CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-725

APPROVAL LETTER

ANDA 75-725

DEC 19 2000

Mylan Pharmaceuticals, Inc.
Attention: Frank R. Sisto
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

Dear Sir:

This is in reference to your abbreviated new drug application dated October 20, 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 December 23, 1999; January 18, July 19 (2 submissions), and October 2, 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 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,

/ Gary Buehler 12/19/00
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-725

APPROVED DRAFT LABELING

MYLAN PHARMACEUTICALS INC.

SOTALOL HCl TABLETS
80 MG, 120 MG, 160 MG and 240 MG

ANDA # 75-725

NDC 0378-0305-01

MYLAN®

SOTALOL HYDROCHLORIDE TABLETS 80 mg

100 TABLETS ℞ only

80 mg

3 0378-0305-01 4

APPROVED DEC 19 2000

NDC 0378-0305-01

MYLAN®

SOTALOL HYDROCHLORIDE TABLETS 80 mg

100 TABLETS ℞ only

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MYLAN®

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100 TABLETS ℞ only

80 mg

3 0378-0305-01 4

APPROVED DEC 19 2000

MYLAN PHARMACEUTICALS INC.

SOTALOL HCl TABLETS
80 MG, 120 MG, 160 MG and 240 MG

ANDA # 75-725

Each tablet contains:
Sotalol hydrochloride 120 mg

N 3 0378-0310-05 6

120 mg

APPROVED DEC 19 2000

NDC 0378-0310-05

MYLAN®

SOTALOL HYDROCHLORIDE TABLETS 120 mg

500 TABLETS

℞ only

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

Keep container tightly closed.

Keep this and all medication out of the reach of children.

STORE AT CONTROLLED ROOM TEMPERATURE 15° TO 30°C (59° TO 86°F) (See USP).

Dosage: See accompanying prescribing information.

This is a bulk container and not intended for dispensing for household use.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

Each tablet contains:
Sotalol hydrochloride 120 mg

N 3 0378-0310-05 6

120 mg

APPROVED DEC 19 2000

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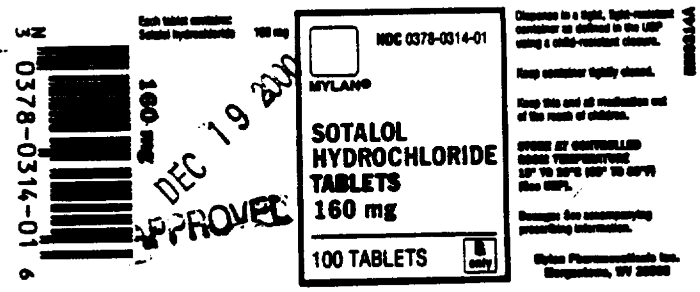
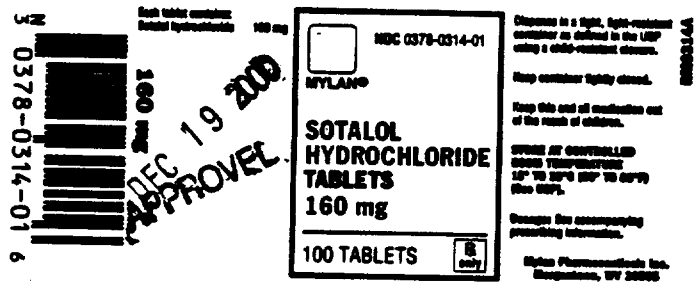
SOTALOL HCl TABLETS
80 MG, 120 MG, 160 MG and 240 MG

ANDA # 75-725





MYLAN PHARMACEUTICALS INC.

SOTALOL HCl TABLETS
80 MG, 120 MG, 160 MG and 240 MG

ANDA # 75-725

Each tablet contains:
Sotalol hydrochloride 160 mg

3 0378-0314-05 4

160 mg

NDC 0378-0314-05

MYLAN®

SOTALOL HYDROCHLORIDE TABLETS 160 mg

500 TABLETS

℞ only

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

Keep container tightly closed.

Keep this and all medication out of the reach of children.

STORE AT CONTROLLED ROOM TEMPERATURE 15° TO 30°C (59° TO 86°F) (See USP).

Dosage: See accompanying prescribing information.

This is a bulk container and not intended for dispensing for household use.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

Each tablet contains:
Sotalol hydrochloride 160 mg

3 0378-0314-05 4

160 mg

NDC 0378-0314-05

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SOTALOL HYDROCHLORIDE TABLETS 160 mg

500 TABLETS

℞ only

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Morgantown, WV 26505

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3 0378-0314-05 4

160 mg

NDC 0378-0314-05

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Morgantown, WV 26505

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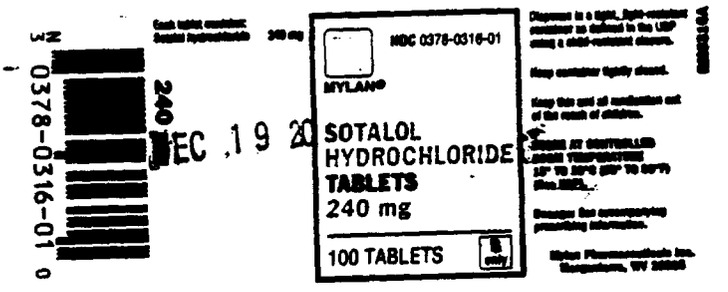
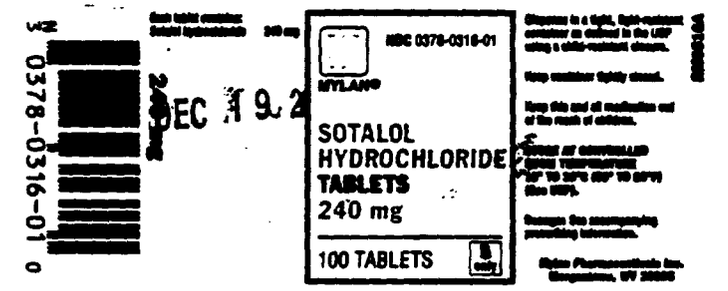
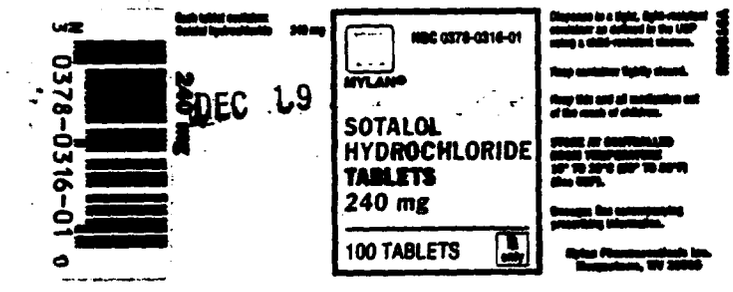
SOTALOL HCl TABLETS
80 MG, 120 MG, 160 MG and 240 MG

ANDA # 75-725



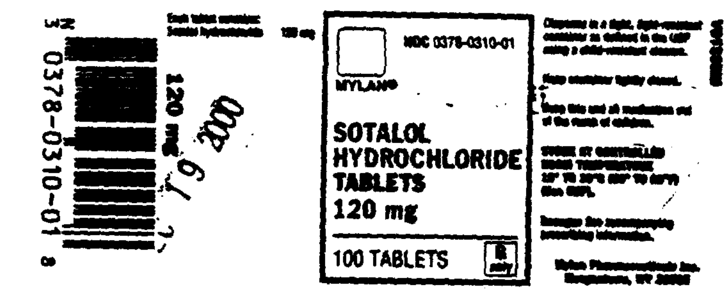


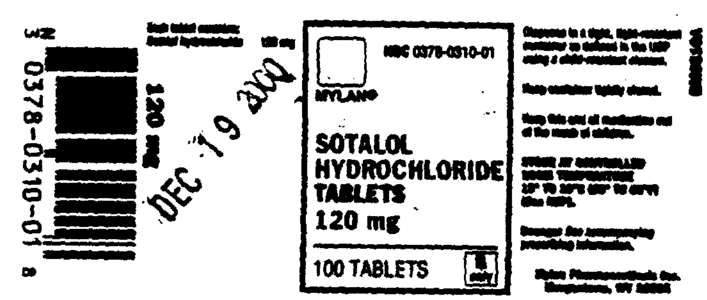


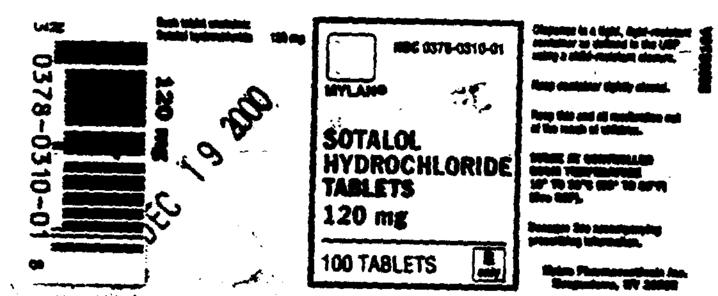
MYLAN PHARMACEUTICALS INC.

SOTALOL HCl TABLETS
80 MG, 120 MG, 160 MG and 240 MG

ANDA # 75-725







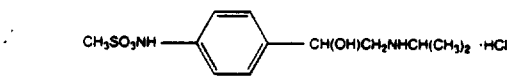
SOTALOL HYDROCHLORIDE TABLETS

80 mg, 120 mg, 160 mg and 240 mg

℞ only

To minimize the risk of induced arrhythmia, patients initiated or 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 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.

DESCRIPTION: Sotalol is an antiarrhythmic drug with Class II (beta- adrenoreceptor blocking) and Class III (cardiac action potential duration prolongation) properties. 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 is 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 and structural formula are as follows:



$C_{12}H_{20}N_2O_3S \cdot HCl$

Sotalol hydrochloride tablets for oral administration contain 80 mg, 120 mg, 160 mg or 240 mg of sotalol hydrochloride. In addition, each tablet contains the following inactive ingredients: anhydrous lactose, colloidal silicon dioxide, FD&C yellow #6 lake, magnesium stearate, microcrystalline cellulose, pregelatinized (corn) starch and sodium lauryl sulfate.

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 hydrochloride 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 of the beta-blocking activity. The beta-blocking effect of sotalol hydrochloride 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-blockade 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 to 100 msec in QT and 10 to 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 8 joules (range 2 to 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 hydrochloride produced a 26% 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 VPCs, paired VPCs and non-sustained ventricular tachycardia (NSVT); the response was dose-related through 640 mg/day with 80 to 85% of patients having at least a 75% reduction of VPCs. Sotalol was also superior, at the doses evaluated, to propranolol (40 to 80 mg TID) and similar to quinidine (200 to 400 mg QID) in reducing VPCs. 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 of 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 were 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, had the lowest two-year mortality (13% vs. 22%), the lowest two-year VT recurrence rate (30% vs. 80%), and the lowest withdrawal rate (38% vs. about 75 to 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 = 1,456), sotalol hydrochloride was given as a non-titrated initial dose
produce a significant increase in survival (7.3% mortalit
(p = 0.3), but overall did not suggest an adverse effect on
gestion of an early (i.e., first 10 days) excess mortality (3%
second small trial (n = 17 randomized to sotalol) where sot
at high doses (e.g., 320 mg twice daily) to high-risk post-
< 40% and either > 10 VPC/hr or VT on Holter), there wer
namic/electrical adverse events within two weeks of initiatr

Pharmacokinetics: In healthy subjects, the oral bioavailabilit
administration, peak plasma concentrations are reached in 2
concentrations are attained within 2 to 3 days (i.e., after 5 to 6
Over the dosage range 160 to 640 mg/day sotalol hydrochlor
respect to plasma concentrations. Distribution occurs to a cen
partment, with a mean elimination half-life of 12 hours. Dosing
ma concentrations which are approximately one-half of those

Sotalol does not bind to plasma proteins and is not metab
subject variability in plasma levels. The pharmacokinetics of
essentially identical. Sotalol crosses the blood brain barrier p
the kidney in the unchanged form, and therefore lower dose
impairment (see DOSAGE AND ADMINISTRATION). Age pe
pharmacokinetics of sotalol, but impaired renal function in p
minal elimination half-life, resulting in increased drug accumu
reduced by approximately 20% compared to fasting when
meal. Since sotalol is not subject to first-pass metabolism, p
no alteration in clearance of sotalol.

INDICATIONS AND USAGE: Oral sotalol hydrochloride is i
mented ventricular arrhythmias, such as sustained ventricu
of the physician are life-threatening. Because of the proarrh
INGS), including a 1.5 to 2% rate of torsade de pointes or ne
or supraventricular arrhythmias, its use in patients with l
patients are symptomatic, is generally not recommended.
matic ventricular premature contractions should be avoided

Initiation of sotalol treatment or increasing doses, as we
to treat life-threatening arrhythmias, should be carried out u
ment should then be evaluated by a suitable method (e.g.,
continuing the patient on chronic therapy. Various approach
response to antiarrhythmic therapy, including sotalol.

In the ESVEM Trial, response by Holter monitoring was ten
of ventricular tachycardia, 90% suppression of non-sustained
and 75% suppression of total VPCs in patients who had at lea
tative response was confirmed if VT lasting 5 or more beats wa
cise testing using a standard Bruce protocol. The PES protoc
stimuli at three pacing cycle lengths and two right ventricula
defined as prevention of induction of the following: 1) monom
non-sustained polymorphic VT containing more than 15 beats
a history of monomorphic VT; 3) polymorphic VT or VF greate
a history of aborted sudden death without monomorphic VT
VT or VF of greater than 15 beats in a patient presenting wit
NSVT producing hypotension during the final treadmill test w

In a multicenter open-label long-term study of sotalol in pa
arrhythmias which had proven refractory to other antiarrhyth
monitoring was defined as in ESVEM. Response by PES was d
VT by at least double extrastimuli delivered at a pacing cycle
and arrhythmia recurrence rates in this study were similar to
was no comparative group to allow a definitive assessment of

Antiarrhythmic drugs have not been shown to enhance
arrhythmias.

Sotalol is also indicated for the maintenance of normal sinu
of atrial fibrillation/atrial flutter (AFIB/AFL)] in patients with
rently in sinus rhythm and is marketed under the brand name
for the AFIB/AFL indication and should not be substituted for
AF is distributed with a patient package insert that is appropr

CONTRAINDICATIONS: Sotalol hydrochloride is contraindic
ma, sinus bradycardia, second and third degree AV block, un
ent, congenital or acquired long QT syndromes, cardiogenic
failure, and previous evidence of hypersensitivity to sotalol.

**WARNINGS: Mortality: The National Heart, Lung, and Blood
pression Trial I (CAST I) was a long-term, multi-center,
asymptomatic, non-life-threatening ventricular arrhythmias
dial infarction. Patients in CAST I were randomized to recei
doses of encainide, flecainide, or moricizine. The Cardiac A
II) was similar, except that the recruited patients had had
before randomization, patients with left ventricular ejection
admitted, and the randomized regimens were limited to pa**

**CAST I was discontinued after an average time-on-treatm
discontinued after an average time-on-treatment of 18 mo
ment, all three active therapies were associated with increa
ty, and encainide and flecainide were associated with signi
tality as well. The longer-term mortality rate associated wi
statistically distinguished from that associated with placebo**

The applicability of these results to other populations (e
infarction) and to other than Class I antiarrhythmic agents is
l effects, and in a large (n = 1,456) controlled trial in patients
who did not necessarily have ventricular arrhythmias, sotal
creased mortality at doses up to 320 mg/day (see Clinical Act
post-infarction study using a non-titrated initial dose of 320
randomized trial in high-risk post-infarction patients treated
have been suggestions of an excess of early sudden deaths

Proarrhythmia: Like other antiarrhythmic agents, sotalol can
lar arrhythmias in some patients, including sustained ventricu
tion, with potentially fatal consequences. Because of its effec
val prolongation), torsade de pointes, a polymorphic ventricu
the QT interval and a shifting electrical axis is the most com
ed with sotalol, occurring in about 4% of high risk (history o
of torsade de pointes progressively increases with prolongati
also by reduction in heart rate and reduction in serum potass

Because of the variable temporal recurrence of arrhythmia
gnosis between a new or aggravated arrhythmic event and the
(Note, however, that torsade de pointes is usually a drug-indu
tially normal QT_C.) Thus, the incidence of drug-related events
that the occurrence rates provided must be considered approx
arrhythmias may often not be identified, particularly if they occ
less frequent monitoring. It is clear from the NIH-sponsored C

SOTA:R2

)E TABLETS
1 240 mg

1 or re-initiated on sotalol should be
se) in a facility that can provide car-
nitoring. Calculations of creatinine
nstructions regarding dose selection
DOSAGE AND ADMINISTRATION.
rhythm [delay in time to recurrence
symptomatic AFIB/AFL who are cur-
name Betapace AF. Sotalol is not
stituted for Betapace AF because only
hat is appropriate for patients with

beta- adrenoreceptor blocking) and
rties. Sotalol hydrochloride is a white,
chiic, soluble in water, propylene gly-
mically, sotalol hydrochloride is d,l-N-
sulfonamide monohydrochloride. The

$CH_2NHCH(CH_3)_2 \cdot HCl$

80 mg, 120 mg, 160 mg or 240 mg
following inactive ingredients: anhy-
magnesium stearate, microcrystalline
ite
has both beta-adrenoreceptor block-
tial duration prolongation (Vaughan
nolide is a racemic mixture of d- and
ffects, while the l-isomer is responsi-
king effect of sotalol hydrochloride is
maximal at doses between 320 and
ane stabilizing activity. Although sig-
significant Class III effects are seen

cardiac action potential in the isolated
lar or atrial muscle (Class III activity).
nduction and increases the refractory
e
ffects of sotalol are manifested by in-
V nodal conduction and increased AV
's in man include prolongation of the
ctive refractory period prolongation of
ory pathways (where present) in both
160 to 640 mg/day, the surface ECG
nd 10 to 40 msec in QT_C. (See WARN-
de pointes type arrhythmias.) No sig-

ators treated concurrently with sotalol,
15 joules) compared to a mean of 16
eiving amiodarone.
on measured invasively in 12 patients
nycardia (9 sustained and 3 non-sus-
rochloride produced a 28% reduction
rs post dosing at steady-state. Con-
showed non-significant increases of
ressure increased significantly from
the study. One patient was discontin-
erial pressure, mean pulmonary artery
Exercise and isoproterenol induced
rance increases by a small amount.
ons in both systolic and diastolic
nodynamically, caution should be
terioration in cardiac performance

ess severe arrhythmias. In patients
is significantly superior to placebo
nycardia (NSVT); the response was
aving at least a 75% reduction of
anolol (40 to 80 mg TID) and sim-
ts with life-threatening arrhythmias
was studied acutely (by suppression
by suppression of Holter monitor evi-

rocainamide given intravenously (total
mide over 90 minutes), sotalol sup-
namide ($p = 0.2$).
ersus Electrocardiographic Monitoring
y PES suppression vs. Holter monitor
in patients with a history of sustained
ely and chronically of sotalol was com-
ne, propafenone, imipramine and pr-
was 39% for sotalol and 30% for the
ized using suppression of PES induc-
gs. Using the Holter monitoring end-
on of NSVT, 80% suppression of VPC
41% response vs. 45% for the other
erapy identified acutely as effective (by
other drugs, had the lowest two-year
e rate (30% vs. 60%), and the lowest
only used doses of sotalol hydrochlo-
ith 16% receiving 240 mg/day or less

ontrolled comparison of sotalol vs. no
efibrillators) whether sotalol response
od prognosis.
ntion (post-infarction) trial ($n = 1,456$),
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 hydrochloride 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 is 90 to 100%. After oral administration, peak plasma concentrations are reached in 2.5 to 4 hours, and steady-state plasma concentrations are attained within 2 to 3 days (i.e., after 5 to 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 judgment 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 to antiarrhythmic therapy, including sotalol.

In the ESVEM Trial, response by 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 had proven refractory to other antiarrhythmic medications, response by Holter monitoring was defined as in ESVEM. Response by PES was defined as non-inducibility 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 hydrochloride 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 patient's 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 is 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 torsade 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 Torsade 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 proarrhythmias (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 8.1% 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.

...ed with the beta-blocking activity of sotalol.

Abrupt Withdrawal: In patients with ischemic heart disease, abrupt withdrawal of beta-blocker therapy has been observed in patients withdrawn from beta-blocker therapy. Cases of increased frequency or severity 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 alternate 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 DISEASES 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 β_2 receptors may be minimized.

Anaphylaxis: While taking beta-blockers, patients with a history of anaphylactic reaction to a variety of allergens may have a more severe reaction on repeated challenge, either accidental, diagnostic or therapeutic. Such patients may be unresponsive to the usual doses 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 the 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 fluorimetric 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. Chromatogr. 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/m2) or in mice, during a 24-month study at 4141 to 7122 mg/kg/day (approximately 450 to 750 times the MRHD as mg/kg or 36 to 63 times the MRHD as mg/m2).

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/m2) 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 hydrochloride (160 mg/kg/day) at 16 times the MRHD as mg/kg (6 times the MRHD as mg/m2) 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 hydrochloride, 100 times the MRHD (18 times the MRHD as mg/m2), 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.

...ere are no adequate and well-controlled studies in pregnant women. Sotalol has been ...n 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 nursing or 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	160 mg (n=832)	240 mg (n=263)	320 mg (n=835)	480 mg (n=459)	640 mg (n=324)	Any Dose* (n=1292)	% Patients 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	8	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 problem	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 to16 grams) of sotalol hydrochloride 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 occur-

...ence of hypotension follow... phase, half-life of 30 hours)... hypotension. In addition, the...

Bradycardia or Cardiac Asys...

Heart Block:

Hypotension:

Bronchospasm:

Torsade de pointes:

DOSAGE AND ADMINISTRAT...

...and doses increased in a hos... (INDICATIONS AND USAGE)... ment (see INDICATIONS AND... patient on the basis of therape... at initiation of therapy, but als...

Dosage of sotalol should b... order to attain steady-state pl... dose adjustment will help prev... arrhythmia. The recommende... essary, after appropriate eval... patients, a therapeutic respon... or three divided doses. Some... require doses as high as 480 t... the potential benefit outweigh... Because of the long terminal ... usually not necessary.

Dosage in Renal Impairment: ...elimination half-life is prolonge... divided doses) of sotalol shou... according to the following tabl...

Creatinine Clearance mL/min	
> 60	
30-59	
10-29	
< 10	

*The initial dose of 80 mg and ... lowing paragraph for dosage ...

Since the terminal eliminatio... longer duration of dosing is re... should be done after administra...

Extreme caution should be e... ing hemodialysis. The half-life ... however, can be partly removed ... dialysis is completed. Both safet... closely monitored.

Transfer to Sotalol: Before sta... withdrawn under careful monito... cal condition permits (see PREC... patients receiving I.V. lidocaine ... not be initiated until the QT inter...

Transfer to Betapace AF from ... currently receiving sotalol for t... Betapace AF because of the s... Betapace AF dosing administrati...

HOW SUPPLIED: Sotalol hydroc... 240 mg of sotalol hydrochloride.

The 80 mg tablet is a light ora... **305** below the score on one side ... lows:

The 120 mg tablet is a light o... score and **310** below the score ... available as follows:

The 160 mg tablet is a light o... score and **314** below the score ... available as follows:

The 240 mg tablet is a light o... score and **316** below the score ... available as follows:

STORE AT CONTROLLED ROOM...

Dispense in a tight, light-resis... sure.

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 nursing or 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	160 mg (n=832)	240 mg (n=283)	320 mg (n=835)	480 mg (n=459)	640 mg (n=324)	Any Dose* (n=1292)	% Patients 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	18	2
chest pain	4	3	10	10	14	18	< 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 problem	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 to16 grams) of sotalol hydrochloride 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/min) 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 escalations in renal impairment should be done after administration of at least 5 to 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 to 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 tablets are available containing 80 mg, 120 mg, 160 mg and 240 mg of sotalol hydrochloride.

The 80 mg tablet is a light orange, round, biconvex tablet debossed with M above the score and 306 below the score on one side of the tablet and blank on the other side. They are available as follows:

NDC 0378-0305-01
bottles of 100 tablets
NDC 0378-0305-05
bottles of 500 tablets

The 120 mg tablet is a light orange, round, biconvex tablet debossed with M above the score and 310 below the score on one side of the tablet and blank on the other side. They are available as follows:

NDC 0378-0310-01
bottles of 100 tablets
NDC 0378-0310-05
bottles of 500 tablets

The 160 mg tablet is a light orange, round, biconvex tablet debossed with M above the score and 314 below the score on one side of the tablet and blank on the other side. They are available as follows:

NDC 0378-0314-01
bottles of 100 tablets
NDC 0378-0314-05
bottles of 500 tablets

The 240 mg tablet is a light orange, round, biconvex tablet debossed with M above the score and 318 below the score on one side of the tablet and blank on the other side. They are available as follows:

NDC 0378-0318-01
bottles of 100 tablets
NDC 0378-0318-05
bottles of 500 tablets

STORE AT CONTROLLED ROOM TEMPERATURE 15° TO 30°C (59° TO 86°F) (See USP).

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

MYLAN®

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

REVISED SEPTEMBER 2000
SOTA:R2

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-725

CHEMISTRY REVIEW(S)

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Abbreviated New Drug Application Review

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1. **CHEMISTRY REVIEW NO.** 2

2. **ANDA #** 75-725

3. **NAME AND ADDRESS OF APPLICANT**
Mylan Pharmaceuticals Inc.
Attention: Frank R. Sisto
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

4. **LEGAL BASIS FOR SUBMISSION**
Innovator Product: Betapace®
Innovator Company: Berlex Laboratories
Exclusivity Expiration: 10/30/99

On pages 8 - 16 the applicant includes the Patent Certification and Exclusivity Statements.

5. **SUPPLEMENT(s)**
N/A

6. **PROPRIETARY NAME**
N/A

7. **NONPROPRIETARY NAME**
Sotalol Hydrochloride

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

9. **AMENDMENTS AND OTHER DATES:**
Firm:
10/20/99 - Original submission
12/23/99 - Bio Amendment
01/18/00 - Bio Amendment
07/19/00 - Major Amendment
10/02/00 - Labeling Amendment

FDA:
11/30/99 - Acceptance for filing

05/12/00 - Deficiency letter

10. **PHARMACOLOGICAL CATEGORY**
Anti-arrhythmic

11. **Rx or OTC**
Rx

12. **RELATED IND/NDA/DMF(s)**
See review element #37

13. **DOSAGE FORM**
Tablets/oral

14. **POTENCIES**
80 mg, 120 mg, 160 mg & 240 mg

15. **CHEMICAL NAME AND STRUCTURE**
Chemical name:
Methanesulfonamide, *N*-[4-[1-hydroxy-2-[(1-methylethyl)amino]ethyl]phenyl]-, monohydrochloride

Chemical Formula	Molecular Weight	Cas Number
$C_{12}H_{20}N_2O_3S \cdot HCl$	308.82	959-24-0

16. **RECORDS AND REPORTS**

17. **COMMENTS**
CMC: Satisfactory
Labeling: Satisfactory per A. Vezza on 10/26/00
Bio: Satisfactory per P. Sathe on 2/11/00
EER: Acceptable on 4/26/00
MV: Need MV since non-U.S.P. drug substance and drug product.

18. **CONCLUSIONS AND RECOMMENDATIONS**
This application may be approved.

19. **REVIEWER:** Bita Mirzai-Azarm
DATE COMPLETED: 11/28/00

Page(s) 30

Contain Trade Secret, Commercial/Confidential Information and are not releasable.

chem Rev. 2.

11/28/00

MAY 12 2006

38. **Chemistry Comments to be Provided to the Applicant**

ANDA: 75-725 APPLICANT: Mylan Pharmaceuticals Inc.

DRUG PRODUCT: Sotalol Hydrochloride Tablets 80 mg, 120 mg, 160 mg and 240 mg.

The deficiencies presented below represent MAJOR deficiencies.

A. Chemistry Deficiencies:

1. Your description of the container/closure systems indicated that the closure innerseal is a Safe-Gard Your USP <671> was performed using PS-22 (pages 4058, 4074, 4090, 4105 & 4114). Please clarify.

2. According to your description of the container/closure systems, the closure for the 250cc HDPE bottle is a 45mm fine-ribbed beige plastic. Your USP <671> was performed using 45mm beige metal closure (page 4105). Please clarify.

3. According to your description of the container/closure systems, the closure for the 18oz HDPE bottle is a 53mm beige plastic. Your USP <671> was performed using 53mm beige metal closure (page 4114). Please clarify.

4. Please set a target for tablet hardness and tablet thickness specifications.

5. The Division of Bioequivalence has set the following specs for the dissolution testing which is conducted in 900 mL of deaerated water, at 37°C using USP Apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:

   Not less than 80%(Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

   Please incorporate the dissolution specifications and testing method recommended by the Division of Bioequivalence into your stability and finished product testing specifications.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-725

BIOEQUIVALENCE

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-725 APPLICANT: Mylan Laboratories

DRUG PRODUCT: Sotalol Hydrochloride Tablet 240 mg, 160 mg, 120 mg and 80 mg.

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

The following dissolution testing will need to be incorporated into your stability and quality control programs:

> The dissolution testing should be conducted in 900 mL of deaerated water, at 37°C using USP Apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:
>
> Not less than of the labeled amount of the drug in the dosage form is dissolved in 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

Sotalol HCl
80 mg, 120 mg, 160 mg, 240 mg Tablets
ANDA 75-725
Reviewer: Pradeep M. Sathe, Ph.D.
File: C\wpfiles\75725sdw.O99

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505
Submission Dates:
October 20, 1999,
December 23, 1999,
January 18, 2000

Review of Two In-Vivo Bioequivalence Studies And Dissolution Data

BACKGROUND:

Sotalol is indicated in the treatment of arrhythmias, such as sustained ventricular tachycardia. Sotalol HCl acts by beta-adrenoreceptor blockade (Vaughan Williams Class II) and cardiac action potential duration prolongation (Vaughan Williams Class III). Sotalol HCl is a racemic mixture of d- and l-isomers. Both isomers have similar Class III antiarrhythmic effects. The l-isomer is however responsible for virtually all of the beta-blocking activity. The beta-blocking effect of sotalol is non-cardioselective. Sotalol HCl is nearly completely absorbed after oral administration and undergoes no first-pass hepatic metabolism. It's bioavailability is 90-100%. Peak plasma concentrations are reached 2-4 hours after an oral dose. The absorption of sotalol HCl is reduced to up to 20% when administered with a standard meal. Concurrent administration of antacids does not appear to alter absorption. Sotalol HCl is not bound to plasma proteins, and its apparent volume of distribution ranges from 1.2-2.4 liters/kg. The primary route of elimination is by renal excretion. Approximately 80-90% of the dose is excreted in the urine unchanged. A small amount is also excreted in the feces, bile or other intestinal secretions. The total body clearance averages 150 mL/min in subjects with normal renal function. The terminal elimination half-life of the drug is 10-20 hours.

CURRENT APPLICATION: The application consists of two bio-equivalence (one fasting and another a 'food challenge') studies on the 160 mg strength, coupled with comparative dissolution data on all strengths. Based on the dissolution and formulation proportionality information, the firm is seeking bio-study waivers for the 80 mg, 120 mg and 240 mg strengths. At present there are other generic Sotalol HCL tablets on the market, implying that this is not a first generic. The Orange Book lists Berlex Lab's 160 mg Betapace^{R} tablet as the reference product for the bio-equivalence assessment.

I. SINGLE DOSE FASTING BIOEQUIVALENCE STUDY #SOTA-9901

A. STUDY INVESTIGATORS AND CONTRACT LABORATORY

The bioequivalence study was conducted at the Georgetown-PAREXEL, 3900 Reservoir Road, Washington, D.C., 20007. The Georgetown-PAREXEL is a joint venture between the Georgetown University and PAREXEL, located at Medical Center of the Georgetown University. The study investigator was Dr. Jean T. Barbey, M.D.

B. INFORMED CONSENT AND IRB APPROVAL

The clinical portion of this study was conducted as per the Institutional Review Board regulations 21 CFR § 56 and Informed Consent regulations 21 CFR § 50.

C. STUDY OBJECTIVE

The objective of this study was to investigate the bioequivalence of Mylan sotalol HCl tablets to Betapace® (Berlex Laboratories) tablets following a single, oral (160 mg) dose under fasting conditions.

D. STUDY DESIGN

This study was designed as a randomized, two-period, two-treatment, two-sequence crossover study to complete 24 healthy male subjects.

E. SUBJECT SELECTION CRITERIA

A sufficient number of healthy, non-smoking, adult, volunteers were enrolled from the general population with the intent to complete 24 subjects. Subjects who failed to complete the study ("Drop-outs") were not replaced.

Non-smoking, adult volunteers ages 18 to 45 were accepted into the clinical phase of the study. Subjects were at least 60 kg and within 10% of their ideal body weight, as referenced by the Table of "Desirable Weights of Adults" by the Metropolitan Life Insurance Company, 1983. All subjects were judged to be normal and healthy during a pre-study medical evaluation (physical examination, laboratory evaluation and 12-lead ECG). The subjects had no history of significant chronic diseases, hepatitis or drug/alcohol abuse. Subjects who were considered ineligible for the study were institutional subjects; had abnormal and clinically significant laboratory test results or ECG tracings; donated more than 450 mL of blood or plasma within 28 days prior to the initial dose of study medication; use of any tobacco products; had any change in dietary or exercise habits throughout the duration of the study; use of any medication within the last 14 days prior to the initial dose of study medication; use of any medication known to alter hepatic enzyme activity within 28 days prior to the initial dose of study medication; history of any significant chronic disease and/or hepatitis; history of drug and/or alcohol abuse; acute illness at the time of either the prestudy medical evaluation or dosing; had consumed vitamins, alcohol, caffeine- or xanthine-containing foods or beverages within 48 hours prior to the initial dose of study medication; allergy or hypersensitivity to sotalol HCl or any other anti-arrhythmic agents; had

received investigational drug within 30 days prior to the initial dose of study medication; history of difficulty in swallowing or gastrointestinal disease which could affect drug absorption.

F. STUDY SCHEDULE

Twenty-three subjects were enrolled and completed the study. Due to the safety issues and precautions required for the dosing Sotalol HCl, the subjects were dosed in three groups: Group A (No. 1-8), Group B (No. 9-16), and Group C (No. 17-23). Subjects were housed on the evening prior to dosing until 48 hours after the blood draw. Following a supervised overnight fast (of at least 10 hours), each subject received a single, oral 160 mg (1 x 160 mg) dose of either a Mylan sotalol HCl or Berlex Betapace® tablet with 240 mL of water at ambient temperature. Subjects received a standardized meal 5 hours post-dose. The evening meal was given 10 hours after dosing and snacks at appropriate times thereafter. Subjects consumed 240 mL of ambient temperature water 1hour before and 1 hour after the dose. Besides these restrictions, water was allowed at all other times. Subjects were monitored throughout the confinement for adverse reactions to the study formulations and/or procedures. Subjects were released after the 48-hour blood draw, but were required to return to the clinic for the 72-hour blood draw. At least a 10-day washout period separated each study phase. Group A, Period 1 was dosed on May 27, 1999 and Period 2 was dosed on June 7, 1999. Group B, Period 1 was dosed on May 31, 1999 and Period 2 was dosed on June 10, 1999. Group C, Period 1 was dosed June 3, 1999 and Period 2 was dosed on June 14, 1999.

Serial blood samples (10 mL) were collected pre-dose and at 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 6.0, 8.0, 12, 16, 24, 36, 48 and 72 hours post-dose. Plasma was stored in suitably labeled tubes at -70^{0}C ± 15^{0}C until analysis. Blood pressure, pulse rate, and ECG (by telemetry) were measured before dosing, at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10, 11, 12, 16, 20, and 24 hours post-dosing. A 12-lead ECG was also measured before dosing and at 3 hours after dosing.

G. DRUG TREATMENTS

Treatment A = (reference)	Berlex Betapace® Tablets 160 mg (1 x 160 mg), Fasting Administration Lot #W80099, Exp. 5/02 Commercial Lot Assay Potency: 99.5%
Treatment B = (test)	Mylan Sotalol HCl Tablets 160 mg (1 X 160 mg), Fasting Administration Lot #2E009N, Exp. TBE Theoretical Lot Size: 160,000 Manufacturing Date: 12/28/1998 Assay Potency: 99.5%

H. ANALYTICAL METHODS

I. CHROMATOGRAMS

Chromatograms of the standard curves, quality control samples and unknown sample assay for Subject #'s 6, 9, 10, 12 and 15 are provided in the Analytical Report of the application.

J. PHARMACOKINETIC AND STATISTICAL ANALYSIS

Single-dose pharmacokinetic parameters for sotalol were calculated using non-compartmental techniques. Actual times were used when blood draw deviations occurred. Otherwise protocol times were used. The maximum concentration (CPEAK) and the time at which it occurred relative to the administered dose (TPEAK) were determined from the observed plasma concentration-time profile over the sampling time interval. The elimination rate constant (KEL) was determined by linear regression of the terminal linear phase of the log plasma concentration-time profile. Area under the plasma concentration-time curve (AUCL) is the sum of the linear trapezoidal estimation of the areas from the time of dosing to the time of the last quantifiable concentration (TLQC). The area under the plasma concentration-time curve from zero to infinity (AUCI), was calculated as: AUCI = AUCL + LQC/KEL where LQC is the last quantifiable concentration. The elimination half-life was calculated as: HALF = 0.693/KEL.

Statistical analyses were performed on the pharmacokinetic parameters using the General Linear Models Procedure (PROC GLM) of SAS Software (SAS Institute, Cary, NC). The model tested for treatment effects in the parameter means at an alpha level of 0.05. The parameters: AUCL, AUCI, CPEAK, TPEAK, KEL and HALF were analyzed statistically using the non-transformed data. The natural log transformed parameters: LNAUCL, LNAUCI and LNCPEAK were also analyzed. The tests were performed to analyze for statistically significant differences in the pharmacokinetic parameters and to determine the test to reference ratios of the pharmacokinetic parameters using Least Squares Means. Ninety percent (90%) confidence intervals were constructed using the two one-sided tests procedure.

Initially since the subjects were dosed in three groups, potential group effects were evaluated by an ANOVA model which included following factors: cohort, sequence, sequence by cohort interaction, subject within sequence by cohort interaction, period, period by cohort interaction, treatment, treatment by cohort interaction.

K. CLINICAL NOTES

Group A, Period 1 was dosed on May 27, 1999 and Period 2 was dosed on June 7, 1999. Group B, Period 1 was dosed on May 31, 1999 and Period 2 was dosed on June 10, 1999. Group C, Period 1 was dosed on June 3, 1999 and Period 2 was dosed on June 14, 1999. The study subjects were healthy males between the ages of 21 and 43. Of the 23 subjects who began the study, all subjects completed both periods. A total of seven post-dose adverse events were experienced by five subjects during the study. Of the seven adverse events listed, two were listed as possibly drug related. One adverse event was listed as remotely drug related and four were listed as unrelated. All events were listed either mild or moderate in severity. There were no serious or life threatening adverse events reported for this study. Adverse events are summarized in Table 3.

L. RESULTS OF FASTING BIOEQUIVALENCE STUDY

The mean concentration versus time profiles (n=23) are given in Figure 1. Mean plasma profiles and %CV's of the Mylan sotalol HCl tablets and Berlex Betapace® tablets are given in Table 4. Summary of the pharmacokinetic parameters is shown in Table 5. The test and reference formulations demonstrated similar mean pharmacokinetic parameters and variability. The 90% confidence intervals fall within 80-125% for the test to reference ratio for the natural log transformed parameters: LNAUCL, LNAUCI and LNCPEAK.

II. IN-VIVO FOOD EFFECTS STUDY CONDUCTED UNDER FASTING AND NON-FASTING CONDITIONS (PROTOCOL #): SOTA-9902

A. STUDY INVESTIGATORS AND CONTRACT LABORATORY

Same as in the fasting study.

B. INFORMED CONSENT AND IRB APPROVAL

The clinical portion of this study was conducted as per 21 CFR § 56 and 21 CFR § 50.

C. STUDY OBJECTIVE

To investigate the relative bioavailability of Mylan sotalol HCl tablets to Betapace® (Berlex Laboratories) tablets following a single, oral 160 mg (1 x 160 mg) dose under fed conditions.

D. STUDY DESIGN

This study was designed as a randomized, three-period, three-treatment, six-sequence crossover study to complete eighteen healthy subjects.

E. SUBJECT SELECTION CRITERIA

Same as the previous study.

F. STUDY SCHEDULE

Subjects were housed on the evening prior to dosing until 48 hours after dosing. Subjects were dosed in three enrollments of seven subjects each. After a supervised overnight fast, subjects who received Treatment A (Betapace®, fed) and Treatment B (Mylan, fed) were given a standard breakfast 30 minutes before dosing that was consumed within 15 minutes. Breakfast consisted of 1 buttered English muffin, 1 fried egg, 1 slice of Canadian bacon, 1 slice of American cheese, 1 serving of hashed brown potatoes, 6 ounces of orange juice and 8 ounces of whole milk. Subjects who received Treatment C (Mylan, fasting) were required to fast 10 hours prior to and 5 hours after dosing. Each subject then received either a single, oral 160 mg (1 x 160 mg) dose of Mylan sotalol HCl tablets or Berlex Betapace® tablets with 240 mL of water at ambient temperature. Subjects received a standard meal 5 hours post dose followed by an evening meal 10 hours after dosing and snacks at appropriate times thereafter. Subjects consumed 240 mL of ambient temperature water at 1 hour prior to and at 1 hour after dosing. The predose water was completed 1 hour prior to dosing. Water was not permitted from 1 hour before and until 1 hour after dosing, but was allowed at all other times. Subjects were monitored throughout confinement for adverse reactions to the study formulations and/or procedures. Subjects were released 48 hours after dosing, but were required to return to the clinic for the 72 hour blood draw. A washout period of at least 10 days separated each period. On the mornings of June 24, 1999, and June 28, 1999, Group 1, Period 2 and Group 3, Period 1 were not given the required fried egg, Canadian bacon, and slice of American cheese with breakfast prior to dosing. The sponsor was contacted on June 28, 1999 after the periods were complete. Due to safety issues related to sotalol, it was decided to redose the periods for those groups affected to avoid exposing more healthy volunteers at risk in a new clinical trial. In this report, the repeat periods will be designated with an 'R' preceding the period number. Group 1, Period 1 was dosed on June 17, 1999, Period 2 was dosed on June 28, 1999, Period R2 was dosed on July 8, 1999 and Period 3 was dosed on July 19, 1999. Group 2, Period 1 was dosed on June 21, 1999, Period 2 was dosed

on July 1, 1999, and Period 3 was dosed on July 12, 1999. Group 3, Period 1 was dosed on June 24, 1999, Period R1 was dosed on July 5, 1999, Period 2 was dosed on July 15, 1999 and Period 3 was dosed on July 26, 1999. Serial blood samples 10 mL (1 x 10 mL) were collected at predose and at 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 6.0, 8.0, 12, 16, 24, 36, 48 and 72 hours post-dose. Plasma samples were stored in suitably labeled tubes at -70°C ± 15°C until analysis. Due to the additional period for Group 1 and Group 3, the volume of blood draws was reduced from 10 mL to 7 mL for Group 1, Periods R2 and 3, Group 2, Period 3, and Group 3, Periods 2 and 3.

G. DRUG TREATMENTS

Treatment A = Berlex Betapace® tablets (160 mg)
1 x 160 mg, Administered with Food
Lot# W80099, Exp. 5/02
Commercial Lot
Assay Potency - 99.5%

Treatment B = Mylan sotalol HCl tablets (160 mg)
1 x 160 mg, Administered with Food
Lot# 2E009N, Exp. TBE
Theoretical Lot Size: 160,000
Manufacturing Date: 12/28/1998
Assay Potency: 99.5%

Treatment C = Mylan sotalol HCl tablets (160 mg)
1 x 160 mg, Fasting Administration
Lot #2E009N, Exp. TBE
Theoretical Lot Size: 160,000
Manufacturing Date: 12/28/1998
Assay Potency: 99.5%

H. ANALYTICAL METHODOLOGY

I. CHROMATOGRAMS

Chromatograms of the standard curves, quality control samples and unknown sample assay for Subject #'s 2, 4, 8, and 10 are provided in Application's 'Analytical Report' of the food bioequivalence study.

J. STATISTICAL ANALYSIS

Single-dose pharmacokinetic parameters for sotalol were calculated using noncompartmental techniques. The maximum concentration (CPEAK) and the time at which it occurred relative to the administered dose (TPEAK) were determined from the observed plasma concentration-time profile over the sampling time interval. The elimination rate constant (KEL) was determined by linear regression of the terminal linear phase of the log plasma concentration-time profile. Area under the plasma concentration-time curve (AUCL) is the sum of the linear trapezoidal estimation of the areas from time of dosing to the time of the last quantifiable concentration (TLQC). Area under the plasma concentration-time curve from zero to infinity (AUCI), was calculated as: AUCI = AUCL + LQC/KEL where LQC is the last quantifiable concentration. The elimination half-life was calculated as HALF = 0.693/KEL. Due to protocol deviations, Period 2 of Group 1 and Period 1 of group 3 were not used in this study and were replaced by Period R2 of Group 1 and Period R1 of Group 3, respectively. However, a standard three-way crossover model was used in this study. The "R" used to designate the repeated periods were then removed in the statistical analyses. Statistical analyses were performed on the pharmacokinetic parameters using the General Linear Models Procedure (PROC GLM) of SAS Software (SAS Institute, Cary, NC). The model tested for treatment effects in the parameter means at an alpha level of 0.05. The parameters: AUCL, AUCI, CPEAK, TPEAK, KEL and HALF were analyzed statistically using the non-transformed data. The natural log transformed parameters: LNAUCL, LNAUCI, LNCPEAK were also analyzed. The tests were performed to analyze for statistically significant differences in the pharmacokinetic parameters and to determine the test to reference ratios of the pharmacokinetic parameters using Least Squares Means. Since subjects were dosed in three groups, potential group effects were evaluated by an ANOVA model which included the following factors: cohort, sequence, sequence by cohort interaction, subject within sequence by cohort interaction, period, period by cohort interaction, treatment, treatment by cohort interaction. If there was a significant treatment by cohort interaction for a parameter, an ANOVA using standard crossover model would be performed on the parameter separately in each cohort. If there was no cohort*treatment interaction but cohort*period was significant for a parameter, the period by cohort interaction would be tested for the parameter in a reduced model which included the following factors: cohort, sequence, sequence by cohort interaction, subject within sequence by cohort interaction, period, period by cohort interaction, treatment. If there was a cohort*period interaction, then the reduced model was the final model used to analyze the parameter. The results of this model were then used to estimate the mean ratios. If there was no cohort*treatment nor cohort*period interaction for a parameter, all cohorts were combined and the parameter was analyzed using the standard crossover model.

K. CLINICAL NOTES

On the mornings of June 24, 1999, and June 28, 1999, Group 1, Period 2 and Group 3, Period 1 were not given the required fried egg, Canadian bacon, and slice of American cheese with breakfast prior to dosing. The sponsor was contacted on June 28, 1999 after the periods were complete. Due to safety issues related to sotalol, it was decided to redose the periods for those groups affected to avoid exposing more healthy volunteers at risk in a new clinical trial. In this report, the repeat periods will be designated with an 'R' preceding the period number. Group 1, Period 1 was dosed on June 17, 1999, Period 2 was dosed on June 28, 1999, Period R2 was dosed on July 8, 1999 and Period 3 was dosed on July 19, 1999. Group 2, Period 1 was dosed on June 21, 1999, Period 2 was dosed on July 1, 1999, and Period 3 was dosed on July 12, 1999. Group 3, Period 1 was dosed on June 24, 1999, Period R1 was dosed on July 5, 1999, Period 2 was dosed on July 15, 1999 and Period 3 was dosed on July 26, 1999. The study subjects were healthy males between the ages of 19 and 42. [Table 3 of the firm's food bioequivalence report summarizes the respective demographic data of the subjects enrolled in this study]. Of the 21 subjects who began this study, 19 subjects completed all periods. Subject #6 failed to report for Period 3 due to personal reasons that were not study related. Subject #7 failed to report for Period R2 due to personal reasons that were not study related. There were 13 post-dose adverse events (8 subjects) reported for this study (Table 10). Of those, 10 were listed as remotely drug related, 1 was listed as possibly drug related and 2 were listed as unrelated to the study drug. Of the 13 adverse events, 10 were listed as mild in severity and 3 were listed as moderate. There were no serious or life threatening adverse events reported for this study.

L. RESULTS OF FOOD BIOEQUIVALENCE STUDY

Data are presented for nineteen subjects who completed the study. [The presentation of data and pharmacokinetic analysis can be found in Attachment 1 of the firm's food bioequivalence report]. The mean concentration versus time profile (Table 7) is illustrated graphically in Figure 2. Mean plasma profiles are similar between Mylan sotalol HCl 160 mg tablets and Berlex Betapace® 160 mg tablets under fed conditions. The statistical analyses for treatment by cohort interaction are presented in Attachment 2A of the food bioequivalence report. There were no statistically significant treatment by cohort interactions for LNAUCL and LNAUCI. However, a significant treatment by cohort interaction was found in LNCPEAK. The statistical analyses for LNAUCL and LNAUCI were then performed using the reduced model excluding the term for treatment by cohort interaction. The results are presented in Attachment 2B of the food bioequivalence report. There were statistically significant period by cohort interactions for both LNAUCL and LNAUCI. Therefore, the final model for analysis of these parameters was the reduced model. Table 8 presents the mean test to reference ratios for LNAUCL and LNAUCI. They are all within the 0.8 and 1.20 range for bioequivalence under fed conditions. Since a significant cohort by treatment interaction was found in LNCPEAK, statistical analyses using a standard crossover model were performed separately for the three groups. The results are presented in Attachment 2C of the food bioequivalence report and are summarized in Table 9. The mean test to reference ratios for LNCPEAK for each group are all within the 0.80 and 1.20 range for bioequivalence under fed conditions.

II. **PRODUCT FORMULATION**: Please refer Table 11.

III. **IN-VITRO DISSOLUTION TESTING RESULTS**: Please refer Table 12.

IV. **REQUEST FOR WAIVER OF IN-VIVO BIOEQUIVALENCE:**

Pursuant to 21 CFR Paragraph 320.22(d)(2) of the bioavailability and bioequivalency requirements, the firm is requesting a waiver of the *in vivo* bioequivalence testing requirements for the 80 mg, 120 mg and 240 mg strengths of the drug product. The bioequivalence studies were conducted using the 160 mg strength instead of the highest strength of Sotalol Hydrochloride Tablets (240 mg) pursuant to the 19th edition of the Approved Drug Products with Therapeutic Equivalence Evaluations ("Orange Book"). In the Prescription Drug Product Lists of the Orange Book, the Agency has identified Betapace® Tablets, 160 mg as the reference listed drug product.

TABLE 1-PRE-STUDY ASSAY VALIDATION - SOTALOL

Within-Day Accuracy and Precision

Spiked Concentration (μg/mL)	N	Assayed Concentration Mean ± SD (μg/mL)	Error (%)	Coefficient of Variation (%)
0.05	6	0.050 ± 0.003	-0.2	6.5
0.15	6	0.144 ± 0.004	-3.7	2.7
0.75	6	0.719 ± 0.006	-4.2	0.8
2.0	6	1.915 ± 0.016	-4.3	0.8

TABLE 2 - DURING STUDY ASSAY VALIDATION FOR FASTING STUDY -#SOTA-9901

Between-Day Accuracy and Precision Summary: Quality Control Values

Spiked Concentration (μg/mL)	N	Assayed Concentration Mean ± SD (μg/mL)	Error (%)	Coefficient of Variation (%)
0.150	48	0.154 ± 0.008	2.6	5.0
0.750	48	0.754 ± 0.025	0.6	3.3
2.000	48	2.016 ± 0.067	0.8	3.3

Between-Day Accuracy and Precision Summary: Standard Curve Values

Spiked Concentration (μg/mL)	N	Assayed Concentration Mean ± SD (μg/mL)	Error (%)	Coefficient of Variation (%)
0.050	14	0.050 ± 0.001	0.1	2.7
0.100	14	0.100 ± 0.005	0.3	4.6
0.150	14	0.149 ± 0.007	-0.8	4.5
0.250	14	0.251 ± 0.008	0.2	3.3
0.500	14	0.500 ± 0.009	0.1	1.8
0.750	14	0.748 ± 0.014	-0.2	1.8
1.000	14	1.011 ± 0.031	1.1	3.1
1.500	14	1.494 ± 0.014	-0.4	0.9
2.000	14	2.003 ± 0.030	0.1	1.5
2.500	14	2.497 ± 0.048	-0.1	1.9
3.000	14	2.992 ± 0.063	-0.3	2.1

TABLE 3

ADVERSE EVENTS – 'Fasting' BIOEQUIVALENCE STUDY

Subject	Treat.	Period	Adverse Reaction	Severity	Action taken
3	B	1	Chest pressure	Mild	None
4	B	2	Headache	Moderate	Tylenol
5	A	2	Gas pains	Mild	None
8	A	1	Cold	Moderate	None
8	B	2	Rhinorrhea	Mild	None
8	B	2	Study Nose/Sinus	Moderate	None
9	B	1	Wisdom Tooth Eruption	Moderate	Orageł topical cream

TABLE 4

FASTING BIOEQUIVALENCE STUDY, MEAN SOTALOL PLASMA CONCENTRATIONS [μg/mL] VERSUS TIME (CV%) [N=23]

	Treatment				
	A (Betapace #W80099)		B (Sotalol HCl #2E009N)		B VS A
	Mean (ug/mL)	%CV	Mean (ug/mL)	%CV	P(|T|>t)
Draw Time					
0.00 hours	0.00	.	0.00	.	----
0.50 hours	0.19	96.16	0.16	111.96	0.4951
0.75 hours	0.36	64.57	0.33	76.18	0.6121
1.00 hours	0.51	46.90	0.45	59.90	0.0962
1.50 hours	0.68	48.24	0.63	45.21	0.2242
2.00 hours	0.85	44.40	0.86	45.66	0.8436
2.50 hours	0.94	34.94	0.91	42.60	0.7174
3.00 hours	0.90	32.85	0.91	39.92	0.8663
3.50 hours	0.83	33.71	0.86	35.14	0.6472
4.00 hours	0.79	37.60	0.80	36.38	0.8481
6.00 hours	0.62	32.89	0.64	34.83	0.7244
8.00 hours	0.50	29.40	0.50	28.43	0.7388
12.00 hours	0.34	28.07	0.35	26.87	0.7534
16.00 hours	0.25	25.59	0.26	26.04	0.7117
24.00 hours	0.15	25.81	0.15	26.02	0.9166
36.00 hours	0.06	61.35	0.06	56.56	0.4423
48.00 hours	0.01	227.18	0.01	227.25	0.6800
72.00 hours	0.00	.	0.00	.	----

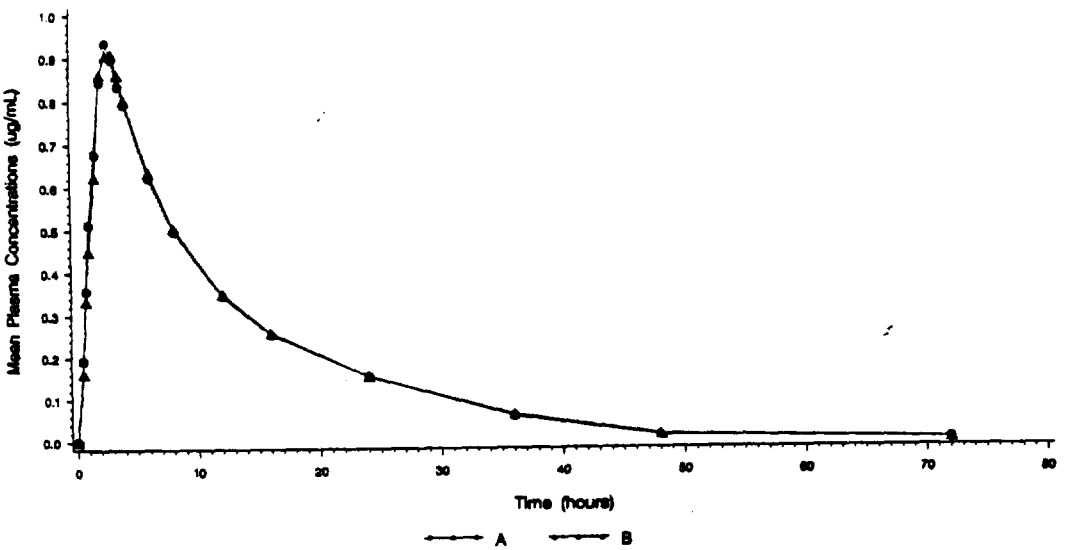
FIGURE 1

SOTALOL HCl (SOTA – 9901)

Total Dose: 160mg (1x160mg Tablets), Study Type: Fasting

Mean Sotalol Plasma Concentrations

N = 23



Treatment A is A (Betapace #W80099)
Treatment B is B (Sotalol HCl #2E009N)

TABLE 5

MEAN (%CV) SOTALOL PHARMACOKINETIC PARAMETERS IN TWENTY-THREE HEALTHY SUBJECTS FOLLOWING A SINGLE ORAL 160 MG (1 x 160 MG) DOSE OF SOTALOL HCL TABLETS UNDER FASTING CONDITIONS (PROTOCOL SOTA-9901)				
Parameter	**Arithmetic Mean A = Betapace®**	**Arithmetic Mean B = Mylan**	**LSMEANS Ratio (B/A)***	**90% Confidence Interval****
AUCL (μgx hr/mL)	10.94 (25.99)	11.10 (27.61)	1.01	94% - 109%
AUCI (μg x hr/mL)	12.17 (23.54)	12.51 (23.31)	1.02	96% - 109%
CPEAK (μg/mL)	1.077 (33.15)	1.080 (33.65)	0.99	87% - 113%
KEL (hr^{-1})	0.0652 (21.50)	0.0663 (26.10)	-----	----
HALF (hr)	11.14 (22.90)	11.64 (46.43)	-----	-----
TPEAK (hr)	2.500 (35.68)	2.790 (37.31)	-----	-----

*Ratio (B/A) = e [LSMEAN of LNB - LSMEAN of LNA]

**Used natural Log Transformed Parameter

TABLE 6 - ASSAY VALIDATION FOR FOOD EFFECTS STUDY #SOTA-9902

SOTALOL

Between-Day Accuracy and Precision Summary: Quality Control Values

Spiked Concentration (μg/mL)	N	Assayed Concentration Mean ± SD (μg/mL)	Error (%)	Coefficient of Variation (%)
0.15	38	0.150 ± 0.008	-0.1	5.6
0.75	38	0.740 ± 0.030	-1.3	4.1
2.00	38	1.975 ± 0.081	-1.2	4.1

Between-Day Accuracy and Precision Summary: Standard Curve Values

Spiked Concentration (μg/mL)	N	Assayed Concentration Mean ± SD (μg/mL)	Error (%)	Coefficient of Variation (%)
0.05	11	0.050 ± 0.001	-0.6	2.4
0.10	11	0.101 ± 0.004	0.8	4.2
0.15	11	0.151 ± 0.004	0.6	2.4
0.25	11	0.251 ± 0.006	0.5	2.6
0.50	11	0.503 ± 0.007	0.6	1.3
0.75	11	0.741 ± 0.014	-1.2	1.9
1.00	11	0.992 ± 0.019	-0.8	1.9
1.50	11	1.500 ± 0.025	-0.01	1.6
2.00	11	2.002 ± 0.029	0.1	1.5
2.50	11	2.514 ± 0.027	0.6	1.1
3.00	11	2.986 ± 0.060	-0.5	2.0

TABLE 7

POST-PRANDIAL SINGLE-DOSE IN VIVO BIOEQUIVALENCE STUDY #SOTA-9902
ARITHMETIC MEAN SOTALOL PLASMA CONCENTRATIONS
[μg/mL] VERSUS TIME (CV%) IN 19 SUBJECTS

	Treatment						
	A(Betapace #W80099--fed)		B(Sotalol HCl #2E009N --fed)		C (Sotalol HCl #2E009N--fast)		B VS A
	Mean(ug/mL)	%CV	Mean (ug/mL)	%CV	Mean (ug/mL)	%CV	P(|T|>t)
Draw Time							
0.00 hours	0.00	.	0.00	.	0.00	.	----
0.50 hours	0.07	185.81	0.03	156.95	0.17	95.78	0.2782
0.75 hours	0.21	129.14	0.09	105.52	0.35	65.08	0.0888
1.00 hours	0.30	118.29	0.22	112.71	0.60	54.27	0.4432
1.50 hours	0.49	81.05	0.50	63.58	0.68	49.20	0.9542
2.00 hours	0.67	50.49	0.72	50.32	0.91	50.04	0.6663
2.50 hours	0.78	35.70	0.85	43.04	1.00	34.86	0.4261
3.00 hours	0.86	29.85	0.92	31.78	1.02	28.58	0.5054
3.50 hours	0.88	21.60	0.90	23.82	1.00	19.77	0.6576
4.00 hours	0.88	18.65	0.90	14.35	0.97	16.31	0.6012
6.00 hours	0.71	16.88	0.75	18.17	0.74	19.38	0.2596
8.00 hours	0.58	15.27	0.59	16.50	0.60	18.76	0.6179
12.00 hours	0.40	16.37	0.40	16.15	0.41	20.40	0.8868
16.00 hours	0.29	17.31	0.29	16.19	0.30	25.45	0.9342
24.00 hours	0.17	19.58	0.17	21.05	0.18	30.02	0.6698
36.00 hours	0.07	42.47	0.08	45.32	0.07	73.82	0.8589
48.00 hours	0.02	138.31	0.03	126.01	0.03	127.27	0.4608
72.00 hours	0.00	.	0.00	.	0.00	.	----

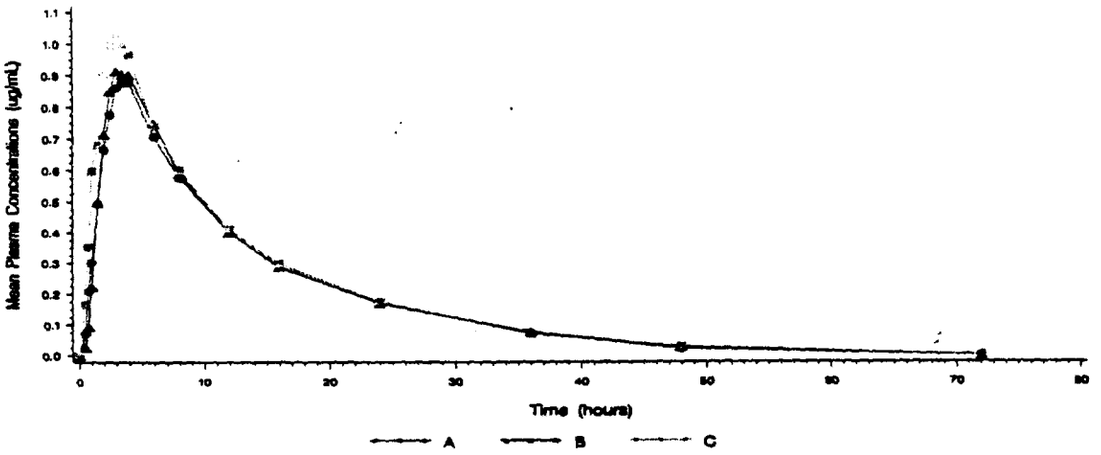
FIGURE 2

SOTALOL HCl (SOTA – 9902)

Total Dose: 160mg (1x160mg Tablets), Study Type: Fed

Mean Sotalol Plasma Concentrations

N = 19



Treatment A is A (Betapace #W80099 – – fed)
Treatment B is B (Sotalol HCl #2E009N – – fed)
Treatment C is C (Sotalol HCl #2E009N – – fast)

TABLE 8

MEAN (%CV) SOTALOL PHARMACOKINETIC PARAMETERS IN NINETEEN HEALTHY MALE SUBJECTS FOLLOWING A SINGLE ORAL 160 MG(1 X 160 MG) DOSE OF SOTALOL HCL TABLETS IN A FOOD STUDY

(Protocol SOTA-9902)

Parameter	Arithmetic Mean A = Betapace® (Fed)	Arithmetic Mean B = Mylan (Fed)	Arithmetic Mean C = Mylan (Fasting)	LSMEANS* Ratio (B/A)
AUCL (μg x hr/mL)	12.07 (17.24)	12.32 (18.34)	13.06 (21.82)	1.03
AUCI (μg x hr/mL)	13.32 (15.16)	13.50 (18.26)	14.39 (21.15)	1.02
CPEAK (μg/mL)	1.001 (23.10)	1.041 (20.93)	1.243 (23.64)	1.04
KEL (hr^{-1})	0.062 (20.30)	0.063 (25.35)	0.065 (29.14)	----
HALF (hr)	11.79 (24.76)	11.81 (29.51)	11.52 (30.40)	----
TPEAK (hr)	3.263 (32.05)	3.342 (35.28)	3.093 (25.04)	----

* Ratio (A/B) = $e^{[\text{LSMEAN of LNA- LSMEAN of LNB}]}$

TABLE 9

MEAN (%CV) SOTALOL CPEAK IN THREE GROUPS FOLLOWING A SINGLE ORAL 160 MG (1 X 160 MG) DOSE OF SOTALOL HCL TABLETS IN A FOOD STUDY Protocol SOTA-9902				
Parameter	**Arithmetic Mean A = Betapace® (Fed)**	**Arithmetic Mean B = Mylan (Fed)**	**Arithmetic Mean C = Mylan (Fasting)**	**LSMEANS* Ratio (B/A)**
CPEAK, Group 1 (μg/mL)	0.9312 (15.59)	0.9946 (15.29)	1.475 (17.01)	1.08
CPEAK, Group 2 (μg/mL)	1.066 (24.15)	1.074 (24.16)	1.308 (22.08)	1.01
CPEAK, Group 3 (μg/mL)	0.9849 (27.00)	1.040 (22.83)	1.012 (14.63)	1.08

- Ratio (B/A) = $e^{[\text{LSMEAN of LNB - LSMEAN of LNA}]}$

TABLE 10

ADVERSE EVENTS – 'Food Challenge' BIOEQUIVALENCE STUDY

Subject	Treat.	Period	Adverse Reaction	Severity	Action taken
2	C	1	3-beats wide complex QRS	Mild	None
5	C	R2	Papular chest rash	Moderate	10% hydrocortis one cream
5	C	R2	Sore throat	Mild	None
5	C	R2	Diarrhea	Mild	None
7	A	1	Diarrhea	Moderate	None
7	A	1	Dizziness	Mild	None
7	B	2	Itching red bumps on the forearm	Mild	10% hydrocortis one cream
13	A	3	Nausea	Mild	None
14	B	2	Run of irregular wild tachycardia	Moderate	No feature of Torsades De Pointes or Long QT. Can not 100% exclude artifact
15	A	2	Papular Rash	Mild	None
16	C	1	Telemetry– Ventricular couplet	Mild	None
16	A	2	Headache	Mild	None
17	A	1	Telemetry– junctional rhythm	Mild	None

TABLE 11

COMPARATIVE QUANTITATIVE COMPOSITIONS

SOTALOL HYDROCHLORIDE TABLETS, 80MG, 120MG, 160MG AND 240MG

	80mg		120mg		160mg		240mg	
ACTIVE COMPONENTS	MG PER TABLET	%	MG PER TABLET	%	MG PER TABLET	%	MG PER TABLET	%
Sotalol Hydrochloride								
INACTIVE COMPONENTS								
FD&C Yellow #6								
Colloidal Silicon Dioxide, NF								
Magnesium Stearate/Sodium Lauryl Sulfate (94/6)								
Lactose, NF								
Microcrystalline Cellulose, NF								
Pregelatinized Starch, NF Low Moisture								
TOTAL THEORETICAL WEIGHT								

TEST: Mylan's 80 mg, 120 mg, 160 mg and 240 mg Sotalol HCl tablets are light orange, round, biconvex tablets debossed with **M** *above* the **score** and **305, 310, 314 and 316 respectively** *below* the **score.** The tablets are blank on the other side.

REFERENCE: Berlex's BETAPACE[R] tablets are **capsule shaped, light blue colored, scored, imprinted with the respective strength and BETAPACE[R]**

TABLE 12
SOTALOL HYDROCHLORIDE TABLETS, 80MG, 120MG, 160MG AND 240MG
DISSOLUTION PROFILE SUMMARY

	15 MINUTES	30 MINUTES	45 MINUTES	60 MINUTES
Mylan Lot 2E007N (80mg)				
Mean	91%	98%	99%	99%
Range	84% - 96%	95% - 102%	96% - 103%	97% - 103%
RSD	3.9%	2.6%	2.5%	2.4%
Betapace® Lot W80169 (80mg)				
Mean	85%	96%	98%	98%
Range	73% - 91%	94% - 99%	96% - 100%	97% - 100%
RSD	7.7%	1.6%	1.3%	1.1%
Mylan Lot 2E008N (120mg)				
Mean	79%	95%	96%	97%
Range	79% - 86%	77% - 99%	86% - 99%	92% - 99%
RSD	10.5%	6.2%	3.7%	2.2%
Betapace® Lot W80213 (120mg)				
Mean	64%	93%	97%	98%
Range	53% - 81%	91% - 95%	95% - 99%	96% - 100%
RSD	11.8%	1.9%	1.4%	1.4%
Mylan Lot 2E009N (160mg)				
Mean	77%	94%	96%	96%
Range	72% - 80%	92% - 96%	94% - 97%	94% - 98%
RSD	3.1%	1.5%	0.9%	0.9%
Betapace® Lot W80099 (160mg)				
Mean	84%	92%	94%	95%
Range	74% - 90%	90% - 94%	93% - 96%	94% - 97%
RSD	5.2%	1.6%	1.1%	0.9%
Mylan Lot 2E010N (240mg)				
Mean	71%	92%	96%	97%
Range	60% - 79%	83% - 99%	93% - 99%	94% - 99%
RSD	8.4%	5.8%	2.2%	1.6%
Betapace® Lot W80074 (240mg)				
Mean	69%	93%	96%	97%
Range	51% - 86%	89% - 96%	93% - 98%	95% - 99%
RSD	15%	2.8%	1.8%	1.4%

CONDITIONS: Dissolution Medium: 900mL of water @ 37°C ± 0.5°C

Apparatus:	2 (Paddles)
Speed:	50 rpm
Sample Times:	@ 15, 30, 45 and 60 minutes
Agency proposed (Q):	NLT 80% (Q) in 30 minutes

APPENDIX

Randomization schemes

SOTA-9901 (fasting study)

Sequence	Subjects
AB	1, 4, 7, 8, 10, 12, 14, 15, 19, 20, 22, 23
BA	2, 3, 5, 6, 9, 11, 13, 16, 17, 18, 21

SOTA-9902 (food challenge study)

Sequence	Subjects
ABC	3, 7, 14
ACB	5, 8, 17, 19
BAC	6, 9, 15, 20
BCA	4, 12, 18
CAB	1, 11, 16
CBA	2, 10, 13, 21

- Note: The ratio of log transformed parameters in the ESD file represents the geometric means ratios.
- Due to a significant cohort by treatment interaction for LNCPEAK in the Food bioequivalence study, statistical analyses for LNCPEAK were performed separately for the three groups. However, only Group 1's LNCPEAK data was listed in the ESD Data file. Please refer to the other Groups' LNCPEAK data in the EVA Companion Document.
- The values for LNCPEAK in the food bioequivalence study are negative (<0). Tney are reported as such in the ESD Myl9908.001 file.

Appendix (contd.) TABLE 13
SOTALOL HYDROCHLORIDE TABLETS, 80MG, 120MG, 160MG AND 240MG
DISSOLUTION PROFILE USING 0.1 N HCl

	15 MINUTES	30 MINUTES	45 MINUTES	60 MINUTES
Mylan Lot 2E007N (80mg)				
Mean	85%	99%	100%	100%
Range	74% - 99%	96% - 103%	99% - 103%	99% - 103%
RSD	8.2%	1.8%	1.1%	1.1%
Betapace® Lot W80169 (80mg)				
Mean	97%	101%	101%	101%
Range	90% - 104%	98% - 103%	100% - 103%	100% - 104%
RSD	4.0%	1.4%	1.2%	1.0%
Mylan Lot 2E008N (120mg)				
Mean	83%	100%	101%	101%
Range	79% - 88%	97% - 102%	98% - 103%	98% - 103%
RSD	3.6%	1.5%	1.4%	1.3%
Betapace® Lot W80213 (120mg)				
Mean	84%	100%	101%	102%
Range	70% - 95%	98% - 103%	99% - 103%	99% - 105%
RSD	9.0%	1.6%	1.2%	1.7%
Mylan Lot 2E009N (160mg)				
Mean	74%	96%	100%	100%
Range	61% - 79%	88% - 102%	96% - 103%	97% - 103%
RSD	7.3%	3.5%	1.5%	1.4%
Betapace® Lot W80099 (160mg)				
Mean	89%	97%	99%	100%
Range	81% - 97%	94% - 100%	96% - 101%	97% - 101%
RSD	5.8%	2.0%	1.6%	1.3%
Mylan Lot 2E010N (240mg)				
Mean	68%	95%	101%	101%
Range	49% - 77%	79% - 102%	93% - 104%	98% - 104%
RSD	10.2%	6.0%	2.8%	1.6%
Betapace® Lot W80074 (240mg)				
Mean	94%	100%	101%	102%
Range	67% - 101%	96% - 104%	98% - 104%	99% - 104%
RSD	9.5%	2.2%	1.7%	1.5%

CONDITIONS: Dissolution Medium: 900mL 0.1N HCl @ 37°C ± 0.5°C

Apparatus:	2 (Paddles)
Speed:	50 rpm
Sample Times:	@ 15, 30, 45 and 60 minutes
Proposed Limit (Q):	NLT 80% (Q) in 60 minutes

COMMENTS:

Fasting Study

1. Table 4 indicates that the mean plasma levels of the two treatments are comparable along with their respective coefficients of variations. Table 5 indicates that the 90% confidence intervals of the mean difference of the two treatments are within the 80-125% regulatory limit implying equivalence of the two products under fasting conditions. The mean AUCt parameter is more than 88% of the mean AUCinf parameter, indicating adequacy of the sampling scheme.

2. The pharmacokinetic parameters were analyzed using analysis of variance with a general linear model. The classes were Sequence, Period, Treatment and Subject(Sequence). The reviewer calculations resulted in confidence interval numbers slightly different than those reported by the firm. The 90% confidence intervals were nevertheless within the bounds of 80-125% for log transformed parameter analysis. The statistical analysis was also conducted by the Division statistician to ascertain the contribution of a group effect. The classes were Cohort, Sequence, Cohort*Sequence, Subject(Cohort*Sequence), Period, Cohort*Period, Treatment and Cohort*Treatment. The results are given in Attachment 1. There was no statistically significant cohort by treatment interaction in this study for all pharmacokinetic parameters. The cohort by treatment interaction was then excluded in the reduced model. Subsequent analysis using the reduced model suggested there were no statistically significant period by cohort interaction. Therefore, a standard two-way crossover model for bioequivalence study was considered adequate.

Food Challenge Study

3. The mean plasma levels and the respective %CVs following the 'food challenge' for the two treatments are comparable. Food appears to have reduced the extent of absorption. This observation thus confirms the labeling statement regarding 'food effect'.

4. Given that 'food challenge' reduces the extent of absorption, it was not clear why the firm had to repeat two phases for the 'food challenge' study. To assure the integrity of the study, in a telephone call (placed by the project manager), the firm was asked to verify the reasons behind the repeated phases. This being a cardio-active agent, the firm was also asked about safety related issues in this incident. In a response dated 12/20/99, the firm confirmed that Phases II and III were repeated because "It was found that the breakfast served on June 24, 199 (group 3, period 1) and on June 28, 1999 (group 1, period 2) did not contain required fried egg, Canadian bacon, and American cheese. Due to safety issues related to dosing sotalol in healthy volunteers, it was decided that the affected periods were repeated in these two groups to avoid exposing additional healthy volunteers at risk in a new trial". It was further pointed out that there was no untoward subject-safety related issue.

5. The firm has conducted analysis of variance and has calculated the 90% confidence intervals. At present, the 90% confidence interval approach is not used for evaluating the 'food effect' study results. The treatment LSMeans were therefore evaluated using the usual point estimate approach.

Formulation Proportionality

6. All four formulations are exactly proportional with respect to their active and inactive ingredients.

Dissolution:

7. At present, there are no USP or PF dissolution specifications for this drug product. The firm had initially (application date: October 20, 1999) conducted dissolution using 0.1 N HCl. Though dissolution data were comparable across the strengths (Appendix, Table 13), to be consistent with the innovator and other generic products, in a telephone call dated January 13, 2000, the firm was asked to conduct dissolution using the following conditions:

   Apparatus: USP II (paddle)
   RPM: 50
   Medium: 900 ml deaerated Water at 37°C
   Q: Not less than 80% dissolved in 30 minutes.

In a telephone amendment dated January 18, 2000, the firm provided comparative dissolution data on the 80 mg, 120 mg, 160 mg and 240 mg strengths along with the statistics such as mean, %CV and minimum-maximum range for dissolution at each sample point. Also, 'f2' similarity index for the mean profiles was reported. The results could be seen in Table 12.

RECOMMENDATIONS:

1. The comparative dissolution testing conducted by Mylan Pharmaceuticals (Amendment dated January 18, 2000) on its Sotalol Hydrochloride 80 mg, 120 mg, 160 mg and 240 mg, lot numbers 2E007N, 2E008N, 2E009N and 2E0010N respectively, is acceptable.

2. The firm has conducted acceptable in-vivo fasting and food challenge bioequivalence studies comparing its 160 mg Sotalol Hydrochloride tablet of the test product with 160 mg Betapace® tablet of the reference product manufactured by Berlex Laboratories.

3. The formulations for the 80 mg, 120 mg and 240 mg strength are proportionally similar to the 160 mg strength of the test product which underwent bioequivalence testing. The waivers of in-vivo bioequivalence study requirements for the 80 mg, 120 mg and 240 mg strengths of the test products are granted. The 80 mg, 120 mg and 240 mg test products are therefore deemed bioequivalent to the 80 mg, 120 mg and 240 mg Betapace® tablets of the reference product manufactured by Berlex Laboratories.

4. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 ml of deaerated water at 37°C using USP 23 apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:

Not less than of the labeled amount of the drug in the dosage form is dissolved in 30

minutes.

2/11/00

Pradeep M. Sathe
Division of Bioequivalence,
Review Branch II

RD Initialed by SGNerurkar
FT Initialed by SGNerurkar 2/11/2000

Concur: 2/22/00

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #: 75-725 SPONSOR: Mylan Pharmaceuticals

DRUG AND DOSAGE FORM: **Sotalol HCl tablet**

STRENGTH(S): **80mg, 120mg, 160mg, 240mg**

TYPES OF STUDIES: Single Dose fasting study, Single Dose 'food challenge' study

CLINICAL STUDY SITE(S): **Georgetown-Parexel, Georgetown University**

ANALYTICAL SITE(S): **Mylan Labs., Morgantown, West Virginia**

STUDY SUMMARY: Fasting and 'food challenge' study results acceptable

DISSOLUTION: **Dissolution acceptable**

DSI INSPECTION STATUS

Inspection needed: No	Inspection status:	Inspection results:
First Generic No	Inspection requested: (date)	
New facility _____	Inspection completed: (date)	
For cause _____		
Other _____		

PRIMARY REVIEWER: Pradeep M. Sathe, Ph.D. BRANCH: II

INITIAL: _____ DATE: 2/11/00

TEAM LEADER: Shrinivas G. Nerurkar, Ph.D. BRANCH: II

INITIAL: _____ DATE: 2/11/2000

DIRECTOR, DIVISION OF BIOEQUIVALENCE: DALE P. CONNER, Pharm. D.

INITIAL: _____ DATE: 2/22/00

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-725 APPLICANT: Mylan Laboratories

DRUG PRODUCT: Sotalol Hydrochloride Tablet 240 mg, 160 mg, 120 mg and 80 mg.

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

The following dissolution testing will need to be incorporated into your stability and quality control programs:

> The dissolution testing should be conducted in 900 mL of deaerated water, at 37°C using USP Apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:
>
> Not less than 80%(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:

75-725

ADMINISTRATIVE DOCUMENTS

ANDA APPROVAL SUMMARY

✓ANDA #: 75-725

DRUG PRODUCT: Sotalol Hydrochloride

FIRM: Mylan Pharmaceuticals Inc.

DOSAGE FORM: Tablets

STRENGTHS: 80 mg, 120 mg, 160 mg, 240 mg

CGMP STATEMENT/EIR UPDATE STATUS:
An acceptable EER was issued on 04/26/00

Facilities include:

Galbraith Laboratories Inc.
Function: drug substance other tester

Mylan Pharmaceuticals Inc.
Function: finished dosage manufacturer

Oneida Research Services Inc.
nction: drug substance other tester

Profarmaco Nobel SRL
Function: drug substance manufacturer

BIO STUDY:
Was found acceptable on 02/11/00 by Pradeep M. Sathe.

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

Not less than 80%(Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):
The method validation sent to Philadelphia District Laboratory on 11/28/00.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?:
ntainer closure same as that described in the container closure ection.

Post-approval Protocol and Commitment: Satisfactory

Stability Data: The following lots were studied:
80 mg tablets, lot 2E007N - package sizes 100 and 500
120 mg tablets, lot 2E008N - package sizes 100 and 500
0 mg tablets, lot 2E009N - package sizes 100 and 500
0 mg tablets, lot 2E010N - package sizes 100 and 500

Expiration Date: 24 months supported by accelerated and CRT data.

LABELING:
Satisfactory per A. Vezza on 10/26/00.

STERILIZATION VALIDATION (IF APPLICABLE):
N/A

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?):
Sotalol HCl tablets, 80 mg: lot 2E007N, tablets
Sotalol HCl tablets, 120 mg: lot 2E008N, tablets
Sotalol HCl tablets, 160 mg: lot 2E009N, tablets
Sotalol HCl tablets, 240 mg: lot 2E010N tablets

DMF remains acceptable as of 10/23/00.

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

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?:
Production Batch Size:
Sotalol HCl tablets, 80 mg: tablets
Sotalol HCl tablets, 120 mg: tablets
Sotalol HCl tablets, 160 mg: tablets
Sotalol HCl tablets, 240 mg: tablets

Meets OGD 22-90 scale-up criteria; manufacturing process for scale-up batches similar to the exhibit batch using same process conditions and in-process parameters; equipment used are of similar design and/or operating principles.

CHEMIST: Bita Mirzai-Azarm DATE: 12/06/00 Bita M. Azarm 12/12/00

SUPERVISOR: Ubrani Venkataram, Ph.D. DATE: 12/7/00
U. V. Venkataram 12/12/2000

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

ANDA Number: **75-725** Date of Submission: **October 20, 1999**

Applicant's Name: **Mylan Pharmaceuticals Inc.**

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

Labeling Deficiencies:

1. GENERAL COMMENT

   Revise your storage temperature recommendations 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 500s

   See GENERAL COMMENT above.

3. INSERT

   a. General Comment

      Delete "hydrochloride" except in the following places:

      i. CLINICAL PHARMACOLOGY

         A). Mechanism of Action

            1). Second sentence, first instance

            2). Fourth sentence

         B). Hemodynamics - First sentence

         C). Clinical Actions

            1). Second paragraph, second instance

            2). Third paragraph, last sentence

            3). Fifth paragraph

               a). First sentence

               b). Last sentence, first instance

         D). Pharmacokinetics - Third sentence

      ii. INDICATIONS AND USAGE

         First paragraph

iii. CONTRAINDICATIONS

First instance

iv. WARNINGS

Third paragraph, second sentence, second instance

v. PRECAUTIONS

Pregnancy, Teratogenic Effects, Pregnancy Category B

A). Second sentence

B). Third sentence

vi. OVERDOSAGE

Symptoms and Treatment of Overdosage, second sentence

b. PRECAUTIONS

i. Relocate the "Antacids" subsection to be between the "Other" and the "Drugs Prolonging the QT Interval" subsections.

ii. Antacids - C_{max} (subscript)

c. DOSAGE AND ADMINISTRATION

Transfer to Sotalol - ... (see PRECAUTIONS, Drug Interactions).

d. HOW SUPPLIED

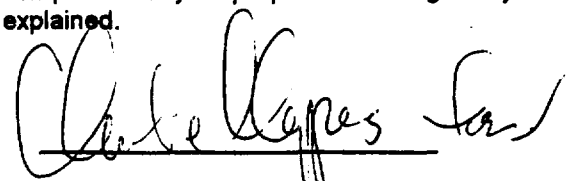
See GENERAL COMMENT (1) above.

Please revise your labels and labeling, as instructed above, and submit 4 draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other features (print size, prominence, etc) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

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.



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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-725

CORRESPONDENCE

labeling review
finished 10/25/00
A Vega

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

October 2, 2000

NDA DRUG AMENDMENT AF

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

TELEPHONE AMENDMENT
(LABELING)

RE: SOTALOL HYDROCHLORIDE TABLETS
80 mg, 120 mg, 160 mg and 240 mg
ANDA 75-725
RESPONSE TO AGENCY TELEPHONE REQUEST OF JULY 19, 2000

Dear Mr. Buehler:

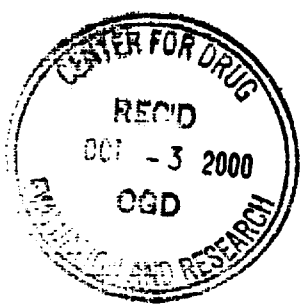
We wish to amend the above-referenced application with a revised final printed outsert. Enclosed in Attachment 3 are twelve (12) copies of the outsert code SOTA:R2; revised SEPTEMBER 2000. The DESCRIPTION, CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE, PRECAUTIONS, OVERDOSAGE and DOSAGE AND ADMINISTRATION sections have been revised pursuant to recent changes in the labeling of the reference listed drug (RLD) product (Betapace®) that were approved by the Agency on July 7, 2000. Mylan was notified of these labeling changes in a telephone conversation with the Agency on July 19, 2000. The Agency also provided a copy of the revisions via a facsimile on July 19, 2000. A copy of the Agency's July 19, 2000 facsimile is provided in Attachment 1 for the reviewer's reference. To facilitate the review, a side-by-side comparison of Mylan's revised final printed outsert (SOTA:R2) to the previously-submitted outsert (SOTA:R1) is provided in Attachment 2.

Should you have any questions regarding this amendment, please contact the undersigned by telephone at (304) 599-2595, ext. 6600 or via facsimile at (304) 285-6407.

Sincerely,

Andrea B. Miller for
Frank R. Sisto
Vice President
Regulatory Affairs

ems/enclosures



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Department—Fax Numbers		Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Accounting	(304) 285-6403	Label Control	(800) 848-0463	Quality Control	(304) 598-5407
Administration	(304) 599-7284	Legal Services	(304) 598-5408	Research & Development	(304) 285-6409
Business Development	(304) 599-7284	Maintenance & Engineering	(304) 598-5411	Sales & Marketing	(304) 598-3232
Human Resources	(304) 598-5406	Medical Unit	(304) 598-5445		

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

NDA ORIG AMENDMENT
N/AB
AC-Bm Mail 12/12/00

July 19, 2000

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

BIOEQUIVALENCE AMENDMENT
(CMC INFORMATION INCLUDED)

RE: SOTALOL HYDROCHLORIDE TABLETS, 80MG, 120MG, 160MG AND 240MG
ANDA 75-725
RESPONSE TO AGENCY CORRESPONDENCE DATED MAY 12, 2000

Dear Mr. Buehler:

Reference is made to the ANDA identified above, which is currently under review, and to the comments from the Division of Bioequivalence pertaining to this application which were included in the Agency's correspondence that was forwarded to Mylan via facsimile on May 12, 2000. In response to the May 12th correspondence from the Division of Bioequivalence, Mylan wishes to amend the application as follows:

1. REGARDING BIOEQUIVALENCE ISSUES:

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

The following dissolution testing will need to be incorporated into your stability and quality control programs:

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

Not less than of the labeled amount of the drug in the dosage form is dissolved in 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.

Department—Fax Numbers		Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Accounting	(304) 285-6403	Label Control	(800) 848-0463	Quality Control	(304) 598-5407
Administration	(304) 599-7284	Legal Services	(304) 598-5408	Research & Development	(304) 285-6409
Business Development	(304) 599-7284	Maintenance & Engineering	(304) 598-5411	Sales & Marketing	(304) 598-3232
Human Resources	(304) 598-5406	Medical Unit	(304) 598-5445		

MYLAN RESPONSE: The dissolution testing requested by the Division of Bioequivalence will be incorporated into Mylan's stability and quality control programs. Mylan has revised the finished product specifications, dissolution procedure, and post-approval stability protocols for Sotalol Hydrochloride Tablets, 80mg, 120mg, 160mg and 240mg to incorporate the requested changes for dissolution. The revised documents are provided in Attachments A, B and C, respectively.

It is acknowledged and understood that the bioequivalency comments expressed in the correspondence dated May 12, 2000 are preliminary and may be revised after review of the entire application. It is also understood that the 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.

For your reference, a copy of the May 12, 2000 Agency correspondence is provided in Attachment D. Responses to the chemistry comments contained in the May 12th correspondence along with revised labeling, also requested in the Agency's correspondence of May 12, 2000, will be forwarded simultaneously in a separate amendment to this application. The revised finished product specifications, dissolution procedure and post-approval stability protocols will also be included in the CMC amendment.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6600 or via facsimile at (304) 285-6407.

Sincerely,

Frank R. Sisto
Vice President
Regulatory Affairs

FRS/dn

Enclosures

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

OCT 20 1999

ELECTRONIC DATA ENCLOSED
BIOEQUIVALENCE DATA ENCLOSED

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

RE: SOTALOL HYDROCHLORIDE TABLETS, 80MG, 120MG, 160MG AND 240MG

Dear Mr. Sporn:

Pursuant to section 505(j) of the Federal Food, Drug and Cosmetic Act and 21 CFR § 314.92 and 314.94, we submit the enclosed abbreviated new drug application for:

Proprietary Name: None
Established Name: Sotalol Hydrochloride Tablets, 80mg, 120mg, 160mg and 240mg
This application consists of a total of 23 volumes.
Archival Copy - 10 volumes.
Review Copy - 11 volumes.
Technical Section For Chemistry - 3 volumes.
Technical Section For Pharmacokinetics - 8 volumes.
Analytical Methods - 2 extra copies; 1 volume each.

NOTE: The Technical Section for Pharmacokinetics of the review copy and the archival copy each contain a set of data diskettes for the bioequivalence studies conducted in support of this application. In addition, the diskettes providing the Bioequivalence Electronic Submission ESD (BA/BE) EVA will be forwarded to the Agency within the 30 day grace period.

This application provides for the manufacture of Sotalol Hydrochloride Tablets, 80mg, 120mg, 160mg, and 240mg. All operations in the manufacture, packaging, and labeling of the drug product are performed by Mylan Pharmaceuticals Inc., 781 Chestnut Ridge Road, Morgantown, WV 26505-2730. *

It should be noted that this Abbreviated New Drug Application has been organized according to the Agency's February 1999 Guidance for Industry - 'Organization of an ANDA'. Pursuant to this guidance, Mylan commits to resolve any issues identified in the methods validation process after approval.

G:\PROJECT\ANDA\Sotalol-HCl-Tabs\SECTIONS-01THRU07.doc

Department—Fax Numbers
Accounting (304) 285-6403
Administration (304) 599-7284
Business Development (304) 599-7284
Human Resources (304) 598-5406
Information Systems (304) 285-6404
Label Control (800) 848-0463
Legal Services (304) 598-5408
Maintenance & Engineering (304) 598-5411
Medical Unit (304) 598-5445
Purchasing (304) 598-5401
Quality Control (304) 598-5407
Research & Development (304) 285-6409
Sales & Marketing (304) 598-3232

As required by 21 CFR 314.94(d)(5), we certify that a true copy of the technical sections of this application, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office. The following Table of Contents and Reader's Guide detail the documentation submitted in support of this application.

All correspondence regarding this application should be directed to the attention of the undersigned at Mylan Pharmaceuticals Inc., P.O. Box 4310, 781 Chestnut Ridge Road, Morgantown WV, 26504-4310. Telephone and facsimile inquiries may also be directed to the undersigned at telephone number (304) 599-2595, extension 6600 and/or facsimile number (304) 285-6407.

Sincerely,

Frank R. Sisto
Vice President
Regulatory Affairs

FRS/dn

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

OCT 20 1999

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

Re: SOTALOL HYDROCHLORIDE TABLETS,
80MG, 120MG, 160MG AND 240MG
NO RELEVANT PATENTS CERTIFICATION

Dear Mr. Spom:

Pursuant to Section 505(j)(2)(a)(vii) of the Federal Food, Drug and Cosmetic Act, Mylan certifies that in it's opinion and to the best of its knowledge, according to the patent information published by the FDA in that document entitled "Approved Drug Products With Therapeutic Equivalence Evaluations" (19th Edition through Cumulative Supplement 6) there are no patents that claim the listed drug referred to in this application.

Mylan further certifies that according to the exclusivity information published by the FDA in the "Approved Drug Products with Therapeutic Equivalence Evaluations" (19th Edition through Cumulative Supplement 6), the referenced product is covered by an orphan drug exclusivity provision which expires on October 30, 1999.

Mylan will market its Sotalol Hydrochloride Tablets, 80mg, 120mg, 160mg and 240mg upon the expiration of the exclusivity provision and approval of this application.

Sincerely,

Dawn Beto

Dawn J. Beto, Esq.
Corporate Counsel

DJB/pp

Enclosures

Department—Fax Numbers
Accounting (304) 285-6403
Administration (304) 599-7284
Business Development (304) 599-7284
Human Resources (304) 598-5406
Information Systems (304) 285-6404
Label Control (800) 848-0463
Legal Services (304) 598-5408
Maintenance & Engineering (304) 598-5411
Medical Unit (304) 598-5445
Purchasing (304) 598-5401
Quality Control (304) 598-5407
Research & Development (304) 285-6409
Sales & Marketing (304) 598-3232

ANDA 75-725

Mylan Pharmaceuticals Inc.
Attention: Frank R. Sisto
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

NOV 30 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.

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

DATE OF APPLICATION: October 20, 1999

DATE (RECEIVED) ACCEPTABLE FOR FILING: October 21, 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) 827-5846

Sincerely yours,

for

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

ANDA 75-725

cc:

Endorsement:

_____date 11/30/99
_____date 11/30/99
_____date

:k

Labeling review drafted 7/26/00 A. Vazza

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

July 19, 2000

NDA ORIG AMENDMENT FPL AC

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

MAJOR AMENDMENT
(CMC AND LABELING INFORMATION ENCLOSED)

RE: SOTALOL HYDROCHLORIDE TABLETS, 80MG, 120MG, 160MG AND 240MG
ANDA 75-725
RESPONSE TO AGENCY CORRESPONDENCE DATED MAY 12, 2000

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above which is currently under review and to the Agency's correspondence pertaining to the review of this application dated May 12, 2000 (provided in Attachment L). In response to the Agency's comments of May 12th, Mylan wishes to amend this application as follows.

CENTER FOR DRUG REC'D JUL 20 2000 OGD

A. CHEMISTRY DEFICIENCIES

FDA COMMENT 1 Your description of the container/closure systems indicated that the

Page(s) 3

Contain Trade Secret, Commercial/Confidential Information and are not releasable.

7/19/00

Pg. 2-4

C. **REGARDING LABELING DEFICIENCIES**

MYLAN RESPONSE: Regarding the labeling deficiencies, Attachment O contains twelve (12) copies of the following final printed bottle labels and outsert for Sotalol Hydrochloride Tablets, 80mg, 120mg, 160mg and 240mg.

BOTTLE LABELS

80mg
Code RM0305A - Bottles of 100 Tablets
Code RM0305B - Bottles of 500 Tablets

120mg
Code RM0310A - Bottles of 100 Tablets
Code RM0310B - Bottles of 500 Tablets

160mg
Code RM0314A - Bottles of 100 Tablets
Code RM0314B - Bottles of 500 Tablets

240mg
Code RM0316A - Bottles of 100 Tablets
Code RM0316B - Bottles of 500 Tablets

OUTSERT

Code SOTA:R1, Revised May 2000

The enclosed labeling incorporates the revisions requested in the Agency's letter of May 12, 2000. A copy of this correspondence is provided in Attachment L for the convenience of the reviewer.

In order to facilitate the review of this labeling, Attachment M contains a side-by-side comparison of the final printed bottle labels to those previously submitted and Attachment N contains a side-by-side comparison of the final printed outsert (SOTA:R1) to the outsert that was previously submitted. It is noted that prior to approval of this application, the Agency may find the color or other factors in the final printed labeling unacceptable and may request further changes to the labeling. In addition, Mylan may have to revise the labeling pursuant to approved changes for the referenced listed drug. Mylan will monitor FDA's website for any approved labeling changes.

As previously noted, the dissolution testing as requested by the Division of Bioequivalence has been incorporated into Mylan's stability and quality control programs. Revised finished product specifications, dissolution procedure and post-approval stability protocols reflecting the Agency's requests are provided in Attachments C, D and E, respectively. This information is also included in Mylan's response to the May 12, 2000 bioequivalency amendment which will be forwarded simultaneously in a separate amendment to this application.

Pursuant to 21 CFR 314.96(b), we certify that a true copy of the technical sections of this amendment, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6600 or via facsimile at (304) 285-6407.

Sincerely,

Frank R. Sisto
Vice President
Regulatory Affairs

FRS/dn

Enclosure

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

DEC 23 1999

ORIG AMENDMENT

N/AB

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

TELEPHONE AMENDMENT

RE: SOTALOL HYDROCHLORIDE TABLETS, 80MG, 120MG, 160MG AND 240MG
ANDA #75-725
RESPONSE TO DECEMBER 23, 1999 TELEPHONE REQUEST

Dear Mr. Sporn:

Reference is made to the Abbreviated New Drug Application identified above, which is currently under review, and to a December 23, 1999 telephone conversation with Ms. Jennifer Fan and Dr. Pradeep Sathe from the Division of Bioequivalence, Office of Generic Drugs concerning the Sotalol Hydrochloride Tablets Post-Prandial *In Vitro* Bioequivalence Study (SOTA-9902). Dr. Sathe requested that Mylan provide information that identifies the cohort specification in the data set. Accordingly, Mylan is amending the referenced application to provide an updated data disk for the post-prandial study (SOTA-9902) that incorporates the cohort identification with the data. In addition, a paper copy of the data provided on the updated disk is provided.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned by phone at (304) 599-2595, ext. 6600, or by facsimile at (304) 285-6407.

Sincerely,

Frank R. Sisto
Vice President
Regulatory Affairs

G:\PROJECT\ANDA\Sotalol-HCl-Tabs\AGENCY-CALL-OF-122399.doc

Department—Fax Numbers		Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Accounting	(304) 285-6403	Label Control	(800) 848-0463	Quality Control	(304) 598-5407
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MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

JAN 18 2000

TELEPHONE AMENDMENT
(Bioequivalence Information Enclosed)

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

ORIG AMENDMENT
N/AB

RE: SOTALOL HYDROCHLORIDE TABLETS, 80MG, 120MG, 160MG AND 240MG
ANDA 75-725
RESPONSE TO AGENCY TELEPHONE CALL OF JANUARY 13, 2000

Dear Mr. Sporn:

Reference is made to the Abbreviated New Drug Application identified above and to the Agency's telephone request of January 13, 2000. During the January 13 telephone call with Ms. Jennifer Fan, it was requested that Mylan repeat the submitted dissolution studies for Sotalol using 900mL of deaerated water at 37°C as the dissolution medium and the paddle method at 50rpm. The Agency requested that Mylan provide comparative dissolution profiles on both the test and reference products for all strengths. Also, the Agency indicated that Mylan needs to provide F_2 values for the mean profiles.

In response to the Agency's requests, the requested dissolution data and F_2 values are provided in Attachments A and B, respectively.

Pursuant to 21 CFR 314.96(b), we certify that a true copy of this amendment, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office.

This amendment is being submitted in duplicate to the above referenced application. Should you have any questions regarding this amendment please contact the undersigned at (304) 599-2595, extension 6600 or via facsimile at (304) 285-6407.

Sincerely,

Frank R. Sisto
Vice President
Regulatory Affairs

FRS/tlr

enclosures

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
JAN 19 2000
OGD

Department—Fax Numbers		Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
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