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APPROVAL PACKAGE FOR:

APPLICATION NUMBER
19-865/S-010

Clinical Pharmacology and Biopharmaceutics Review

Clinical Pharmcology and Biopharmaceutics Review

NDA:	19-865 (SLR-040) SE_8-010
Volumes:	1 – 11 volumes
Compound:	Betapace (Sotalol)
Submission Date:	19 Oct 1999 / 22 May 2000
Sponsor:	Berlex Laboratories, Inc.
Primary Reviewer:	Joga Gobburu and Julie Canal
Pharmacometrics Reviewer:	Joga Gobburu

Background

Sotalol HCl has been previously approved for treating VT and SVT in adults. Thus far formal studies, to characterize the pharmacokinetics and pharmacodynamics of Sotalol, in pediatric patients have not been conducted. The approved label does not contain any information for dosing Sotalol in this population. A written request was issued to the sponsor, by the FDA, to conduct studies in the pediatric population on January 15, 1999. Section 505A of the Federal Food, Drug, and Cosmetic Act (FDAMA) permits certain applications to obtain an additional 6 months of exclusivity, if in accordance with the statute, the sponsor submits requested information relating to the use of the drug in the pediatric population. The exclusivity was granted and it is the label changes that the sponsor proposed that are being reviewed here.

In the present submission the sponsor provides results from two clinical studies to characterize the pharmacokinetics and pharmacodynamics (effects on QTc and RR) of Sotalol in children (neonates, infants, pre-school and school aged). Another study to evaluate the ruggedness of the sotalol syrup preparation (to be given to neonates and infants) was also conducted. The first study was a single – dose (30 mg/m^2 q 8h) study and only sotalol PK were characterized. The second study was a multiple – dose (10, 30, 70 mg/m^2 q 8h) and both PK and PD were characterized.

Results (proposed by the sponsor)

1. **Study 98173:** The BSA normalized doses used in this study led to similar drug exposures in children with a BSA $\geq$ 0.33 m^2. The 4 smallest patients with a BSA < 0.33 m^2 experienced greater drug exposure: increase of 71% in AUC (8934.20 hr x ng/mL), increase of 23% in Cmax (688.09 ng/mL).
2. **Study 98217:** The exposure (based on AUC), adjusted for BSA was similar for children with a BSA $\geq$ 0.33 m^2, whereas children with a BSA < 0.33 m^2 had higher drug exposure at the 3 (10, 30, 70 mg/m^2) dose levels. A concentration – dependent effect on QTc and RR interval was found which could be described using a linear model. It was also proposed that this relationship was age dependent (younger patients are more sensitive to Sotalol).
3. **Study TO 99-01:** The results show that the compounding procedure (preparation of simple syrup of ground Sotalol tablets) is rugged and has acceptable stability.

Overall Comments (for internal purpose)

1. The studies were executed as per the protocol. The data collection methods are acceptable.
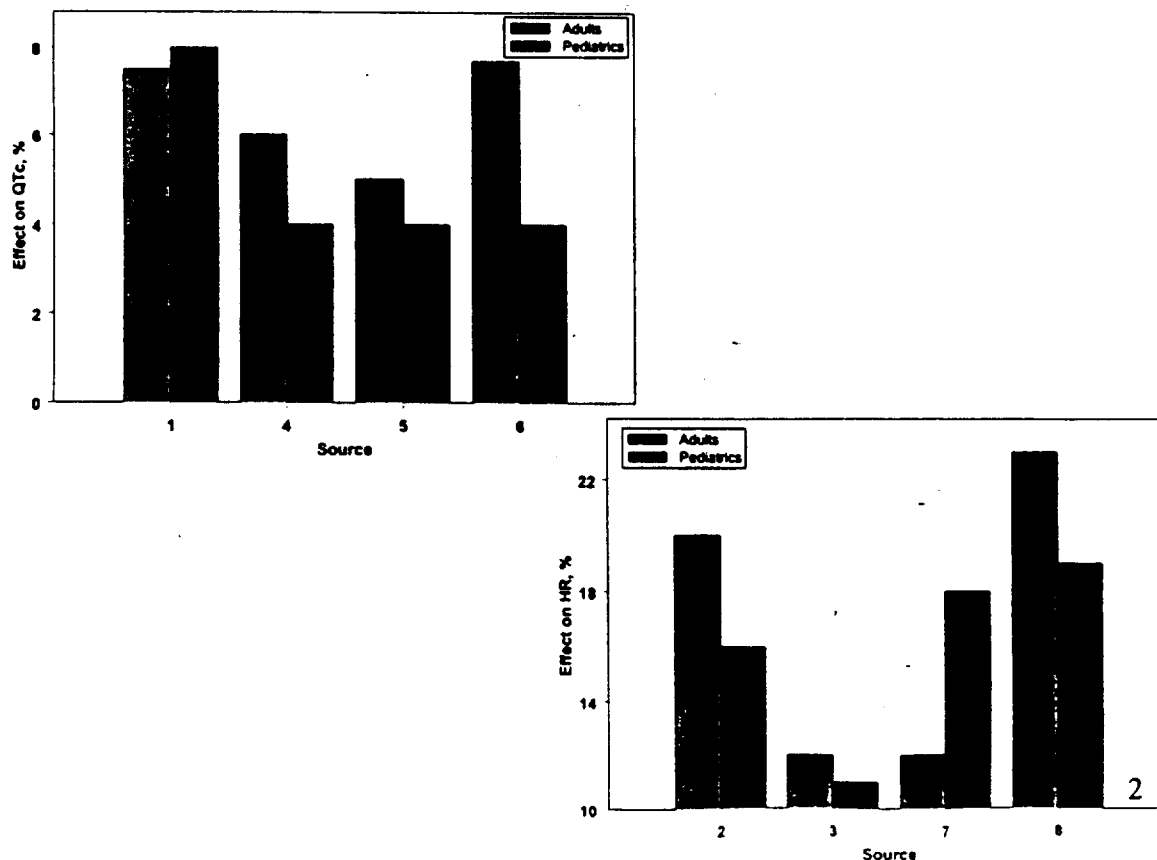
2. The overall approach to data analysis is well done and is commendable. However, the interpretation of the results is debatable. Different interpretation of the results led to revised analysis of the data presented by the reviewer. No attempt to compare the beta-blocking effect to sotalol in pediatrics and adults was made by the sponsor. Infact, the sponsor's model suggests that the baseline HR and slope of the concentration – HR relationship increase with age.

3. The protocol assumes that divided dosing (q 8 h versus q 12 h (adults)) offers a safer manner of administering drugs, in general, although theoretically dosing adjustment can be done according to q 12 h regimen in pediatrics. Clinical experience is limited to q 8 h dosing.

Key points from the reviewer's re-analysis

A detailed summary is provided in the subsequent sections. The key points from the review are enlisted here:

➢ Pharmacokinetics in pediatrics are predictable from that in adults. Primary determinants for prediction are body weight and age.

➢ Pediatrics with age less than 2 yrs need special dosing adjustment.

➢ Extreme caution needs to be exercised when using sotalol in pediatrics with renal impairment (no direct data available for dosing recommendations).

➢ Class III effects in pediatrics and adults are similar (See Figure S1 below).

➢ Beta – blocking effects in pediatrics and adults are, by and large, similar, although not definitive (See Figure S1 below).

Figure S1. Comparison of effects of sotalol on QTc and HR in adults and pediatrics. Please note that only those sources that allowed direct comparison of the effects are shown in this figure. A detailed comparison is presented under the summary section below.

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Summary of reviewer's re-analysis

Detailed information regarding the specific studies, design, analysis and interpretation are provided for each study separately. Only the summary of results / conclusions are discussed here. The summary is organized to answer the following questions:

Q1. Are the exposure – Class III and beta – blocking effect relationships of sotalol in adults and pediatrics similar? (See point #1 below)

Q2. Are the pharmacokinetics of sotalol in pediatrics predictable from from that in adults? (See points#2,3,4,5 below)

Q3. How should the dose adjustment in pediatrics be made (based on body – size, age, etc)? (See points#6)

1. Several sources of data on the Class III and beta-blocking effects of sotalol have been considered to answer the question "Are the effects of sotalol on HR and QTc similar in adults and pediatrics?"

The following is the summary of the pharmacokinetics – pharmacodynamics modeling performed by this reviewer (for additional details please see the pharmacometrics review at the end) based on the data from clinical trials 98173 and 98217 in pediatrics:

Effect of Sotalol on QTc could be described using a linear function:

QTc = 405 [baseline, msec] + 0.0158 [msec/ug/L]*Sotalol concentration [ug/L]. (equation 1)

The inter-individual variability in baseline QTc is about 5% (CV).

Baseline HR decreases with body – weight. Effect of Sotalol on HR interval could be described using an Emax function:

HR = 96 [bpm]*(WT[kg]/20)$^{-0.25}$·(1-0.16[Emax,fraction]*conc[ug/L] /(790[EC50,ug/L]+conc[ug/L])). (equation 2)

Dosing in adults is not adjusted for body – size, hence the doses in mg were transformed to mg/m^2 by dividing the dose by 1.73 m^2. Thus, total daily doses 40, 80, 160, 320, 480, 640 mg correspond to 23, 46, 93, 185, 275 and 370 mg/m^2 respectively.

<u>Source#1</u> (Total Daily Doses = 160, 320, 640, 960 mg; N=17; patients with chronic stable ventricular premature complexes)

Wang et al. Concentration – dependent pharmacologic properties of sotalol. *Am. J. Cardiol.* 1986;57:1160-1165.

Heart Rate: Figure 1 shows the concentration – QTc, HR (exercise induced) relationship for sotalol. The effect of sotalol on HR was described using an Emax function with an EC50 = 809 ug/L and an Emax = 50%. The results from the HR model need to be interpreted with caution owing to fact that the effects were observed after induction via exercise that may be different from that at resting. The sensitivity (EC50) of sotalol for resting and exercised states is similar although the Emax is different. The EC50 estimated from the pediatrics data is 790 ug/L, which is very close to that reported.

QTc: The effect on QTc as depicted in Figure 1 below, is in accordance with the effects observed in pediatrics. For example, a concentration of 2000 ug/L will translate into an effect of about 7.5% by visual inspection of the second panel. The QTc model predicts a change of 32 msec from baseline (=405 msec) or about 8% change.

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<u>Source#2</u> **(Total Daily Doses = 1 mg/kg Infusion; N=8; patients with symptomatic or documented arrhythmias, both SVT and VT in origin)**
McComb, JM et al. *J. Am. Coll. Cardiol.* 1987;10:211-217.

Heart Rate: Figure 2 shows the dose – response relationship. Unfortunately, the graphs in Figure 2 are plotted with treatment on the x-axis instead of concentration, which would have been more meaningful. In Figure 2, at the MAX (maximum tolerated) dose there is about 20% reduction in the HR (resting). This matches with the estimated 16% reduction in HR in the 2 submitted trials.

QTc: The results in Figure 2 are shown only for QT and not for QTc. Hence these results were not considered for comparison.

<u>Source#3</u> **(Dosing = Bolus infusion of 0.5 mg/kg over 15 min, followed by loading infusion of 0.6 mg/kg/hr over 1 hr and maintenance infusion of 0.2 mg/kg/hr; N=11; patients with acute MI)**
Study# 1633, Page 33 of the original medical review.

Heart Rate: The mean plasma concentration achieved was about 1750 ug/L, as shown in Figure 3. The graph showing the time course of HR suggests that effects mimic the time course of concentrations, hence no delay. The treatment effect is about –10 bpm (changes from baseline), or 12% if assume a mean heart rate of 80 bpm. The effect predicted by the reviewer's HR model is 11%, which is in good agreement with that in adults.

QTc: The effect of sotalol on QT were provided and not those on QTc. Hence these results were not considered for comparison.

<u>Source#4</u> **(Dosing = 80, 160, 320 mg; N=10; healthy volunteers)**
Coz, FL, et al. Prediction of sotalol-induced maximum steady-state QTc prolongation from single-dose administration in healthy volunteers. Clin. Pharmacol. Ther. 1992;52:417-26.

Heart Rate: No heart rate measurements were reported in this study.

QTc: Figure 4 shows the concentration – QTc (peak response) relationship. Unfortunately, the parameter estimates of the linear model were not reported by the authors. Mere extrapolation of the line in Figure 4, offers a baseline QTc value of about 380 msec, which this reviewer believes to underestimate the baseline QTc value. Based on previous experience, a baseline value of 400 msec was used to calculate the effect. Visual inspection of the graph suggests a change of about 25 msec (6%) for a concentration of 1000 ug/L which is in accordance with that predicted by the reviewer's model (16 msec or 4%) for the pediatric population. The model estimated measurement error is about 5% of the QTc value.

<u>Source#5</u> **(Dose = 40, 80, 160 mg; N=18; Healthy Japanese males)**
Heart Rate: No HR measurements were reported.

QTc: Figure 5 shows the concentration – QTc relationship. Visual inspection of the graph suggests a change of 5% at a concentration of 1000 ug/L. The reviewer's model for the pediatric data predicts a change of 16 msec or 4% change, which is similar to the above value for adults.

<u>Source#6</u> **(Doses = 160, 320, 640 mg; N=10; Healthy males)**
Heart Rate: Effects on exercise-induced were measured. No measurements on resting HR were performed. Hence these results were not considered for comparison.

QTc: Figure 6 shows the concentration – QTc relationship. Fortunately, the parameter estimates of the linear model correlating sotalol concentrations and % QTc change from control were

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provided which indicate a slope of about 0.0077 % change per ug/L. According to this report, a concentration of 1000 ug/L elicits a change of 7.7%. The reviewer's model for the pediatric population a change of 4%, similar to the previously reported value.

Source#7 (Doses = 320, 640 mg; N=100 assessed; patients with frequent and repeated ventricular ectopic activity)
Study# 1717, 1718, 1767, 1809, 2062; Page 42 of the original medical review.

(See under source#8 for discussion)

Source#8 (Doses = 40, 160, 320, 640 mg; N=70 assessed; patients with premature ventricular contractions)

The **interpretation of** changes due to treatment as calculated from baseline (as is the case for the current submission and all previous sources) may not be similar to that calculated from a placebo group (as is the case for sources #7 and #8). Further, the comparisons are limited to doses and not concentrations. This is an important aspect to consider as adults received a bid regimen while the pediatrics received a tid regimen.

Results from the previous medical review of the original NDA of Betapace in adults are given in Tables 1 and 2. The summary statistics from the pediatric studies is given in Table 3.

Heart Rate: The values in Table 2 for a dose of 160 mg which is equivalent to about 90 mg/m^2 (based on a person with BSA=1.73 m^2) are –18% and –12.3% for pediatrics and adults, which are similar. Similarly, for a dose of 320 mg (or 185 mg/m^2) in adults and 210 mg/m^2 in pediatrics, the change in HR is –23% and –19%, respectively.
QTc: The effect of sotalol in pediatrics seems to be higher in pediatrics for similar doses. The coefficient of variation is about 100%.

Source#9 (Doses = 80 – 480 mg; N=83 to 336 per dose group; SVT patients across various studies)
Report No. SNYD-BJ-25197 (integrated safety summary) (cited in the current submission to compare pediatrics with adults)
Heart Rate: No data on HR was provided.
QTc: Table 4, provided by the sponsor, indicates that similar doses in adults and pediatrics elicit similar responses. The adult data is derived from a bid regimen and the pediatric data was derived from a tid regimen. Though the overall exposure should be the same given the same total dose, the range of concentrations will not be the same. Adults, because of higher doses, will have higher concentrations. Figure 7 shows the dose – response data for adults and pediatrics. The data seemingly tend towards an asymptote while one would the area under the effect curve to keep increasing with increasing doses (sotalol is not known to exhibit an inverse U shape concentration – effect curve). The concentration – effect curve from the reviewer's analysis seems to be in the linear range, hence the comparison is reasonable.

Source#10 (Doses = 160, 240, 320 mg/day; N = 200; patients with prior symptomatic atrial fibrilation or flutter)

Heart Rate: The % change in HR after 160 mg/day dose in pediatrics is slightly higher than that for the adults (Table 5). But after 320 mg/day dose the effect seems to be similar in both the populations. The limitation of this comparison is the lack of time of data collection. Responses were measured at random time points.

Qtc: The %change in QTc is also higher in pediatrics than in adults at both the doses studied (Table 5). The same limitation as discussed for HR applies here too.

The sponsor proposed a PK/PD model for: (1) RR – interval in which both the intercept (baseline) and slope (sensitivity) were directly proportional to age and (2) effects on QTc in which the intercept was different for males and females. Essentially, these models indicate that the sensitivity of sotalol for the effects on RR – interval is different in pediatrics and adults and that on QTc is similar in pediatrics and adults.

Overall, evidence from the above sources demonstrates that the Class III and beta – blocking effects of sotalol in adults and pediatrics are not very different. The evidence that the Class III effects are similar in adults and pediatrics is stronger than that for the beta-blocking effects. An important point to note is that the effect on HR interval is not very different among the 4 age groups studied. Should there be a difference between the adults and pediatrics, one can expect to see differences in effects on HR between neonates and school-going children.

Note to the Medical Reviewer: The differences in the patient populations studied under each source need to be taken into account. Such a consideration should allow a more thorough comparison of effects in pediatrics and adults.

Figure 1. Concentration – effect relationships of sotalol. The effects on HR were measure after exercise. Ref: Wang et al. Concentration – dependent pharmacologic properties of sotalol. *Am. J. Cardiol.* 1986;57:1160-1165.
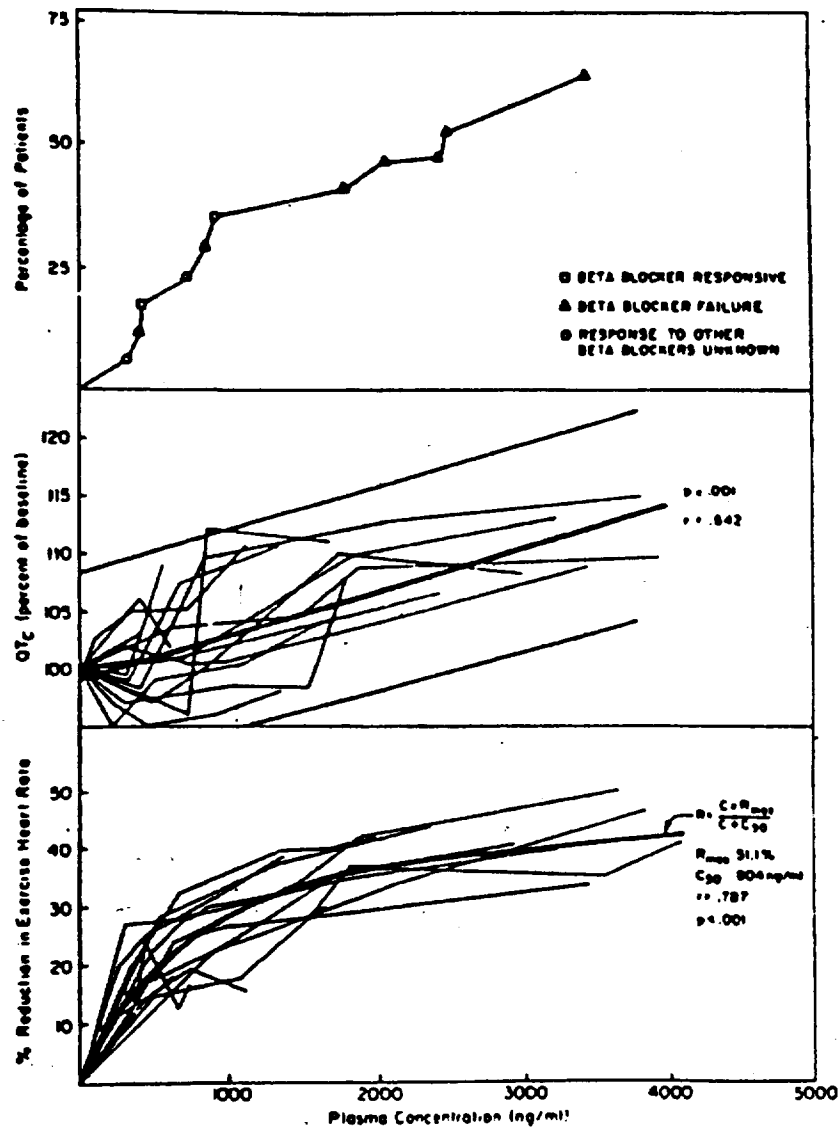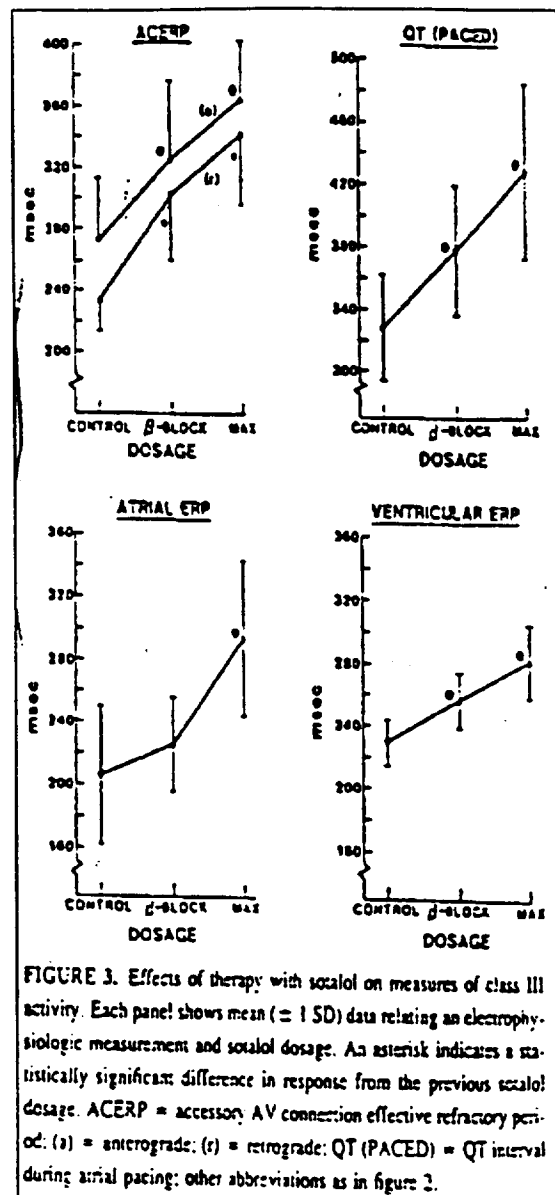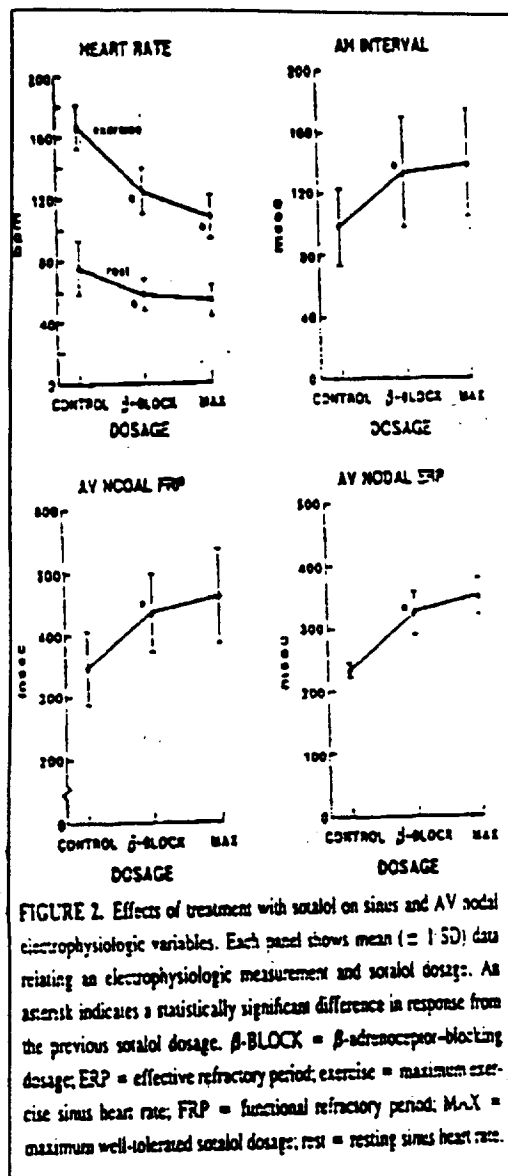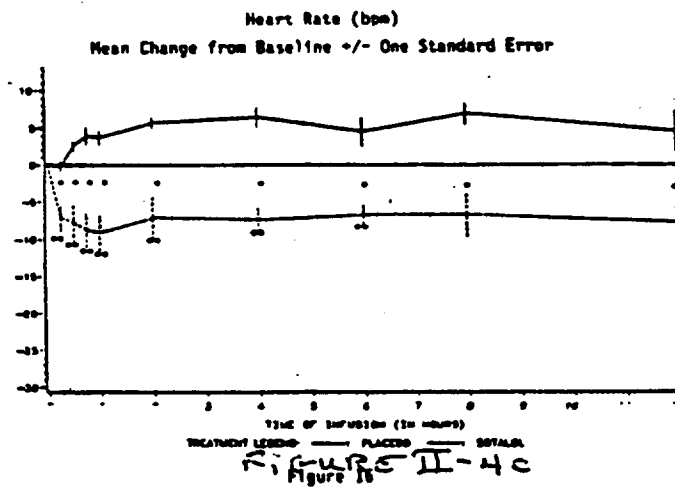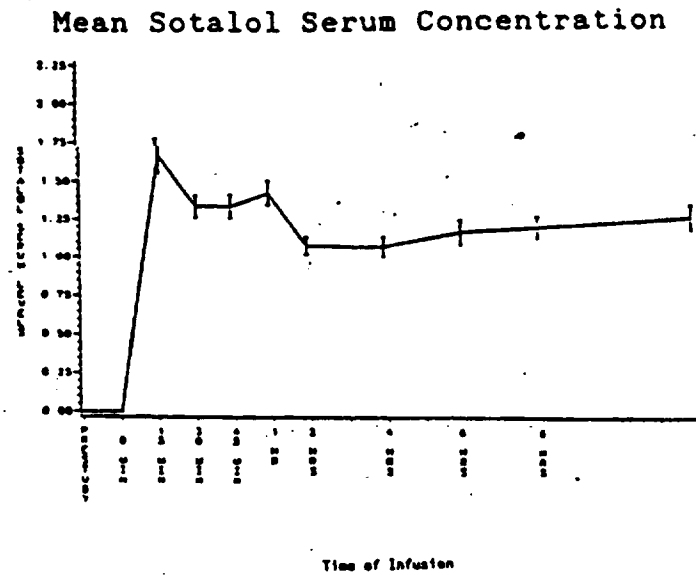
Figure 2. Treatment effect on heart rate (top left panel) after 1 mg/kg infusion. Reference: McComb, JM et al. *J. Am. Coll. Cardiol.* 1987;10:211-217.

FIGURE 2. Effects of treatment with sotalol on sinus and AV nodal electrophysiologic variables. Each panel shows mean (= 1 SD) data relating an electrophysiologic measurement and sotalol dosage. An asterisk indicates a statistically significant difference in response from the previous sotalol dosage. β-BLOCK = β-adrenoceptor-blocking dosage; ERP = effective refractory period; exercise = maximum exercise sinus heart rate; FRP = functional refractory period; MAX = maximum well-tolerated sotalol dosage; rest = resting sinus heart rate.

FIGURE 3. Effects of therapy with sotalol on measures of class III activity. Each panel shows mean (= 1 SD) data relating an electrophysiologic measurement and sotalol dosage. An asterisk indicates a statistically significant difference in response from the previous sotalol dosage. ACERP = accessory AV connection effective refractory period; (a) = anterograde; (r) = retrograde; QT (PACED) = QT interval during atrial pacing; other abbreviations as in figure 2.

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Figure 3. Time courses of concentrations and HR change in patients given sotalol as an infusion (See source#3 for details).

Figure II-1

Mean Sotalol Serum Concentration

Time of Infusion

Heart Rate (bpm)
Mean Change from Baseline +/- One Standard Error

TIME OF INFUSION (IN HOURS)
TREATMENT LEGEND —— PLACEBO —— SOTALOL

Figure II-4c

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Figure 4. Concentration – QTc relationship. Data from source#4.

Figure 5. Concentration – QTc data from source#5.

Figure 6. Concentration – QTc relationship based on data from source#6.

$$\Delta QT = 0.0077 C_p + 0.34$$
$$r = 0.846$$
$$p < 0.001$$

QTc prolongation (% from control)

Sotalol [Cp] (ng/ml)

FIGURE 3. *Plot of percent QTc prolongation as a function of sotalol plasma concentration. Linear fit and 95% confidence interval for prediction in an individual are shown.*
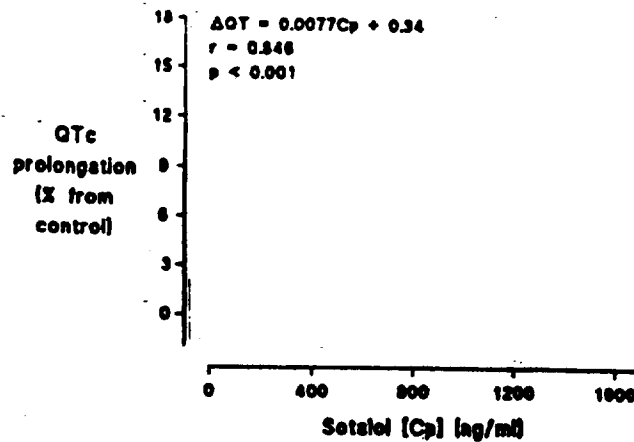
Table 1. Mean HR and QTc (change from placebo) absolute responses at 2 hr after dosing at steady state, from the previous medical review. Ref: Page 68, Table III-17, medical review of NDA 19-865 for adults.

%Change	HR	QTc
320 mg	-23.3	3.8
640 mg	-30.1	4.5

Table 2. Mean placebo corrected HR and QTc effects from the previous medical review. Ref: Page 127, Table III-59, medical review of NDA 19-865 in about 20 adults. (*Treatment responses from column entitled 'assessment' were used*).

%Change	HR	QTc
40 mg	-9.6	-2.35
160 mg	-12.3	0.95
320 mg	-23.1	4.25
640 mg	-28	3.47

Table 3. Summary statistics of the effects of sotalol on HR, QTcB 2 hr after dosing (at Tmax) in 20 pediatric patients. The total daily doses are also provided. (page 86 and 94 of vol.6)

%Change	30 mg/m²	90 mg/m²	210 mg/m²
Mean (HR)	-14	-17.6	-18.6
SD	9	11	10
Mean (QTc)	5.7	8.9	13.6
SD	4	4	7

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Table 4. Mean effect on QTc (expressed as area under the curve over time) in adults (Report no. SNYD-BJ-25197) and pediatrics (current submission).

Text Table 13: Comparison of the Dose-Response Relationship for the Class III Effect of Sotalol in Pediatric and Adult Patients. Traditional Approach

	Dose[a] mg/m²	Daily Dose mg/m²	ΔAUEss/Time[b,c] msec
Adults	23.1	46.2	11
	46.3	92.5	15
	92.5	185.0	28
	138.8	277.5	34
Children	10.0	30.0	2
	30.0	90.0	14
	70.0	210.0	29

[a] Adults on a q12 h regimen, children on a q 8 h regimen
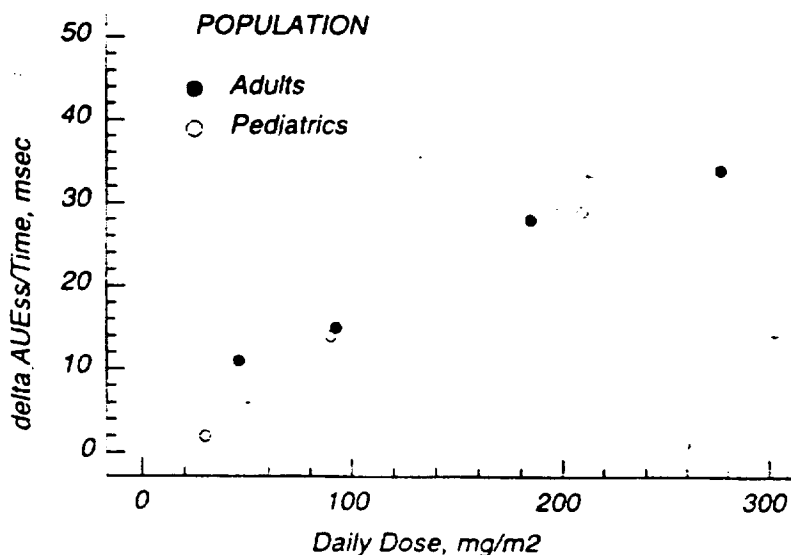[b] For children, Report No. 99009
[c] For adults, Report No. SNYD-BJ-25197, p 122

Table 5. Mean effect (at presumed steady-state and at random time) in adults (study 05).

%Change	HR	QTc
Placebo	4	0.62
160 mg/day	-11	2
240 mg/day	-17	3
320 mg/day	-20	6

Figure 7. Daily dose vs. change in area under the QTc effect curve for adults and pediatrics.

Figure 10: Comparison of ΔAUEss(QTc)/Time Values in Adult Patients on a q12 h Regimen and Pediatric Patients on a q 8 h Regimen. Traditonal Approach, PK-PD Study

POPULATION
● Adults
○ Pediatrics

delta AUEss/Time, msec

Daily Dose, mg/m2

2. Overall, the pharmacokinetics in pediatrics are predictable from PK in adults. The clearance increases with body – size and age in a nonlinear fashion and volume of distribution increases with body – size in a linear fashion. The terminal half – life of sotalol in pedatrics is about 9 hr, for all age groups (including adults).

3. Considerable portion of the observed inter-individual variability can be explained by body weight and age (or serum creatinine). The following formula is recommended for use: Clearance (L/h) = 2 ·(WT/20)$^{0.78}$ · (1 + AGE/(0.1+AGE))   (equation 3)

For example, a 1 yr old child weighing 3 kg will, according to the above formula, exhibit a clearance of about 0.87 L/h and thus a total daily starting dose of 5.22 mg. A 0.08 yr child weighing 3 kg will exhibit a clearance of about 0.66 L/h and thus a total daily starting dose of 3.9 mg. The capacity of the kidney function increases with increasing age (until about 2 yr). Hence the 0.08 yr neonate should be dosed less. The recommended formula is reasonable and will be a more conservative approach to dosing sotalol. A linear function to adjust for body – size will offer doses that might be higher than those predicted by the above suggested nonlinear function with weight as a covariate. Practicality in measuring the dose and preparation of the simple syrup needs to be taken into account should this formula be included in the label.

4. In case of renal impairment initial dose can be derived using the following formula: Clearance (L/h) = 4 ·(WT/20)·e$^{-1.2\,SCR}$ (where SCR stands for serum creatinine in mg/dL) (equation 4)

For example, a 1 yr child weighing 10 kg and having an SCR of 0.4 mg/dL will exhibit a clearance of 1.24 L/h, while a 10 kg child with SCR = 0.2 mg/dL will exhibit a clearance of 1.57 L/h. The higher the serum creatinine, than expected, the lower the kidney function. It is important to note that no studies to characterize the PK of sotalol have been conducted in pediatrics with renal impairment. However, some standard for calculating the initial dose in renal impaired children is necessary. The recommended formula is reasonable and will be a more conservative approach to dosing sotalol.

5. It should be noted that using WT adjusted dosing may not offer any great advantage over BSA adjusted dosing. Nevertheless, one model needs to be chosen. There are two criteria for selecting the appropriate model, from a practical stand point: 1) physiological / statistical reasoning and 2) prior experience with using BSA adjusted dosing in the 2 trials submitted. While physiologically both BSA and WT reflect the variation in body – sizes among the patients, statistically the model with WT performs moderately better than the BSA model. The second criterion is rather a weak one since both BSA and WT essentially serve the same purpose. The modeling exercise suggests that the clearance is not related to BSA in a linear fashion but it is in a nonlinear fashion, as opposed to the per - m^2 dosing proposed by the sponsor.

6. **Illustration of dose calculation:** Total daily dose = Average Steady-State Concentration ·48·(WT/20)$^{0.78}$·(AGE/(0.1+AGE)) (equation 5). For example, the average steady-state concentration from the PK study was about 250 ug/L (Cmax,ss=350, Cmin,ss=186 ug/L after a dose of 30 mg/m^2). Thus the total daily dose would be 35 mg for subject # 47004 (subject #s are those used for NONMEM analysis) (AGE=11.67 yr, WT=32.6 kg, BSA=1.12 m^2) or 11.7 mg q 8h. For this patient, a per m^2 BSA dosing would result in a total daily starting dose of 34 mg, which is very similar to that resulting from the above formula. On the other hand, for subject #

37001 (AGE=0.011 yr, WT=9.9 kg, BSA = 0.17 m²), the total daily starting dose to achieve a steady – state concentration of 250 ug/L would be 7.5 mg or 2.5 mg t.i.d. Whereas using the per m² BSA dosing, the starting dose would be 5 mg t.i.d, which is twice that calculated using the WT and AGE. Two times increase in the concentrations (within the range of concentrations studied in study#98217) will produce 2 times higher change in the QTc interval. Purely body – size adjusted, that too in a linear fashion, dose calculation would not allow for differentiation based on AGE, especially for the neonates. **For patients below 2 yrs, the above formula (equation 5) offers a more precise estimation of the starting dose.**

Comments on suggested label changes (in bold) (refer to Appendix on page 24 for proposed changes):

1. The effect of Sotalol on QTc, has been shown by the sponsor and the reviewer, is related to the concentration in a linear fashion. Hence there is a continuous dependence of QTc change on Sotalol plasma concentration. It is not clear what the sponsor implies by "*electrophysiological effects seen at daily doses of 210 mg/m²...*". No target or therapeutically relevant change in QTc has been identified. Hence the first label claim should be changed to the following instead: (***Clinical Pharmacology / Mechanism of action***)

DRAFT

2. The second label claim deals with differences in PD between the two groups based on BSA. The proposed wording suggests that the difference in QTc and RR is due to pharmacodynamic differences. But no relationship of the sensitivity of Sotalol with age and/or body – size could be established. The higher effects in patients with BSA<0.33 m² are due to the higher concentrations and not due to higher sensitivity. Hence the second label claim should be changed to the following instead: *(Clinical Pharmacology / Electrophysiology)*

Draft

3. An average person reading the label may not be conversant with the word 'first – order'. While 'linear' also may not be too widely known, the intention might be clearer. The word 'rapid' is relative and to this reviewer Tmax occuring at 2 – 3 h is not rapid, further it adds little to the use and understanding to the drug. Body weight and age were found to be the most important covariates to describe PK. The younger patients showed higher exposure than the older ones, even after body – size adjustments. It is not clear what ' uniform concentration profile' means – hence deleted. The third label claim should be changed to: *(Pharmacokinetics)*

Draft

4. Label change #4 is acceptable.
5. Deferred to the medical reviewer.
6. *(Dosage and Administration) <u>Children:</u> As in adults the following precautionary measures should be considered when initiating sotalol treatment in children: initiation of treatment in the hospital after appropriate clinical assessment; individualized regimen as appropriate; gradual increase of doses if required; careful assessment of therapeutic response and tolerability; and frequent monitoring of the QTc interval and heart rate. (next para)*

Draft Labeling

7. Label change #7 is acceptable.
8. Label change #8 is acceptable.

Recommendation:

The conduct of the studies is acceptable to the Office of Clinical Pharmacology and Biopharmaceutics. The results, interpretation, and label claims need revision as discussed by the reviewer under relevant sections. The proposed labeling revisions (as presented above) should be implemented by the sponsor.

/S/

Jogarao V.S. Gobburu, Ph.D   17 Aug 2000

RD/FT initialed by Patrick Marroum Ph.D.
Cc list: NDA 19-865, HFD 110, HFD 860 (Mehta, Gobburu), CDER Document room

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<u>Study Title (Study #98173):</u>

Pharmacokinetics of sotalol in a pediatric population with ventricular and supraventricular tachyarrhythmias analyzed by the traditional 2-stage approach.

<u>Study Sites and Investigators:</u>

The study was performed in 24 sites.

Dianne Atkins, MD	University of Iowa Iowa City, IA
Lee Beerman, MD	Children's Hospital Pittsburgh, PA
David Chan, MD	c/o Pediatric Clinical Trials Children's Hospital Columbus, OH
Macdonald Dick, MD	University of Michigan Hospital Ann Arbor, MI
Michael R Epstein, MD	Children's Hospital Medical Center Cincinnati, OH
Christopher Erickson, MD	Arkansas Children's Hospital Little Rock, AR
Frank A Fish, MD	Vanderbilt University Nashville,TN
Steven Fishberger, MD	St. Joseph's Children's Hospital Paterson, NJ The Mount Sinai School of Medicine Clinical Research Center New York, NY
Richard Friedman, MD	Texas Children's Hospital Houston, TX
J Edward Hulse, MD	Children's Mercy Hospital Kansas City, MO
Ronald J Kanter, MD	Duke University Medical Center Durham, NC
Peter Karpawich, MD	Children's Hospital of Michigan

Detroit, MI

Robert Pass, MD

New York Presbyterian Hospital-
Columbia Presbyterian Medical Center
New York, NY

Bertrand Ross, MD

Children's Hospital of the King's Daughters
Norfolk, VA

J Philip Saul, MD

The Children's Heart Center of South Carolina
Charleston, SC

Michael Schaffer, MD

The Children's Hospital
Denver, CO

William Scott, MD

University of Texas Southwestern
Medical Center
Dallas, TX

Margaret J Strieper, DO

The Children's Heart Center
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Ronn Tanel, MD

Children's Hospital of Philadelphia
Philadelphia, PA

John Triedman, MD

Children's Hospital
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George F Van Hare, MD

Pediatric Cardiology
Stanford University School of Medicine
Palo Alto, CA

Frank Zimmerman, MD

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University Hospitals of Cleveland
Cleveland, OH

Objective:

The study objective was to evaluate the pharmacokinetics of Sotalol following a single dose of Sotalol HCl administered orally in solution to a pediatric population in the age range from neonates to children 12 years old. An additional goal of the study was to determine the covariates impacting the pharmacokinetics of Sotalol.

Study Design:

This was a multi-center, open-label, 1-period, single dose study. Patients were hospitalized during the course of the study (for 1 to 2 nights from Sotalol HCl dosing to the evening after collection of final specimen and recording of the vital signs) and received a single dose of 30 mg/m² body surface area (BSA) orally. The treatment and observation period was clocked from time 0 (Sotalol HCl dosing) to 36 hours after dosing (time of the last blood sample).

Blood samples were collected from patients for drug concentration measurement at the following times: 30 minutes, 1, 2, 3, 5, 8, 12, 16, 22, and 36 hours postdose. The drug concentrations were measured by a ━━━ method. Safety was assessed by ECG telemetry, clinical laboratory tests, physical examinations, vital signs, 12-lead ECG measurements, and monitoring of adverse evens.

A total of 34 patients were enrolled in the study. Of these, 33 (97%) patients completed the study: 2 neonates (≤ 1 month), 8 infants (>1 to ≤ 24 months), 6 children >2 to <7 years, 17 children ≥7 to 12 years. The study included patients of any race and sex, with ventricular tachyarrhytmias (VT) or supraventricular tachyarrhythmias (SVT) and who required therapy.

Patients who had congestive heart failure NYHA class III or IV, acquired or inherited long QT syndrome (QTc ≥ 460 msec for patients older than 7 days of age and QTc≥ 480 msec for patients younger than 7 days of age) were excluded from the study.

Test Product:

d,l-Sotalol hydrochloride solution; an extemporaneously compounded formulation was prepared by adding 5 tablets (120 mg each) of Betapace® to 120 mL Simple Syrup (containing 0.1% sodium benzoate) for a final concentration of 5 mg/mL after disintegration.

Batch number: Betapace® (d,l-Sotalol hydrochloride) tablets: CL-2328
                 Simple Syrup: CL-2310

Dose Regimen:

30 mg/m2 body surface area (BSA) d,l-Sotalol HCl, single oral dose.

Analytical Methodology:

The drug concentrations were analyzed by ━━ using a 、 ━━━━
━ runs were conducted to validate the method. Due to ━━━━ problems encountered in the ━━ ' runs using a ━━━━━━━..., the method was cross-validated using a 、━━━━━━━ in the ━━ analytical validation run. '

- Specificity: ι ▬▬
- Calibration curve:
  - limit of quantitation: ▬ng/mL
  - linearity: ranges from ▬ ι ng/mL ˌ ▬)
- Precision and inter-run variability: ranges from ˸ ▬ % CV
- Accuracy of dilution: ▬ % CV
- Stability ▬▬▬ ˸ ▬▬ · stability ranging from ▬ ˵ ▬% CV, ▬▬▬
  stability ranging from ▬ % CV, room temperature stability ranging from ▬▬˥% CV.
- Acceptance criteria:
  - calibration standards: at least ▬% of the individual standards must ▬▬▬
    ▬ ˥% of the nominal concentrations. Each run will include standards assayed in
    ▬ ˋor ▬ concentrations covering the range of ▬ to ▬ng/mL.
  - quality control samples: predicted concentrations of at least · ▬ of the quality control
    samples must be ▬ ˙% of the nominal concentrations.

Methods

All pharmacokinetic analysis was conducted using non – compartmental methods. The data were also analysed using model dependent approach, whose review can be found in the section 'Pharmacometrics Review'.

Results

Demographics:
The data from 33 (97%) of the 34 enrolled patients were analyzed for PK parameters. There were 16 females and 17 males. The racial distribution was 4 Blacks, 27 Caucasians, and 2 Hispanics. 30 patients had SVT only, 2 patients had VT only, and 1 patient had both VT and SVT.

Pharmacokinetics:
The following parameters of Sotalol were obtained with standard model independent methods: Cmax, Tmax, AUC (0-tlast) (total area under the drug concentration time curve measured from time zero to the last data point), λz (rate constant of apparent terminal disposition phase), $t1/2_{\lambda z}$, AUC (total area under the drug concentration time curve measured from time zero to infinite time), CL/F, $V_{\lambda z}/F$.

Figure 8. The mean Sotalol plasma concentration profile vs time for the 4 age groups.

Figure 1-0: Mean (±SD) Plasma Sotalol Concentration (ng/mL) vs Time (Hours)
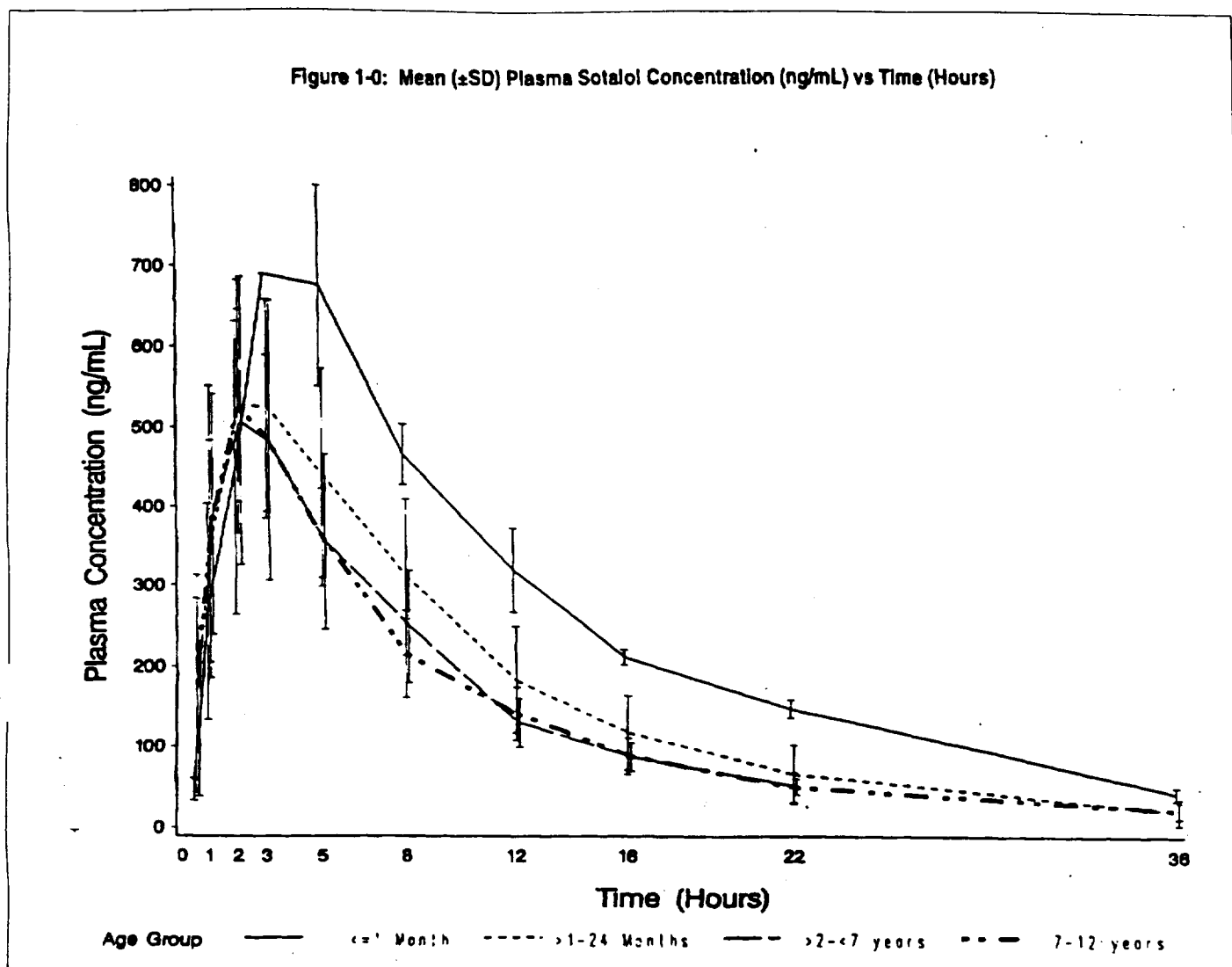
Table 6. Summary Statistics of Pharmacokinetics Parameters and Demographics.

Parameters	Statistics	≤ 1 Month (N=2)	> 1-24 Months (N=8)	>2 - <7 Years (N=6)	7 – 12 Years (N=17)	All Patients (N=33)
Weight	Mean	3.6	8.0	17.2	31.1	21.3
	SD	1.2	2.7	3.9	10.0	13.1
BSA (m²)	Mean	0.23	0.40	0.70	1.07	0.79
	SD	0.04	0.10	0.12	0.22	0.36
CLcr (mL/min/1.73m²)	Mean	54	106	141	136	124
	SD	7	36	28	25	35
Cmax (ng/mL)	Mean	726.21	584.75	527.50	568.68	574.64
	SD	52.22	121.65	178.02	138.23	140.4
	CV%	7.19	20.80	33.75	24.31	24.44
Tmax (hr)	Mean	4.02	2.52	2.33	2.77	2.70
	SD	1.44	1.18	0.52	1.20	1.13
	CV%	35.80	46.88	22.13	43.48	41.83
AUC (hr * ng/mL)	Mean	9492.15	6162.61	5219.82	5153.7	5673.28
	SD	435.86	1612.35	1196.42	919.39	1540.84
	CV%	22.94	44.59	33.77	33.37	57.18
CL/F (mL/min)	Mean	10.74	31.65	63.38	995.23	68.91
	SD	2.46	14.11	21.40	31.78	39.40
	CV%	22.94	44.59	33.77	33.37	57.18
$t1/2_{\lambda z}$ (hr)	Mean	8.40	7.37	9.11	9.22	8.70
	SD	0.27	1.84	2.89	2.96	2.65
	CV%	3.26	24.99	31.66	32.05	30.48
$V_{\lambda z}$/F (L)	Mean	7.79	19.59	49.91	76.45	53.68
	SD	1.54	7.90	22.59	39.90	39.87
	CV%	19.76	40.33	45.26	52.19	74.27

Pharmacokinetic results by age group are provided in Table 6 above.

- Sotalol is absorbed with peak concentrations occurring from 2.33 to 4.02 hours following administration.
- Sotalol is eliminated with a similar mean half-life ranging between 7.37-9.22 hours in the four age groups.
- There are statistically significant linear correlations between CL/F or $V_{\lambda z}$/F and BSA, BW or age. The best predictor is BSA for CL/F and BW for $V_{\lambda z}$/F.
- There is a statistically significant linear correlation between CL/F and CLcr (r^2=0.831, p<0.0001).

- The BSA normalized doses used in this study led to similar drug exposures in children with a BSA $\geq$ 0.33m^2. The 4 smallest patients with a BSA < 0.33m^2 experienced greater drug exposure: increase of 71.0% in AUC (8934.20 hr x ng/mL), increase of 23.1% in Cmax (688.09 ng/mL). Table 7 shows the effect of BSA on Cmax and AUC.

Table 7. Summary of statistics of Cmax and AUC by BSA (<0.33 and >=0.33 m^2)

Parameters		BSA <0.33	BSA ≥0.33
Cmax (ng/mL)	N	4	29
	Mean	688.09	558.99
	SD	134.54	138.05
	CV%	19.55	24.34
	Median	726.21	590.02
	Minimum		
	Maximum		
AUC (hr * ng/mL)	N	4	29
	Mean	8934.20	5223.50
	SD	713.51	964.47
	CV%	7.99	18.46
	Median	8887.37	5278.54
	Minimum		
	Maximum		

Conclusions:

In the 4 pediatric age groups tested (neonates, infants, children >2-<7 years old and children ≥7-12 years old) receiving a single oral dose of 30 mg/m^2 Sotalol HCl using an extemporaneous formulation, the drug was absorbed with peak concentrations occurring on average 2 to 3 hours following administration and then eliminated with a similar $t1/2_{\lambda z}$ value in all 4 age groups.

The 2 neonates and the 2 smallest infants with BSA <0.33 m^2 showed a marked increase in AUC and a less pronounced increase in Cmax compared to older children. The empirically modified dosage regimen applied in this study, which assumes a direct proportional relationship between CL/F and BSA, may not be adequate for the smallest children with the BSA < 0.33 m^2. The pharmacodynamics of Sotalol will have to be taken into account before considering a potential dose adjustment in the smaller children.

The combined effects of congestive heart failure (NYHA Class I or II) and digoxin treatment or the ablation procedures and associated drug administrations appeared not to impact importantly the PK of Sotalol in children. However, these conclusions are based on very few data.
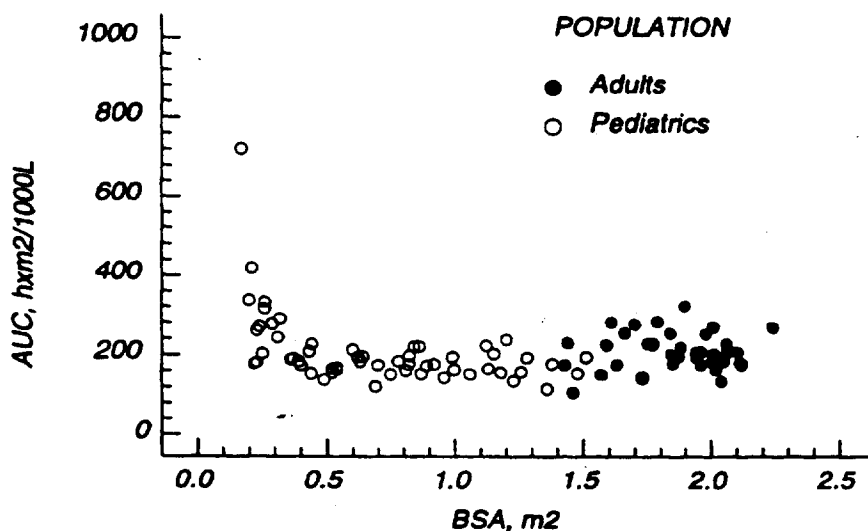
The pharmacokinetics of Sotalol in children with renal impairment have not been investigated. From the observed dependence of CL/F on CLcr and the increase in drug exposure in the smallest

patients, it may be assumed that sotalol is mainly eliminated by the kidney, like in adults. Therefore extreme caution should be exercised if using sotalol in children with renal impairment.

According to the Written Request, as the minimum of 6 neonates required for this PK study was not achieved, Berlex has merged the PK data from the PK study and the PK/PD study and used a population kinetic approach to characterize the PK parameters of Sotalol in each patient.

Reviewer Comments:

1. The pharmacokinetics of Sotalol in children with renal impairment have not been investigated.
2. The systemic clearance and volume of distribution of Sotalol clearly are dependent on BSA, body weight and/or age. Neonates and infants with BSA < 0.33 m^2 seem to exhibit clearances lower than body size adjusted clearances. This probably could be due to the maturing kidney function in neonates and infants. Hence, it is not BSA being less than 0.33 m^2 that might be the determinant but it is age-dependent. Quantitative relations of the covariates with PK parameters are discussed in detail in the pharmacometrics review. The values of the final PK parameters from the pharmacometrics review should be used.
3. The graph below provided by the sponsor shows a trend in the dose-, BSA-adjusted AUC of

Sotalol with BSA. Should body-size alone explain the variability in the drug exposure then the AUCs vs. BSA would be flat (slope = 0). However, the above graph shows a trend towards the lower BSA values. Hence the variability is probably due to some other demographic feature such as age. It is known in medical literature that it takes about 2 y of age in pediatrics for the kidney function (based on GFR) to match that of adults. BSA < 0.33 m^2 fits well with this age group.

4. There is too little evidence to conclude on the implications of CHF on the PK of Sotalol. Nevertheless, it is believed that CHF alters Sotalol PK in adults. The current approved labeling has no mention of effects of CHF on Sotalol PK.

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<u>Study Title (Study #98217):</u>

Pharmacokinetics and pharmacodynamics of sotalol in a pediatric population with ventricular and supraventricular tachyarrhythmias analyzed by the traditional 2-stage approach.

<u>Study Sites and Investigators:</u>

The study was performed in 21 sites.
The list of the investigators who participated in the study is available in Appendix A.

<u>Study Objectives:</u>

The objectives of the study were to delineate:
1. the relationship between the dose or plasma concentration of sotalol and QTc (baseline uncorrected and corrected)
2. the relationship between the dose or plasma concentration of sotalol and the heart rate (baseline uncorrected and corrected) at rest in a pediatric population.

The study data were intended to support derivation of a dosage guidance for d,l-sotalol use in the pediatric population.

In addition, the multiple dose pharmacokinetics (PK) and pharmacodynamics (PD) of sotalol in the pediatric population were investigated.

<u>Study Design:</u>

This was a multicenter, open-label, multiple oral dose study with an upward 3 dose level titration. The patients were hospitalized during the conduct of the study from before the first sotalol dosing to at least 8 hours after the last dose.

An ascending dose titration design using 3 dose levels of 10, 30, 70 mg/m^2 body surface area (BSA) with 3 identical doses administered every 8 hours at each level was used. Blood samples were collected at 0.5, 2, 4 and 8 hours after the third, sixth, and ninth doses. The drug concentrations were measured by a validated ———— method. Baseline QT and RR ECG intervals were determined over a 7.5-hour time interval prior the first dose. QT and RR intervals were measured 0.5, 1.5, 2, 3, 4, and 8 hours after the third, sixth, and ninth doses at rest.

Enrollment of 20 patients each in the neonate ($\leq$ 1 month) and infant (>1 to $\leq$ 24 months) group was planned. Patients of any race and gender, suffering from VT or SVT and requiring therapy were permitted to enter the study. Finally, 25 patients completed the study: 7 neonates, 9 infants, 3 children >2 to <7 years, 6 children $\geq$7 to 12 years. All 25 patients had analyzable PK data. 23 and 22 patients had analyzable PD data on the QTc and RR intervals, respectively.

<u>Dose Regimen:</u>

d,l-sotalol HCl treatment consisted of 3 dose levels: 30, 90, and 210 mg/m^2/day. The daily dose was divided into 3 doses, which were given every 8 hours. Patients received 3 doses at each dose

level starting at the lowest. Depending upon tolerability, the dose was titrated upward every fourth dose.

Dose Level	Unit Dose (mg/m²)	Daily Dose (mg/m²/day)
I	10	30
II	30	90
III	70	210

Test Product:

d,l-sotalol hydrochloride solution; an extemporaneously compounded formulation was prepared by adding 5 tablets (120 mg each) of Betapace® to 120 mL Simple Syrup (containing 0.1% sodium benzoate) for a final concentration of 5 mg/mL after disintegration.
Batch number: Betapace® (d,l-sotalol hydrochloride) tablets: CL-2328
Simple Syrup: CL-2310

Analytical Methodology:

Plasma concentrations of sotalol were determined using a — method with ι. ━━━
Due to ━━━ problems encountered in the . ━━ ' runs using a ι ━━━
━ the method was ι ━━━━━━━━━━━━━ in the . ━
analytical validation run.

- Specificity: ι ━━━━━━━━
- Calibration curve:
  - limit of quantitation: ━ng/mL
  - linearity: ranges from ━' to ━ ng/mL ι ━━━
- Precision and inter-run variability: ranges from ι━to ━% CV·
- Accuracy of dilution: ━% CV
- Stability ι ━━━━━━ v stability ranging from ━to ━% CV,ι ━━━
  stability ranging from ' to % CV, room temperature stability ranging from ━' to ━% CV.
- Acceptance criteria:
  - calibration standards: at least ━% of the individual standards must ━━
    ━ ℣% of the nominal concentrations. Each run will include standards assayed in
    . ━' at ι ━ concentrations covering the range of ━ to ━ ng/mL.
  - quality control samples: predicted concentrations of at least ━ of the quality control samples must be ι ━ ℣% of the nominal concentrations.

Results:

Demographics:
The data from 25 patients, 13 males and 12 females, were analyzed. The racial distribution was 20 (80%) Caucasians, 3 (12%) Blacks, 1 (4%) Hispanic, and 1 (4%) other. 23 patients had SVT only, 1 patient had VT only, and 1 patient had both SVT and VT. 21 patients (84%) had paroxysmal supraventricular tachycardia. All patients had normal renal function.

Pharmacokinetics:

Table 8. Summary of PK Parameters for Sotalol by Dose Level.

Parameter		10 mg/m²	Dose Level 30 mg/m²	70 mg/m²
Cmax	Mean	331.15	· 986.05	2202.67
	CV%	30.39	44.64	28.89
Cmin	Mean	186.42	545.66	1255.77
	CV%	69.92	·79.13	59.91
AUCss	Mean	1973.46	5918.40	13227.85
	SD	868.19	3029.70	5292.39

- The AUCss values in the entire pediatric population studied increased by factors of 3.0 and 6.7 when the dose was increased by factors of 3.0 and 7.0, respectively. The corresponding increases in the Cmax values were 2.98 and 6.65, respectively. The mean fluctuation factors observed at the 3 dose levels were 2.03 (0.52), 2.13 (0.80), and 1.94 (0.58), respectively. Taken together, these results indicated that the pharmacokinetics of sotalol in the pediatric population was first order and dose proportionate.

- There is a statistically significant correlation between CL/F and BSA (r >0.9; p <0.0001) and between CL/F and CLcr (r >0.9; p <0.0001).

- The plot of AUCss against BSA showed a similar drug exposure for children with a BSA ≥ 0.33 m², whereas children with a BSA < 0.33 m² had a important increase in drug exposure at the 3 dose levels as shown in the table below. An examination of the individual data of the smallest patients did not indicate any deviation from linearity of the phamacokinetics of sotalol.

Table 9. Mean Percent Increase in AUCss and Cmax,ss of Children with BSA <0.33 m² (N=10) compared to Children with BSA ≥0.33m² (N=14).

Dose (mg/m²)	% Increase in AUCss	% Increase in Cmax,ss
10	56.5	40.3
30	66.1	43.3
70	53.1	28.9
Overall Mean	58.6	37.5

These pharmacokinetic results indicated that the empirical dose adjustment by BSA used in this study was optimal for the larger children only.

Pharmacodynamics:

The data from 23 (92%) patients were used to analyze the Class III effect of sotalol.
The data from 22 (88%) patients were used to analyze the beta-blocking activity of sotalol.

- Efficacy endpoint outcomes: the plots of the pooled QTcB or QTcF intervals against the corresponding RR intervals at baseline showed that only the correction procedure according to Bazett resulted in an independence of the QTc intervals from heart rate. Therefore, only the results obtained with the QTcB intervals are discussed.

- Baseline: there was no evidence for a systematic time dependency of the QTcB intervals observed during the 7.5-hour baseline session. The baseline values of the QTcB intervals for the pediatric population studied ranged between 335 and 411 msec and were similar among the four age groups. Similarly, the RR interval showed no systematic time dependency during the 7.5-hour baseline session in any of the 4 age groups.

- QTcB interval: PD parameters were determined by dose level as shown in Table 10.

Both the %ΔEmax,ss* (the percent change in the observed maximum steady state effect) and %ΔAUEss (the percent change in the area under effect versus time curve at steady state measured from 0.5 to 8 hours after the third dose) values showed dose dependent increases. The %ΔEmax,ss* values increased by 6 (4), 9 (4), and 14 (7)% and occurred between 2.9 and 3.7 hours after sotalol administration at the 3 dose levels tested. The mean %ΔEmin,ss (percent change in the nominal minimum steady state effect) values at the 3 dose levels were 1 (7), 2 (5), and 5 (7)%, respectively. The %ΔAUEss values obtained at the 3 dose levels which reflected the average Class III effect during a dose interval were 1 (5), 4 (4), and 7(5)%, respectively. These results suggested that a notable and lasting Class III effect was achieved only at the highest sotalol dose level of 70 mg/m^2 in the pediatric patients investigated.

Table 10. Summary Statistics of %ΔQTcBmax,ss*,tQTcBmax,ss*, %ΔQtcBmin,ss and %ΔAUEss (QTcB) by Dose Level.

Parameter		Dose Level		
		10 mg/m^2	30 mg/m^2	70 mg/m^2
%ΔQTcBmax,ss*	N	21	21	220
	Mean	6	9	14
	SD	4	4	7
tQTcBmax,ss*	N	22	22	21
	Mean	3.7	2.9	3.2
	SD	2.8	2.2	2.5
%ΔQTcBmin,ss	N	20	20	19
	Mean	1	2	5
	SD	7	5	7
%ΔAUEss (QTcB)	N	20	19	18
	Mean	1	4	7
	SD	5	4	5

A considerable intersubject variability was observed, indicating that important differences in the responsiveness to the Class III activity of sotalol between individuals existed. There were a few nonresponders among a majority of responders at the 70 mg/m^2 dose level.

- RR interval: PD parameters were determined by dose level as shown in Table 4.

Both the %ΔEmax,ss* and the %ΔAUEss values showed dose related increases. The %ΔEmax,ss* values increased by 18 (12), 23 (16), and 25 (15)5 and occurred on average between 2.2 and 3.3 hours following sotalol administration at the 3 dose levels tested. The %ΔEmin,ss values at each of the 3 dose levels were 1 (12), 7 (14), and 9 (15)%, respectively. The %ΔAUEss values, which reflect the mean beta-blocking effect during a dose interval, were 4 (8), 8 (10), and 12 (13)%, respectively at the 3 dose levels. These results indicated that a notable and lasting beta-blocking activity was achieved at the 30 and 70 mg/m² dose levels in the pediatric population studied. The considerable intersubject variability observed pointed however to important differences in the responsiveness to the beta-blocking effect of sotalol between individual patients. There were a few nonresponders among a majority of responders at the 30 and 70 mg/m² dose levels.

Table 11. Summary Statistics of %ΔRRmax,ss*, tRRmax,ss*, %ΔRRmin,ss, and %ΔAUEss (RR) by Dose Level.

Parameter		Dose Level		
		10 mg/m²	30 mg/m²	70 mg/m²
%ΔRrmax,ss*	N	20	20	20
	Mean	18	23	25
	SD	12	16	15
tRRmax,ss*	N	21	21	21
	Mean	2.2	3.3	3.0
	SD	2.3	3.0	2.3
%ΔRRmin,ss	N	20	20	20
	Mean	1	7	9
	SD	12	14	15
%ΔAUEss (RR)	N	20	19	20
	Mean	4	8	12
	SD	8	10	13

- Subgroups: analysis of the pharmacodynamic data using BSA as the criterion showed that the patients with a BSA < 0.33m² tended to have larger %ΔAUEss values for QTcB and RR intervals than the patients with a BSA ≥ 0.33m², as shown in Table 12 below. Relevant and durable Class III and beta-blocking effects were apparent in the smallest children already at the 30 mg/m² and 10 mg/m² dose levels, respectively.

Table 12. Percent Change from Baseline (±SD) in AUEss by Dose Level and Body Surface Area (m²) N=24.

	% Change from Baseline QTc Mean (±SD)	% Change from Baseline RR Mean (±SD)
BSA < 0.33 (N=10)		
10 mg/m²	5 (6)	7 (9)
30 mg/m²	6 (6)	11 (12)
70 mg/m²	10 (4)	14 (15)

BSA ≥ 0.33 (N=14)		
10 mg/m²	0 (3)	2 (8)
30 mg/m²	2 (3)	7 (9)
70 mg/m²	5 (4)	11 (12)

- 20 values for ΔQTcB > 60 msec were observed in 11 patients. 17 of these values were found at the highest dose level in 10 patients. The majority of elevated values were found in patients with a BSA < 0.33 m². 2 QTcB values exceeding 525 msec were observed in a child with BSA <0.33 m² and a child with BSA > 0.33 m². 2 patients (BSA. 0.33 m²) showed 18 RR intervals exceeding 1000 msec.

Pharmacokinetic-pharmacodynamic results:

- There is a statistically significant correlation (r =0.300; p =0.0671) between AUEss (or the derived parameters ΔAUEss, % ΔAUEss) and AUCss for the QTcB interval. The other endpoints, i.e. Emax,ss or Emin,ss and the related parameters, are not statistically correlated with the drug concentrations.
- No such correlation could be demonstrated for the beta-blocking effect at rest.
- Dose-response relationships: there are statistically significant relationships between Emax,ss*, Emin,ss (or the respective baseline corrected parameters) and the dose level (at 10, 30, and 70 mg/m²) for both QTcB and RR intervals.

<u>Conclusions:</u>

The notable and lasting Class III effects of sotalol are observed in the pediatric population at the highest dose level of 70 mg/m². However, there is no dose equal to 70 mg/m² planned in the Dosage and Administration part of the labeling, the highest dose recommended is 60 mg/m². Important and durable beta-blocking effects are found at the 30 and 70 mg/m² dose levels.

Both effects showed significant intersubject variation indicating important differences in the responsiveness of the individual pediatric patients. Therefore, individual clinical response to sotalol, i.e. heart rate and QTc interval, should be required to adjust the maintenance doses.

The Class III and beta-blocking effects tended to be more pronounced in the smallest children. Relevant and durable Class III and beta-blocking effects were apparent in the smallest children already at the 30 and 10 mg/m² dose levels, respectively. As a result, a dosage guidance should be established for the subgroup of children with BSA< 0.33m².

According to the Written Request, the daily dose was to be divided into three doses. The first dose was to be given at 10:30, the second dose at 16:00 and all other doses were to be given every 8 hours thereafter. Practically, the study was conducted by giving the first dose at 16:00 and all the following doses every 8 hours thereafter. The percentage of the "few nonresponders" among the responders at the 70 mg/m² dose level for QTc interval and at the 30 and 70 mg/m² dose levels for RR interval was not quantified.

Reviewer Comments:

1. Table 5 shows the % change in QTc and RR interval for the two sub-groups divided based on BSA. The effect on QTc seems to be more, for the same given dose, for the patients with BSA < 0.33 m^2. The drug exposure as measured by the area under the concentration – time curve is also higher in this sub-group (8934 vs. 5223 ng.h/mL). It can thus be deduced that the changes in the effects on QTc might be explained by the differences in the pharmacokinetics of these two sub-groups. Similar argument may apply to effect on RR. Please refer to the pharmacometrics review for more discussion on this.

2. The sponsor, consistent with the previous pharmacokinetic analysis, sub-divided the population based on BSA. This may not be appropriate for the same reasons as explained for the previous study.

3. Dose and concentration are related in a linear manner, as indicated by the PK model developed by the sponsor. There was a concentration – effect (QTc, RR) relationship presented in the submission. Yet, the sponsor concludes that no concentration - Emin,ss or Emax,ss relationship could be found.

Appendix A. List of investigators and study sites for study #98217.

Dianne Atkins, MD	University of Iowa Iowa City, IA
Lee Beerman, MD	Children's Hospital Pittsburgh, PA
David Chan, MD	c/o Pediatric Clinical Trials Children's Hospital Columbus, OH
Macdonald Dick, MD	University of Michigan Hospital Ann Arbor, MI
Michael R Epstein, MD	Children's Hospital Medical Center Cincinnati, OH
Christopher Erickson, MD	Arkansas Children's Hospital Little Rock, AR
Frank A Fish, MD	Vanderbilt University Nashville,TN
Steven Fishberger, MD	St. Joseph's Children's Hospital Paterson, NJ The Mount Sinai School of Medicine Clinical Research Center New York, NY
Richard Friedman, MD	Texas Children's Hospital Houston, TX
Robert Pass, MD	Columbia Presbyterian Medical Center Babies Hospital of New York New York, NY
Bertrand Ross, MD	Children's Hospital of the King's Daughters Norfolk, VA
J Philip Saul, MD	The Children's Heart Center of South Carolina Charleston, SC
Michael Schaffer, MD	The Children's Hospital Denver, CO
William Scott, MD	University of Texas Southwestern

Medical Center
Dallas, TX

Margaret J Strieper, DO

The Children's Heart Center
Atlanta, GA

Ronn Tanel, MD

Children's Hospital of Philadelphia
Philadelphia, PA

John Triedman, MD

Children's Hospital
Boston, MA

George F Van Hare, MD

Pediatric Cardiology
Stanford University School of Medicine
Palo Alto, CA

Frank Zimmerman, MD

St Louis Children's Hospital
St Louis, MO

Parvin Dorotstkar, MD

University Hospitals of Cleveland
Cleveland, OH

Technical Operation Report # TO 99-01

Title

Pediatric syrup 5 mg/mL: Ruggedness testing report

Objective

A study was performed to determine the ruggedness of the compounding procedure for the preparation of Sotalol HCl pediatric syrup 5 mg/mL.

Methods

Various compounders composed of a diverse group of 8 people (compounder's backgroud: packaging, packaging, quality assurance, management, pharmacist, auditor, pharmacist, pharmacist). All materials, including an array of measuring devices for the syrup, were supplied. Pharmaceutical technology pharmacist prepared 18 more bottles following six different variations on the compounding procedure.

Results

The results show that the compounding procedure is rugged. The range basically was ꟷꟷꟷ mg/mL which, at the high end, is within 6% of target. There was one outlier of 5.5 mg/mL which was due to an observable lower fill of simple syrup. The analytical results indicate a mean concentration of 5.2 mg/mL against the true ꟷ mg/mL with a RSD 2.9% (various compounders). The pharmaceutical technology pharmacist obtained a syrup with a mean concentration of 5.2 mg/mL and an RSD of 2.01%. All observations were within ±10% of the expected value.

The stability studies of the pediatric preparation indicate that the Betapace pediatric syrup is stable for up to ꟷmonths at ꟷꟷꟷ] and for up to ꟷweeks at · ꟷꟷꟷ

Reviewer's Recommendation

The study results and conclusions are acceptable. The procedure and stability of the pediatric syrup preparation are rugged.

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the approval package consisted of draft labeling