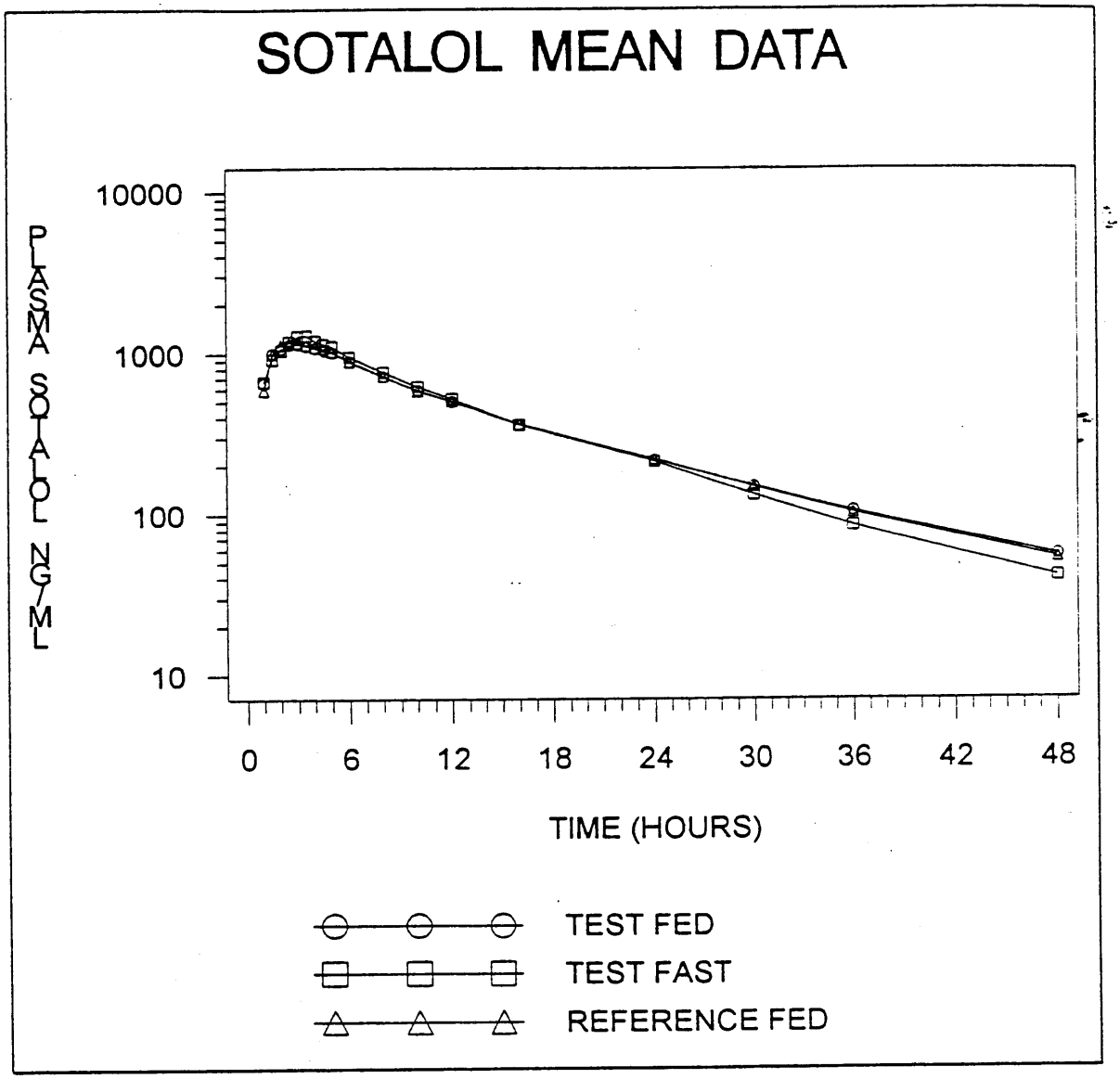
SOTALOL HC1 160 MG TABLET FOOD STUDY
IMPAX 9834613

Linear Plot of Mean Plasma Sotalol Concentrations *vs* Time



SOTALOL HC1 160 MG TABLET FOOD STUDY
IMPAX 9834613

Semi-logarithmic Plot of Mean Plasma Sotalol Concentrations *vs* Time



CC: ANDA # 75-663
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-655/ Reviewer
HFD-655/ Team Leader

V:\NEW\FIRMSAM\IMPAX\LTRS&REV\75663SDW.699.DOC

Endorsements: (Final with Dates)
HFD-655/ TRAN /S/ 10/14/99
HFD-655/ NERURKAR /S/ 10/19/99
HFD-650/ D. Conner /S/ 11/2/99

Bioequivalency- Acceptable

Submission Date: June 30, 1999
Sept. 14, 1999
Oct. 8, 1999

1) Fasting Study (STF)
Clinical: ' ——————
Analytical: ' ——————
Strength: 160 mg
✓ Outcome: AC

2) Food Study (STP)
Clinical: ' ——————
Analytical: ——————
Strength: 160 mg
✓ Outcome: AC

3) Dissolution Waiver (DIW)
✓ Strengths: 80 mg
Outcome: AC

4) Dissolution Waiver (DIW)
✓ Strengths: 120 mg
Outcome: AC

5) Dissolution Waiver (DIW)
✓ Strengths: 240 mg
Outcome: AC

6). Study Amendment (STA)
Strengths: All
✓ Outcome: AC

7). Study Amendment (STA)
Strengths: All
✓ Outcome: AC

Outcome Decisions: AC- Acceptable

Winbio comments:

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA # 75-663 APPLICANT: Impax Pharmaceuticals Inc.
DRUG PRODUCT: Sotalol Hydrochloride,
80,120,160 and 240 mg Capsules

The Division of Bioequivalence has completed its review and has no further questions at this time.
We acknowledge that the following dissolution testing has been incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 900 mL of water at 37°C using USP 23 apparatus 2 (paddle) at 50 rpm. The test product should meet the following dissolution specifications:

Not less than ⌣ (Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

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

Sincerely yours,

/S/

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-663

ADMINISTRATIVE DOCUMENTS

ANDA APPROVAL SUMMARY

ANDA: 75-663 DRUG PRODUCT: Sotalol Hydrochloride

M: IMPAX Laboratories INC. DOSAGE FORM: Tablet

STRENGTH: 80 mg, 120 mg, 160 mg and 240 mg

CGMP STATEMENT/EIR UPDATE STATUS:
CGMP certification is satisfactory (See Page 4866).
EIR update :Acceptable 10/19/00.

BIO STUDY: Satisfactory.
Fasting and food effect bio studies were performed on the 160 mg (lot#970901) tablet. A waiver of *in-vivo* bio study requirements was requested for the 80 mg ,120 and 240 mg tablets.
See the bio.study review by N.TRAN on 10-19-99 and Bioequivalence study is acceptable.

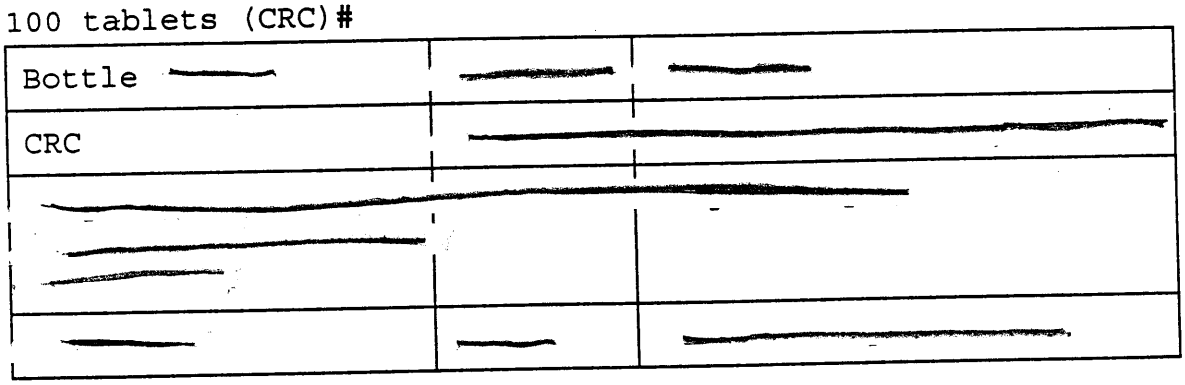
The dissolution testing should be conducted in 900 mL water at 37 degree centigrade using USP 24 apparatus 2 (paddle) at 50 rpm. The test product should meet the following dissolution specifications: NLT —— (Q) of the labeled amount is dissolved in 30 min.

IDATION -(DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):
ding.

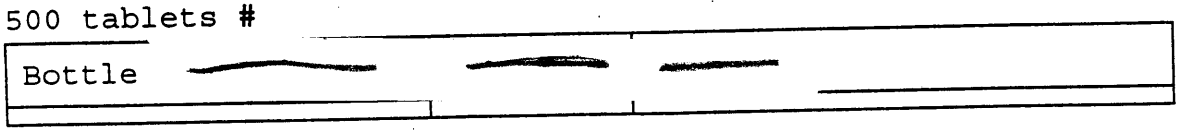
STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?:
Containers used in the stability testing are the same as described in the container section.

Packaging configuration and sizes:

Sotalol Tablets, 80 mg
100 tablets (CRC)#



500 tablets #



Redacted 3

pages of trade secret and/or

confidential

commercial

information

160 mg tablet: Lot # R98028; [redacted]

talol Hydrochloride tablets is compared to the listed drug Betapace. waiver of in vivo bioavailability testing for the 80 mg, 120 mg, 160 mg and 240 mg tablets was requested and granted.

Firm's source of NDS OK : Yes [redacted] DMF# [redacted]

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA THE SAME PROCESS?):

Executed batch sizes:
80 mg tablet: Lot # R99009; [redacted] tablets [redacted]
120 mg tablet: Lot # R98031; [redacted] tablets [redacted]
160 mg tablet: Lot # R98028; [redacted] ablets [redacted]
240 mg tablet: Lot # R-99010; [redacted] tablets [redacted]

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?:

Production batch size for 80 mg tablets: [redacted] tablets [redacted]
Production batch size for 120 mg tablets: [redacted] Tablets [redacted]
Production batch size for 120 mg tablets: [redacted]
Production batch size for 240 mg tablets: [redacted]

ıufacturing process is the same as bio.stability.

/S/

CHEMIST: S. Basaran DATE:10-1-2000

Team Leader: U. Venkataram DATE:10-4-2000

/S/

10/25/2000

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

ANDA Number: 75-663 Date of Submission: **June 30, 1999**

Applicant's Name: **IMPAX Pharmaceuticals, Inc.**

Established Name: **Sotalol Hydrochloride Tablets, 80 mg, 120 mg, 160 mg and 240 mg**

Labeling Deficiencies:

1. GENERAL COMMENT

   Revise your storage temperature recommendation throughout your labels and labeling as follows:

   Store at controlled room temperature 15° to 30°C (59° to 86°F) (see USP).

2. CONTAINER 100s and 1000s

   a. See GENERAL COMMENT above.

   b. We encourage you to differentiate your product strengths by boxing, contrasting colors, or some other means.

   c. Increase the type size of the text on the side panel.

3. INSERT

   a. GENERAL COMMENTS

      i. Use "to" rather than a —— when referring to a range of dosages.

      ii. Delete "————————" throughout the text of the insert except in the TITLE, DESCRIPTION, INDICATIONS AND USAGE (first occurrence), CONTRAINDICATIONS (first occurrence), and HOW SUPPLIED sections and in general whenever a specific dosage is referenced.

   b. TITLE

      We encourage you to add "Rx only" to appear immediately beneath the title of your insert labeling.

c. DESCRIPTION

i. Chemical name - ... [(1-methylethyl) ... (— rather than —)

ii. Structural formula - • HCl

iii. Sotalol hydrochloride tablets contain 80 mg, 120 mg, 160 mg, or 240 mg sotalol hydrochloride. In addition, each tablet contains the ...

iv. We encourage that you alphabetize the listing of inactive ingredients.

d. CLINICAL PHARMACOLOGY

i. Electrophysiology, second paragraph, first sentence - "blockade" rather than "

ii. Hemodynamics, first sentence - ... with a mean ... (add "a")

iii. Clinical Actions, first sentence - "studied" rather than "

iv. Pharmacokinetics - The sixth sentence (Sotalol does not bind ...) begins a new paragraph.

e. INDICATIONS AND USAGE

i. Third paragraph, first sentence - ... response by ... ("by" rather than '

ii. The last sentence begins a new paragraph.

f. WARNINGS

i. First paragraph, last sentence - ... 4 to 90 days ...

ii. Paragraph after the first table, first sentence - ... (females had ... (delete the

iii. Separate the second table as does the reference listed drug.

iv. Thyrotoxicosis, first sentence - "blockade" rather than "

g. PRECAUTIONS

i. Decrease the prominence of the subsection titles "Renal Impairment" and "Drug Interactions".

ii. Drug Interactions

A). First sentence - ... Class III drugs ... (rather than ~~~)

B). Add the following subsection with accompanying text to immediately follow the "Other" subsection:

Antacids: Administration of sotalol within 2 hours of antacids containing aluminum oxide and magnesium hydroxide should be avoided because it may result in a reduction in C_{max} and AUC of 26% and 20%, respectively and consequently in a 25% reduction in the bradycardic effect at rest. Administration of the antacid two hours after sotalol has no effect on the pharmacokinetics or pharmacodynamics of sotalol.

C). Drugs prolonging the QT interval - ... ~~~~~ and astemizole ...

iii. Drug/Laboratory Test Interactions, first sentence - "urine" rather than ~~~

iv. Carcinogenesis, Mutagenesis, Impairment of Fertility - "~~~~~" rather than "Mutagenicity"

v. Delete the ~~~~~ from the subsection titles.

vi. Pregnancy Category B - Revise to read:

Pregnancy: *Teratogenic Effects:* Pregnancy Category B:

vii. Pediatric Use - "~~~~~" rather than "children"

h. ADVERSE REACTIONS

Potential Adverse Effects, first paragraph, last sentence - "pruritus" (spelling)

i. DOSAGE AND ADMINISTRATION

i. Second paragraph, fifth sentence - ... two or three ... (rather than ~~~

ii. Dosage in Renal Impairment - Decrease the prominence of the subsection title.

iii. Transfer to Sotalol

... (see **PRECAUTIONS, Drug Interactions**) ...

j. HOW SUPPLIED

See GENERAL COMMENT (1).

Please revise your container labels and insert labeling, as instructed above, and submit in final print.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes - http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

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

/S/

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-663

CORRESPONDENCE

9/25/00 FAX Amendment routed to (2) CMC, (1) Labeling Reviewer for review. A /S/

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 471-3600 Fax (510) 471-3200

September 18, 2000

FAX AMENDMENT

Gary Buehler
Acting Director, Office of Generic Drugs
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: ANDA 75-663: Sotalol Hydrochloride Tablets, 80 mg, 120 mg, 160 mg, and 240 mg

Attn: Timothy Ames

NDA 075 AMENDMENT FA

Dear Mr. Buehler:

This correspondence responds to minor deficiencies listed in a FAX Amendment, and received by IMPAX Laboratories, Inc. (IMPAX) on August 29, 2000, for the above-referenced ANDA. A copy of your FAX Amendment accompanies this letter.

Each deficiency is reproduced below in bold face type followed by IMPAX's response. In addition to responding to the minor deficiencies, IMPAX acknowledges the following:

1. IMPAX has updated all appropriate ——— specifications to USP 24.
2. IMPAX acknowledges that the suitability of the methods validation is still pending from the FDA District Laboratory.
3. IMPAX acknowledges that an Establishment Evaluation Request is still pending. Please note that the San Francisco District Office has contacted IMPAX and a tentative date of September 25, 2000 set for the Pre-Approval Inspection.

Should you have questions or need any additional information, please contact me by telephone (510-471-3600; ext 305) or by telefax (510-471-3200).

429 5883

Sincerely,
IMPAX Laboratories, Inc.

CENTER FOR DRUG EVALUATION AND RESEARCH RECD SEP 21 2000 OGD

Mark C. Shaw
Director, Regulatory Affairs and Compliance

1 of 4

3/27/00

/S/

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 471-3600 Fax (510) 471-3200

March 20, 2000

MAJOR AMENDMENT

Gary Buehler
Acting Director, Office of Generic Drugs
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MAJOR AMENDMENT Ae

Re: ANDA 75-663: Sotalol Hydrochloride Tablets, 80 mg, 120 mg, 160 mg, and 240 mg

Attn: Timothy Ames

Dear Mr. Buehler:

This letter responds to your January 27, 2000, facsimile, listing deficiencies in the above-referenced ANDA. A copy of your correspondence accompanies this letter.

Each deficiency is listed in boldface type followed by IMPAX's response. As required to complete each response, additional data are provided as attachments in this submission. In addition to responding to the Chemistry and Labeling deficiencies, IMPAX also wishes to add the following information and data in support of this ANDA:

1. IMPAX wishes to add a 500-count package size in addition to the 100- and 1000-count sizes originally submitted. The 500-count bottle size will use the same type of container/closure system used for the 100- and 1000-count sizes. Information supporting this additional packaging size is provided in **Attachment 1**. The Final Printed Labeling has been revised to include this size in the "How Supplied" section.

2. IMPAX is including a revised specification for the _____ used during manufacturing. This specification (code number 5230) replaces the specification originally submitted (code number 1082). The "5230" specification includes references to all the compendial tests currently required in the USP monograph for _____. IMPAX created the "5230" specification in response to a Chemistry comment from another OGD reviewer in connection with a different ANDA currently under review. For consistency, we wish to adopt the "5230" specification for all _____ testing. A copy of the new specification is provided in **Attachment 2**.

3. This submission includes a response to the Labeling deficiencies. As requested, a side-by-side comparison of the labeling changes and twelve (12) copies of the Final Printed Labeling (FPL) are provided. The response to the labeling deficiencies and submission of FPL are provided in a separately jacketed Archival (Blue) binder labeled "Final Printed Labeling". As discussed above, the "How Supplied" section of the labeling has been revised to add a 500-count size. Immediate-container labels for this package size are also provided.

Please note that IMPAX has included FPL that will be used by our marketing division, Global Pharmaceuticals. This FPL incorporates the changes requested by the Division of Labeling and Program Support while reflecting the immediate-container trade dress to be used by Global. On December 14, 1999, IMPAX Pharmaceuticals, Inc. and Global Pharmaceutical Corporation completed a merger. The resulting corporation is now called IMPAX Laboratories, Inc., with Global Pharmaceuticals being a marketing division. Correspondence regarding this name change was submitted to the OGD on January 31, 2000, for this ANDA.

4. In connection with the completion of the merger discussed above, IMPAX has also revised its system for solid oral dosage form (SODF) imprint codes. We are adopting a uniform 4-digit system, in which four numbers are used to represent the product and strength, if applicable. We are also adding the letter "G" to each SODF to designate products marketed by the Global division of IMPAX Laboratories, Inc. We have extended this system to the imprints proposed for the four strengths of sotalol HCl tablets. This submission includes revised copies of any documents that specify the imprint codes. The FPL accompanying this submission also reflects this change.
5. This submission also includes updated long-term stability data for lots R99009, R98031, R98028 and R99010.

Please note that a Field Copy of this submission has been submitted to the San Francisco District Office. A Field Copy certification is provided in Attachment 17.

Should you have any additional questions regarding this response, please contact me by telephone (510-471-3600; ext 305) or by telefax (510-471-3200).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Director, Regulatory Affairs and Compliance

cc: Marshalette Edwards, SFDO

IMPAX
Pharmaceuticals, Inc.
30831 Huntwood Avenue, Hayward, CA 94544
(510) 471-3600 Fax (510) 471-3200

October 8, 1999

TELEPHONE AMENDMENT

Douglas L. Sporn
Director, Office of Generic Drugs
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NDA ORIG AMENDMENT
N/AP

Re: ANDA 75-663
Sotalol Hydrochloride Tablets, 80, 120, 160, 240 mg

Attention: Jennifer Fan, Division of Bioequivalence

Dear Mr. Sporn:

This correspondence provides additional information in support of an Abbreviated New Drug Application (ANDA) for Sotalol HCl. IMPAX Pharmaceuticals, Inc. submitted this ANDA to the Office of Generic Drugs in our correspondence, dated June 30, 1999.

On September 22, 1999, Jennifer Fan of your office contacted IMPAX concerning the need for additional data in support of this application. The request for additional data followed IMPAX's submission of an amendment, dated September 14, 1999, providing additional dissolution data. Ms. Fan requested that IMPAX provide a Certificate of Analysis for the 80-, 120-, and 240-mg strengths of the brand (Betapace®) to augment the full testing provided for the 160-mg strength of the brand. The Certificates of Analysis for the Berlex Reference product (80, 120, and 240 mg) accompany this letter.

This amendment also includes comparative dissolution data for Betapace lot W90067 (80 mg), obtained using conditions requested by the Division of Bioequivalence. The original application and the September 14, 1999 amendment included dissolution profile data for Betapace lot W70245 (80 mg). IMPAX had an insufficient quantity of this lot remaining to complete the full testing requested by the Division of Bioequivalence. Accordingly, IMPAX purchased a new lot of Betapace (W90067).

Should you have any additional questions regarding this ANDA, please contact me by telephone (510-471-3600; ext 305) or by telefax (510-471-3200).

Sincerely,
IMPAX Pharmaceuticals, Inc.

Mark C. Shaw
Director, Regulatory Affairs and Compliance

NDA ORIG AMENDMENT AB

IMPAX
Pharmaceuticals, Inc.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 471-3600 Fax (510) 471-3200

September 14, 1999

TELEPHONE AMENDMENT

Douglas L. Sporn
Director, Office of Generic Drugs
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: ANDA 75-663
Sotalol Hydrochloride Tablets, 80, 120, 160, 240 mg

Attention: Jennifer Fan, Division of Bioequivalence

Dear Mr. Sporn:

This correspondence provides additional information in support of an Abbreviated New Drug Application (ANDA) for Sotalol HCl. IMPAX Pharmaceuticals, Inc. submitted this ANDA to the Office of Generic Drugs in our correspondence, dated June 30, 1999.

On September 3, 1999, Jennifer Fan of your office contacted IMPAX concerning the need for additional data in support of this application. This correspondence provides the following additional data requested by Ms. Fan:

- Certificate of Analysis for the Test and Reference products for all strengths (IMPAX 80, 120, 160 and 240 mg and Berlex 160 mg)
- *In-vitro* dissolution data for all strengths of the Test and Reference product, conducted using USP Apparatus 2 (Paddle) at 50 rpm, in 900 mL water at 37°C. The data summary includes the mean, standard deviation, maximum, minimum, %CV, and f_2 comparison, as requested.

Should you have any additional questions regarding this ANDA, please contact me by telephone (510-471-3600; ext 305) or by telefax (510-471-3200).

Sincerely,
IMPAX Pharmaceuticals, Inc.

Mark C. Shaw
Director, Regulatory Affairs and Compliance

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
SEP 15 1999
OGD

ANDA 75-663

IMPAX Pharmaceuticals, Inc.
Attention: Mark C. Shaw
30831 Huntwood Avenue
Hayward, CA 94544

AUG 3 1999

Dear Sir:

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

Reference is made to the telephone conversation dated July 21, 1999 and your correspondence dated July 26, 1999.

NAME OF DRUG: Sotalol Hydrochloride Tablets, 80 mg, 120 mg, 160 mg and 240 mg

DATE OF APPLICATION: June 30, 1999

DATE (RECEIVED) ACCEPTABLE FOR FILING: July 6, 1999

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

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

Should you have questions concerning this application, contact:

Tim Ames
Project Manager
(301) 827-5849

Sincerely yours,

/S/ per

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

IMPAX
Pharmaceuticals, Inc.
30831 Huntwood Avenue, Hayward, CA 94544
(510) 471-3600 Fax (510) 471-3200

Labeling review
Drafted 8/26/99
/S/

505(b)(2)(a) OK
/S/ 8/2/99
/S/

June 30, 1999

Douglas L. Sporn
Director, Office of Generic Drugs
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: ANDA for Sotalol Hydrochloride Tablets, 80, 120, 160, 240 mg

Dear Mr. Sporn:

In accordance with Section 505 (j) of the Federal Food, Drug and Cosmetic Act, IMPAX Pharmaceuticals, Inc hereby submits an Abbreviated New Drug Application (ANDA) for sotalol hydrochloride tablets, 80, 120, 160, 240 mg. The reference listed drug, Betapace® (sotalol hydrochloride) tablets, 160 mg, is the subject of Berlex Laboratories' approved NDA 19-865. The drug product, which is the subject of this ANDA, differs from the listed product in that the formulation contains different excipients.

This application meets the criteria for an ANDA in that 1) the conditions of use, active ingredient, route of administration, dosage form, and strength are identical to those of the listed drug, 2) bioequivalence has been demonstrated, and 3) patent certification is provided. The labeling complies with all labeling requirements. This application lists IMPAX Pharmaceuticals, Inc. as the manufacturing site for the drug product. The submission contains 15 volumes, organized and jacketed in accordance with FDA-OGD guidelines.

Also included with this ANDA is an electronic submission of the package insert word processor file, prepared in Microsoft Word. Two (2) write-protected diskettes are included in the archival copy of the submission, in a plastic insert. The labeling data contained in the electronic submission is identical to that contained in this hardcopy submission.

Should you have any additional questions regarding this ANDA, please contact me by telephone (510-471-3600; ext 305) or by telefax (510-471-3200).

Sincerely,
IMPAX Pharmaceuticals, Inc.

Mark C. Shaw
Director, Regulatory Affairs and Compliance

CENTER FOR DRUG
REC'D
JUL 06 1999
OGD
EVALUATION AND RESEARCH

IMPAX
Pharmaceuticals, Inc.
30831 Huntwood Avenue, Hayward, CA 94544
(510) 471-3600 Fax (510) 471-3200

July 26, 1999

NEW CORRESPONDENCE

NC

Douglas L. Sporn
Director, Office of Generic Drugs
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Attention: Lt. Greg Davis

Re: ANDA 75-663
Sotalol Hydrochloride Tablets, 80, 120, 160, 240 mg

Dear Mr. Sporn:

This correspondence provides additional information in support of an Abbreviated New Drug Application (ANDA) for Sotalol HCl. IMPAX Pharmaceuticals, Inc. submitted this ANDA to the Office of Generic Drugs in our correspondence, dated June 30, 1999.

On July 21, 1999, Lt. Greg Davis of your office contacted IMPAX concerning the need for additional data in support of this application. This correspondence provides the following additional data requested by Lt. Davis:

- Executed production and packaging batch records for the 80 mg (Lot R99009), 120 mg (Lot R98031), and 240 mg (Lot R99010) tablets. IMPAX had originally included only the records for the 160 mg bio batch (Lot R98028)
- IMPAX test results for the inactive components used in manufacturing the additional tablet strengths (other than the bio batch)
- IMPAX test results for the additional container/closure systems used to package the additional tablet strengths
- USP test results for a _____ - bottle inadvertently omitted from the original ANDA submission

In addition to the information listed above, this correspondence provides an amended analytical method validation report, which has been revised to expand the validated _____ method for the finished product.

Should you have any additional questions regarding this ANDA, please contact me by telephone (510-471-3600; ext 305) or by telefax (510-471-3200).

Sincerely,
IMPAX Pharmaceuticals, Inc.

Mark C. Shaw
Director, Regulatory Affairs and Compliance