CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20545

ADMINISTRATIVE DOCUMENTS

CSO Overview of NDA 20-545
Procanbid (procainamide HCl)
November 13, 1995

JAN 31 1996

Background

This NDA was submitted on December 21, 1994 for twice daily use of extended-release procainamide HCl tablets in the treatment of life-threatening ventricular arrhythmias. The original IND (35,683) was filed by Parke-Davis on October 24, 1990. Procan SR is the Parke-Davis product for four times daily extended-release procainamide HCl (ANDAs 86-065, 87-510 and 88-489).

In the Federal Registers(in the package under Federal Register Notices) of September 8, 1972 and September 17, 1976 (DESI 6320), there is documentation that procainamide hydrochloride preparations have been generally recognized as safe and effective for use in the treatment of premature ventricular contractions, ventricular tachycardia, atrial fibrillation and paroxysmal atrial tachycardia.

The User Fee Goal Date is December 22, 1995.

Medical Review

In his review dated July 7, 1995, Dr. Bunker states that during discussions between Parke-Davis and the Division, an agreement was reached on a parallel trial dosing design. The sponsor's change to crossover dosing weakens the data. The possible residual effect following crossover makes the rhythm data suspect. He states that the study was crippled in its effort to show efficacy because much of the dosing range was sub-therapeutic. The overall scope of the data reflects the sponsor's contention that their BID preparation performs with the efficacy and side-effect profile inherent to the drug. The clinical trial establishes efficacy (although to a much lesser degree than a parallel design with adequate dosing would have done). Both clinical and pharmacological investigations establish safety for this formulation. Dr. Bunker recommends approval.

Statistical Review

Dr. Hung's August 23, 1995 review states that the 2000 mg/day BID formulation of procainamide yielded a significantly greater reduction in ventricular premature depolarizations than placebo. None of the three doses administered QID are significantly different from placebo. He states that the equivalence of BID and QID should be studied at individual dose levels rather than at the pooled dose as the sponsor chose. Dr. Hung believes that the equivalence of the BID and QID formulations is inconclusive.

Pharmacology Review

In his review dated January 27, 1995, Dr. DeFelice states that this application and labeling are approvable for the proposed formulation from the animal pharmacology/toxicology perspective. No further animal studies are required.

Chemistry is advised to confirm that the reformulation (which now includes synthetic black

iron oxide at the 1000 mg strength) will not provide more than 5 mg elemental iron per day (as per 21 CFR 73.1200) at the maximum recommended human dosage. On page of Chemistry Review #1, Mr. Advani writes that the amount of iron oxide used in the 1000 mg strength dosage tablet is % iron per day per patient. This amount is allowable under 21 CFR 73.1200.

Biopharmaceutical Review

In his review dated October 13, 1995, Dr. Borga states that upon implementing the suggested labeling changes listed in his review, this NDA is approvable from the Division of Biopharmaceutics' perspective.

Chemistry Review

Dr. Advani's review dated September 12, 1995 states that the chemistry and manufacturing portion of this NDA is satisfactory.

The CDER Labeling and Nomenclature Committee stated that "the Committee has no reason to find the proposed name unacceptable." The Committee believes "Extended-release" should appear as part of the established name for this product.

Environmental Assessment

A FONSI was signed by Dr. Vincent on May 19, 1995 and by Dr. Jerussi on May 22, 1995.

Summary

1) Exclusivity summary and pediatric page must be signed by Dr. Lipicky.

2) Methods Validation has not been completed.

3) The EER has not been returned from Compliance.

4) Dr. Borga's labeling comments that begin on page 10 of his draft review need to be considered.

5) It should be noted that Parke-Davis has stated that they plan to provide the Agency with observational data for pediatric labeling purposes after NDA approval. (A statement from Parke-Davis regarding this proposal is located in this package under "Proposed Labeling.")

6) Dr. Lipicky stated, prior to the filing meeting, that no DSI audit was necessary for this application.

/S/

Diana M. Willard
Consumer Safety Officer

cc: Original File
HFD-110
HFD-111/DWillard

CSO Review of Labeling JAN 3 1 1996

Application: NDA 20-545

Product: Procanbid (procainamide HCl) Extended-release Tablets

Sponsor: Parke-Davis Pharmaceutical Research

Submission Date: December 18, 1995

Receipt Date: December 19, 1995

Type of Submission: Final Printed Labeling

Background: This NDA was submitted by Parke-Davis on December 21, 1994 for twice daily use of procainamide in the treatment of life-threatening ventricular arrhythmias. The original IND (35,683) for Procainamide BID was filed by Parke-Davis on October 24, 1990. Procan SR is the Parke-Davis product for four times daily extended-release procainamide HCl (ANDAs 86-065, 87-510 and 88-489).

This labeling was submitted in response to the approvable letter issued December 14, 1995 requesting final printed labeling.

Evaluation: Changes made in this final printed labeling from the marked-up draft labeling sent to the sponsor with the December 14, 1995 approvable letter are:

1) The heading of the labeling has been changed to add "*Procanbid is not USP for dissolution."

2) Under **DESCRIPTION,** the following two sentences have been added in the third paragraph after the first sentence:

The release of procainamide hydrochloride is controlled by 2 mechanisms using T-Kote™ technology. The core of the tablet consists of a wax matrix which is then coated with a polymeric, control-release layer.

3) Under **CLINICAL PHARMACOLOGY/Pharmacokinetics and Drug Metabolism/ Absorption/Bioavailability,** the following changes have been made:

to:

The Procanbid T-Kote™ delivery system is designed to control the rate of PA release such that absorption is sustained throughout a 12-hour dosing interval.

b) The last sentence in the second paragraph under this subsection has been changed from:

to:

While corresponding minimum concentrations are slightly lower than those for Procan SR, they remain within the acceptED therapeutic range of 3 to 10 mcg/mL.

c) The following sentence has been added after the first sentence in the third paragraph:

Average peak and trough levels are within the generally accepted therapeutic range of 3 to 10 mcg/mL.

4) Under **CLINICAL PHARMACOLOGY/Pharmacokinetics and Drug Metabolism/ Special Populations/**Age, Gender, and Race, the third and fourth sentences have been changed and replaced with three sentences. These sentences have been changed from:

to:

Steady state plasma procainamide concentrations in women receiving Procanbid are 30 percent higher than those seen in men receiving the same dosing regimen. When corrected for body surface area this difference is only 16 percent. Concentrations of N-acetyl procainamide are not significantly different among men and women whether corrected for body surface area or not.

5) In the first sentence of the fourth paragraph the word ' ' has been changed to "hematologic." The sentence has been changed from:

to:

Because procainamide has the potential to produce serious hematologic disorders

(0.5%), particularly leukopenia or agranulocytosis (sometimes fatal), its use should be reserved for patients in whom, in the opinion of the physician, the benefits of treatment clearly outweigh the risks.

6) In the second sentence of the second paragraph in the first black box under **WARNINGS**, the first time the word appears it has been changed to "procainamide." The sentence has been changed from:

to:

Considering the known proarrhythmic properties of procainamide and the lack of evidence of improved survival for any antiarrhythmic drug in patients without life-threatening arrhythmias, the use of Procanbid as well as other antiarrhythmic agents should be reserved for patients with life-threatening arrhythmias.

7) Under **PRECAUTIONS/Pediatric Use**, the word has been replaced by "pediatric patients."

8) Under **DOSAGE AND ADMINISTRATION**, the following changes have been made:

to:

The dose should be adjusted for the individual patient, based on renal function. For patients who have been receiving another formulation of procainamide, the dose of the other formulation can function as a general guide, but re-titration with Procanbid is recommended.

b) The following has been added after the second paragraph:

CARE SHOULD BE TAKEN WHEN DISPENSING PROCANBID TO ASSURE THE BID DOSAGE FORM HAS BEEN PRESCRIBED AND DISPENSED. Procanbid tablets should be swallowed whole and should not be bitten or cut.

9) Under **HOW SUPPLIED**, the word has been re-written as "Gray.

10) Two general changes have been made throughout the labeling. The notation has been replaced with "mcg." Also, has been replaced with "Procanbid" throughout the labeling. In addition, several minor editorial changes have been made.

11) An asterisk has been added to the established name "Procainamide HCl extended-release tablets" when the name appears at the head of each column of the package insert. The reference associated with the asterisk has been added to the line immediately following the established name. The established name and associated reference appear in the package insert, container and carton labeling as follows:

(Procainamide HCl extended-release tablets)*
**Procanbid is not USP for dissolution.*

On the blister labeling, the established name has been revised as follows:

(Procainamide HCl extended-release tablets, not USP) ,

Comments/Recommendations: Dr. Bunker's review (with Dr. Lipicky's handwritten comment) recommending changes to the labeling before approval is attached.

With the exception of the changes noted above, this final printed labeling is identical to the marked -up draft labeling sent with the December 14, 1995 approvable letter.

Diana M. Willard
Consumer Safety Officer

cc: original file
HFD-110
HFD-111/DWillard
HFD-111/SBenton

DEC 15 1995

CSO Overview of NDA 20-545
Procanbid (procainamide HCl)
Updated December 14, 1995

Background

This NDA was submitted on December 21, 1994 for twice daily use of extended-release procainamide HCl tablets in the treatment of life-threatening ventricular arrhythmias. The original IND (35,683) was filed by Parke-Davis on October 24, 1990. Procan SR is the Parke-Davis product for four times daily extended-release procainamide HCl (ANDAs 86-065, 87-510 and 88-489).

In the Federal Registers (in the package under Federal Register Notices) of September 8, 1972 and September 17, 1976 (DESI 6320), there is documentation that procainamide hydrochloride preparations have been generally recognized as safe and effective for use in the treatment of premature ventricular contractions, ventricular tachycardia, atrial fibrillation and paroxysmal atrial tachycardia.

The User Fee Goal Date is December 22, 1995.

Group Leader Memorandum

Dr. Fenichel states in his memorandum of November 30, 1995, to Dr. Lipicky that while it is easy to argue that Procanbid should not be approved, a case can also be made for approval. Procanbid can not be bioequivalent to a twice-daily procainamide product as there is no such product approved by the FDA. When Procanbid is administered according to proposed regimen and Procan SR is administered according to its approved regimen, however, the serum concentration/time curves of procainamide are so close that they would, if they had arisen from formulations given according to the same regimen, be evidence of bioequivalence.

Medical Review

In his review dated July 7, 1995, Dr. Bunker states that during discussions between Parke-Davis and the Division, an agreement was reached on a parallel trial dosing design. The sponsor's change to crossover dosing weakens the data. The possible residual effect following crossover makes the rhythm data suspect. He states that the study was crippled in its effort to show efficacy because much of the dosing range was sub-therapeutic. The overall scope of the data reflects the sponsor's contention that their BID preparation performs with the efficacy and side-effect profile inherent to the drug. The clinical trial establishes efficacy (although to a much lesser degree than a parallel design with adequate dosing would have done). Both clinical and pharmacological investigations establish safety for this formulation. Dr. Bunker recommends approval.

Statistical Review

Dr. Hung's August 23, 1995 review states that the 2000 mg/day BID formulation of procainamide yielded a significantly greater reduction in ventricular premature depolarizations than placebo. None of the three doses administered QID are significantly different from placebo. He states that the equivalence of BID and QID should be studied at individual dose levels rather

than at the pooled dose as the sponsor chose. Dr. Hung believes that the equivalence of the BID and QID formulations is inconclusive.

Pharmacology Review

In his review dated January 27, 1995, Dr. DeFelice states that this application and labeling are approvable for the proposed formulation from the animal pharmacology/toxicology perspective. No further animal studies are required.

Chemistry is advised to confirm that the reformulation (which now includes synthetic black iron oxide at the 1000 mg strength) will not provide more than 5 mg elemental iron per day (as per.21 CFR 73.1200) at the maximum recommended human dosage. Mr. Advani states that the amount of iron oxide used in the 1000 mg strength dosage tablet is equivalent to (% mg) elemental iron per day per patient. This amount is allowable under 21 CFR 73.1200.

Biopharmaceutical Review

In his review dated October 13, 1995, Dr. Borga states that upon implementing the suggested labeling changes listed in his review, this NDA is approvable from the Division of Biopharmaceutics' perspective.

Chemistry Review

Dr. Advani's review dated September 12, 1995 states that the chemistry and manufacturing portion of this NDA is satisfactory.

The CDER Labeling and Nomenclature Committee stated that "the Committee has no reason to find the proposed name unacceptable." The Committee believes "Extended-release" should appear as part of the established name for this product.

EER was signed acceptable December 1, 1995.

Environmental Assessment

A FONSI was signed by Dr. Vincent on May 19, 1995 and by Dr. Jerussi on May 22, 1995.

Summary

1) Exclusivity summary and pediatric page must be signed.

2) Dr. Borga's labeling comments that begin on page 10 of his review need to be considered.

3) It should be noted that Parke-Davis has stated that they plan to provide the Agency with observational data for pediatric labeling purposes after NDA approval. (A statement from Parke-Davis regarding this proposal is located in this package under "Proposed Labeling.")

4) Dr. Lipicky stated, prior to the filing meeting, that no DSI audit was necessary for this application.

5) On page 1 of Dr. Fenichel's November 30, 1995 memorandum to Dr. Lipicky, under Chemistry, it is stated that "Dr. Wolters noted at the Supervisors' meeting of 8 November that some sort of inspection is still needed." The inspection Dr. Wolters was referring to is the facility inspection. An EER was signed acceptable on December 1, 1995.

/S/

Diana M. Willard
Consumer Safety Officer

cc: Original File
HFD-110
HFD-111/DWillard

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
Food and Drug Administration
Rockville MD 20857
Public Health Service

Memorandum

DATE DEC 14 1995

FROM : Director, Division of Cardio-Renal Drug Products, HFD-110 Lipicky

SUBJECT: NDA 20-545, Procanbid (procainamide, controlled release tablets), Parke-Davis Pharmaceutical Research

TO : NDA 20-545 File

Introductory Comments

Straight forward is not always straight forward, as pointed out by Dr. Fenichel in his insightful overview of NDA 20-545. The reviews by Drs. Bunker, Hung, DeFelice, Borga, Advani, and Zielinski are pretty straight forward and explain their thought process clearly. Pharmacology, Chemistry , Biopharmaceutics, and Environmental Assessment are all satisfied. From their point of view, NDA 20-545 is approvable. This twice-a-day formulation of procainamide (the Parke-Davis, Procanbid) is a reasonable formulation, behaves appropriately (from a biopharmaceutics point of view) and can be manufactured suitably. Considering that procainamide is an approved drug (it has about half a century history in clinical cardiology) and is currently used in practice using a four-times-a-day administration schedule, a twice-a-day formulation can be appreciated as being of value to the medical community and to patients who are receiving procainamide for the treatment of their ventricular arrhythmias.

The Parke-Davis, Procan-SR (a four-times-a-day formulation; the only formulation of procainamide listed in the 1995 PDR) was approved (in 1980) as an ANDA, being judged bioequivalent to Squibb's formulation of immediate release procainamide (Pronestyl, administered every 3 hours; an NDA approved in 1950 and still marketed but not advertised in the PDR). The first wrinkle in the overall consideration; a new dosing interval was introduced on the basis of plasma concentration data alone.

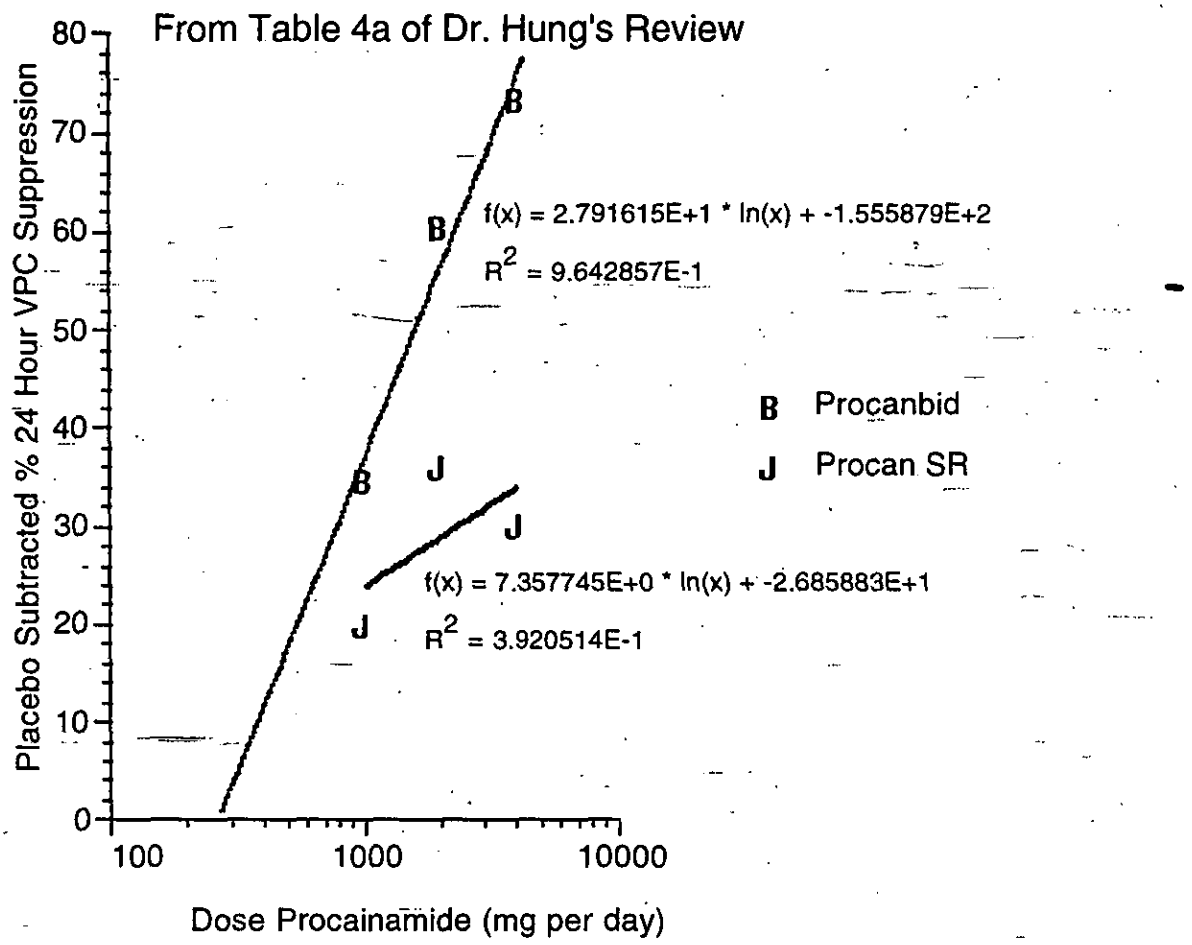
As pointed out by Dr. Bunker, the thought process underlying the development plan for Procanbid (which started in 1987, with meetings between Parke-Davis and the ODE/HFD-110) is not easy to comprehend and the documentation existing for the 3 years between 1987 and 1990 (when the first patient was enrolled in protocols 610-43 & 610-44) indicate that communication between FDA and Parke-Davis was not totally adequate (despite several meetings). The study was completed in 1992 and the NDA was submitted the third week of December, 1994 (essentially 7 years after the initial meeting). So, 8 years after the initial meeting, a judgement about the approvability of Procanbid needs to be made and cannot be made without some historical recognition.

The Problem

It is clear, that approvability of Procanbid was to be based solely upon grounds of "antiarrhythmic activity." I think that decision was appropriate. So, that is not a problem for me and will be discussed no further.

It is also clear that if one requires the trial results to establish "equivalence" (without defining equivalence) between Procan-SR and Procanbid on the basis of bioassay (24 hour VPC suppression), the results of

protocol s 610-43 & 610-44 do not accomplish that aim. Since the results do not differentiate Procan-SR from placebo but do differentiate Procanbid from placebo, one obviously cannot conclude that the two formulations are "equivalent," by any usual definition of "equivalence." The details and alternate analyses of these results are well laid out by Drs. Fenichel, Bunker and Hung; there is no need to repeat them here. A qualitative overview of the problem is shown in the following figure.



The figure shows the 24 hour VPC, placebo subtracted, suppression from the two agents under study. The lines through the data points are logarithmic fits (the equations are shown next to lines). As expressed in the reviews, there is clearly an effect produced by Procanbid and the effect is dose related.

The fit for Procanbid had a correlation coefficient (R^2) of 0.96, a qualitative expression of the statistical significance of the phenomenon expressed by Drs. Bunker, Fenichel, and Hung.

The fit for Procan SR had a correlation coefficient of only 0.39, a qualitative expression of the lack of statistical significance expressed by Drs. Bunker, Fenichel and Hung. Since we are not considering the approval of Procan SR, the apparent lack of effect need not be pondered nor understood.

Basis of Approval

Procanbid is approvable. The results of protocols 610-43 & 610-44 show that Procanbid produced a statistically significant dose-related (linear trend, $p<0.003$) reduction (with respect to placebo, Tables 4a, 4b, and 4c of Dr. Hung's review) of VPCs (an appropriate end-point for determining antiarrhythmic activity). This standard for approval (producing statistically significant, compared to placebo, dose-related effects on an agreed to surrogate) has been the basis for approving controlled-release dosage forms of most of the drugs regulated by this Division. The notion being that we can be certain that the formulation to be marketed is not placebo and that its effects are related to dose; thus, can be titrated to effect. So, approval of Procanbid on such a basis is consistent with the current (as well as recent past) basis for approval of all controlled-release products.

Could approval of Procanbid on this basis represent an error in judgement? Sure, but I do not think so, nor did Dr. Fenichel in his penultimate paragraph of his November 30, 1995 secondary review.

Certainly the plasma concentrations produced by Procanbid are different from those of Procan-SR (there are only 2 peaks with Procanbid vs. 4 peaks with Procan-SR and although the two formulations were nearly bioequivalent with respect to C_{max} and AUC (for procainamide), the T_{Max} was later and the C_{Min} was lower for Procanbid than for Procan-SR. This difference in time-course and particularly the lower C_{Min} could produce a significant difference to the antiarrhythmic activity of procainamide.

In fact, the time course of the principal active metabolite (NAPA) produced from procainamide (see page 23 of Dr. Borga's review) are superimposable(by eye, since there is no quantitative expression in the review). Since NAPA is active (about equipotent with procainamide), the differences in time course of plasma procainamide are intuitively less disturbing.

Moreover, the 24-hour Holter recording plotted as a function of time (e.g., pages 30 and 31 of Dr. Borga's review and page 28 of the Integrated Summary of Safety and Efficacy, show no hint of a decrease in antiarrhythmic activity at the end of the Procanbid dosing interval. So, the "worry " (and the potential error in judgement) about the difference in shape of the plasma concentration-time curve of procainamide, has no empirical support. In fact, the data are reasonably compelling. The "worry" can reasonably be laid to rest.

Miscellaneous Loose Ends

In about 1984, as a consequence of an increased Voluntary Adverse Drug Reaction Reporting of agranulocytosis, there was concern that controlled-release procainamide (Procan-SR) was responsible for the increased rate of reports (compared with the previous years when immediate release procainamide was the only procainamide formulation available. Dr. Bunker revisited this phenomenon in his July 7, 1995 review of NDA 20-545. In his review, as was also concluded by the Division on one previous occasion, Dr. Bunker found no basis for the suspicion that controlled-release procainamide was associated with a greater incidence of agranulocytosis.

There was nothing observed with respect to adverse effects that were surprises nor differentiated Procanbid from Procan-SR.

Summary

An approvable letter should be prepared. Labelling needs to incorporate the comments of the Division of Biopharmaceutics (Pages 10 through 12 of Dr. Borga's 10/13/95 review). We have just issued a letter that adjusts the CAST, etc. warnings to be more consistent across all antiarrhythmic labelling. The appropriate portions of that letter should be incorporated into this action and the marked-up draft labelling that goes out with the approvable letter.

The Dosing and Administration section of labelling should be revised to read as follows.

> **First Paragraph**
> The dose and interval between dose should be adjusted for the individual patient, based on clinical assessment of the degree of underlying myocardial disease, the patient's age, and renal function. For patient's who have been receiving another formulation of procainamide, the dose and interval between doses of the other formulation can function as a rough guide, but re-titration with Procanbid is recommended.

The remainder of the Dosing and Administration section is acceptable.

cc
Orig.
HFD-110
HFD-110/Project Manager
HFD-110/RLipicky

- OF

Minutes
December 6, 1995
NDA 20-545 Procanbid (procainamide Hcl) Extended Release Tablets
Parke-Davis

Attending:

Parke-Davis:	Irwin Martin, Ph.D.		Regulatory Affairs
	David Canter, M.D.		Drug Development
FDA:	Raymond Lipicky, M.D.	HFD-110	Division Director
	Kathleen Bongiovanni	HFD-111	Regulatory Health Project Manager

Background: Parke-Davis was here for a meeting on a different application and asked to discuss NDA 20-545 Procanbid (procainamide HCl) Extended Release Tablets with Dr. Lipicky. This application has a user fee goal date of December 22, 1995.

Meeting:
Dr. Lipicky said that he has not yet looked at the review package for this application, and no decisions have been made. There was a discussion of the results of a study that compared BID with QID administration of the drug. The firm said that there is valuable information from that study, although the results were not perfect, and they encouraged Dr. Lipicky to consider the pharmacokinetic, safety, and efficacy information that the trial provides. They said that they have no additional information to submit.

Parke-Davis offered to come down for additional meetings or to discuss the application with Dr. Lipicky by phone if they could be of any assistance. They also asked whether they could be informed ahead of time of the decision, and Dr. Lipicky agreed.

/S/
Kathleen F. Bongiovanni
12-7-95

cc: NDA 20-545
HFD-110
HFD-111/DWillard
HFD-111/SBenton
kb/12/7/95.

DF

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products

Date: 30 November 1995
From: Robert R. Fenichel, HFD-110 /S/
Subject: extended-release procainamide (PROCANBID, Parke-Davis), NDA 20-545
To: Raymond J. Lipicky, HFD-110

This memorandum is my summary of the data pertinent to approval of a new formulation of procainamide. The new formulation (PROCANBID) is designed to be taken twice daily, replacing the same sponsor's four-times-daily PROCAN SR.

The attachments include the various primary reviews.

Regulatory Issues

Immediate-release procainamide has been available since 1950, and the first dosage form of the PROCAN SR comparator was approved in 1979, long before CAST-based concern about the relation between antiarrhythmic activity (PVC suppression) and antiarrhythmic efficacy (clinical benefit). In early discussion with the sponsor, the Division ruled that this application would not be taken as grounds for reopening the larger question. In particular, the required clinical trial was permitted to use a PVC-suppression endpoint.

Chemistry

Dr. Advani is satisfied with the proposed process and controls; the CDER Labeling and Nomenclature Committee is satisfied with the proposed trade name. The environmental assessment was also satisfactory, but Dr. Wolters noted at the Supervisors' meeting of 8 November that some sort of inspection is still needed.

Biopharmaceutics

The proposed product will be supplied in 500-mg and 1000-mg tablets. These were found to be dose-proportional, and two smaller tablets were equivalent in head-to-head comparison to one of the larger. Some of the other studies in the biopharmaceutics program were devoted to demonstrating (successfully) the equivalence of the to-be-marketed product and the product used in the clinical trials.

The four remaining studies looked for bioequivalence between the proposed product and the PROCAN SR comparator. When multiple-dose regimens were studied, a twice-daily regimen of PROCANBID was compared to a four-times-daily regimen of PROCAN SR.

In general, the two formulations were consistently near-identical in C_{mean}* and C_{max}, but the C_{min} of procainamide was lower with PROCANBID, so that the procainamide trough/peak ratio† was reduced from 0.53-0.60 (PROCAN SR) to 0.44-0.53 (PROCANBID). The trough/peak ratios of N-acetylprocainamide (NAPA) concentration were identical.

Because release of the drug substance is delayed in the new formulation, one might speculate that release in a more distal portion of the gut could lead to differences in metabolism, and thus to differences in the procainamide/NAPA ratio. In fact, this ratio did not appreciably differ between the two products; the ratio of the ratios ranged from 0.90 (C_{max}) to 0.98-1.07 (C_{min}).

Trough concentrations of procainamide and NAPA varied little from dose to dose of either formulation; the variation was slightly greater with PROCANBID (10-19%) than with PROCAN SR (7-13%).

When PROCANBID was coadministered with a high-fat breakfast, changes in the pharmacokinetics‡ were similar to those seen much earlier with PROCAN SR.

Even after correcting for body surface-area, equal doses of PROCANBID given to men and to women resulted in procainamide concentrations in women (measured as C_{max}, C_{mean}, or C_{min}) that were about 20% higher than the corresponding concentrations in men; concentrations of NAPA did not differ by gender.

The trials' power to detect ethnic differences in procainamide pharmacokinetics was small (9 blacks, 90 whites). In any event, no such differences were seen.

On balance, the opinion of the biopharmaceutic reviewers was that the new formulation×regimen (twice-daily PROCANBID) was bioequivalent, by a logical extension of the usual standards applied to formulations given in the same regimen, to the old formulation×regimen (four-times-daily PROCAN SR). If PROCANBID is to be approved, then attention should be paid to the labeling recommendations that appear on pages 10–12 of Dr. Borga's review.

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* Equivalently, in AUC_{∞}.

† Instead of using the trough/peak ratio, Dr. Borga chose to describe fluctuations in serum levels with a "fluctuation index," computed as

$$(C_{max} - C_{min}) / C_{min}$$

This index (or a similar one in which C_{mean} is substituted for C_{min} in the denominator) is apparently conventional in biopharmaceutic circles.

‡ The C_{max} of procainamide was essentially unchanged, as were the C_{max} of NAPA and the AUC_{∞} of NAPA. On the other hand, the AUC_{∞} of procainamide was increased by 15-25%, and t_{max} was increased for both analysands by 19-64%.

Pharmacology/Toxicology

The Division has determined that new pharmacology/toxicology data are not necessary.

PVC Suppression

Because the relation between procainamide/NAPA concentration and efficacy is not well established, the sponsor was asked to perform a clinical trial (using PVC suppression as the endpoint) comparing corresponding regimens of PROCANBID and PROCAN SR. This was conceived as a sort of bioequivalence trial, and there was no thought that PVC suppression constituted, or was even a surrogate for, clinical benefit.

Like other equivalence trials, the requested trial was intended to show similar performance of the two active formulations, with a placebo arm included to demonstrate that the trial could have found differences if there were any. My description of the trial is based on the description in the elegant statistical review by Dr. Hung.

The trial was designed as a randomized, double-blind, 100-patient, 14-center, two-week, seven-armed crossover trial,* with patients randomized to a total daily dose of 0, 1, 2, or 4 grams of procainamide. Within each active-treatment group, patients received (in randomized order) one week of (double-dummy) twice-daily treatment with PROCANBID and one week of treatment with four-times-daily PROCAN SR. The two weeks of treatment followed each other with no pause for washout. 48-hour Holter recordings were performed at baseline and at the end of each week of treatment; the last of these recordings was begun at the beginning of the last full day of treatment, so its second half allowed observation of 30-36 hours of withdrawal from multiple-dose treatment.

Patients enrolled in the trial were adults with known frequent PVCs, already receiving procainamide as PROCAN SR. Patients with malignant ventricular arrhythmias, advanced congestive heart failure, unrelated electrocardiographic abnormalities, and other distracting conditions were all excluded.

After enrollment, patients underwent a one-week washout period before baseline monitoring and the beginning of randomized treatment.

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* The complex history of the design is valiantly disentangled by Dr. Bunker on pages 5–8 of his review. The original design was a 152-patient, 12-day, three-armed (PROCANBID, PROCAN SR, and placebo) parallel-group, forced-escalation trial, with each active-treatment patient exposed to four days of treatment at each of 2, 3, and 4 grams/day of total dose, and with Holter monitoring at baseline and on the last day at each dose level. In 1991, shortly after the sponsor revealed the current design, Dr. Chun† pointed out that the power calculations that accompanied the current design rested upon unrealistically optimistic expectations as to differential rates of PVC suppression with procainamide and with placebo. Dr. Chun's warning went unheeded.

† See her memo of 3 June 1991, here in the package with Minutes of Meetings. The sponsor's prediction of a 10% reduction in PVCs in response to placebo was right on target, in contrast to the historical experience (20–40%) cited by Dr. Chun. On the other hand, the sponsor had estimated that the reduction seen with 4000 mg/day would be 70%, but the actual result was only 43%.

The sponsor expected that PVC frequency would be reduced by 50% in the average patient receiving PROCAN SR, and that there would be no carryover effect from the first to the second arm of the crossover. The sponsor then computed that if 100 patients could be evaluated (25 per dose level, studied for both arms of the crossover), the trial would have 90% power to detect, at the 0.05 significance level, a difference of 30% between the treatments.

As it happened, only 94 patients received both PROCANBID and PROCAN SR, and only 78 of these had at least 24 hours of Holter recording at each required time (baseline, the end of the first period, and the end of the trial). The "primary activity analysis" included 77 of the 78 patients with complete data; one patient was excluded by the sponsor because of anomalous results.* The average extent of PVC suppression was a little more than half of what the sponsor had anticipated.

Because there was no pause for washout between the two treatment periods, one might be concerned about carryover of effect from the first period into the second. The graph of mean PVC rates before and after the end of treatment (reproduced on page 27 of Dr. Bunker's review) makes it biologically implausible that any such effect was large. Nevertheless, Dr. Hung† uncovered some statistical evidence of a carryover or sequence effect,‡ and his preferred analyses are limited to data obtained during the first period of the trial. In the interest of increasing the sample size and thereby milking the most possible information from the trial, and in the belief that the biologically expected values of the carryover and sequence effects are zero, I have optimistically elected to consider the data from both periods, as given in Tables 4a–4c of Dr. Hung's review. If the data thus considered were pivotal to approval, the statistical legitimacy of my approach would need further discussion.

No such discussion is necessary. Even when data from the second period are included, the results of this trial cannot make (or refute) a finding of equivalence. Presumably because the small sample size could not overcome the high intra- and inter-patient variance, the dose-response curve for PROCAN SR was never monotonic, whether one looked at the full intent-to-treat analysis, the nearly-intent-to-treat analysis (omitting the outlier), or the primary activity analysis. Out of 9 different comparisons (three analyses of three doses), PROCAN SR was significantly superior to placebo in only one (nearly-intent-to-treat analysis, 2 grams/day). When the "standard" is indistinguishable from placebo, there is no point in talking about whether or not a comparator is equivalent.

Ignoring PROCAN SR for the moment, the same analyses are encouraging with respect to PROCANBID. The dose-response curves are monotonic in two of the analyses (primary activity analysis and nearly-intent-to-treat), and nearly monotonic in the last of the three (intent-to-treat).§ The 4 grams/day regimen

* This patient, randomized to receive 1 gram/day of procainamide, had an unusually low PVC frequency at baseline. When that frequency regressed upward, his on-treatment PVC frequencies were dramatically higher. If this patient had been retained in the primary activity analysis, the total variance would have doubled.

† See pages 6–7 of his review.

‡ These two effects can not be distinguished in a simple crossover trial.

§ Because the three analyses are highly correlated, one might estimate that this repetitive

was significantly superior to placebo in all three analyses, and the 2 grams/day regimen was significantly superior to placebo in 2 of the 3 analyses. Unfortunately, *PVC suppression was present in this trial only as a metric of bioactivity;* this was not an efficacy trial, and it lost much of its interpretability when PROCAN SR failed to outperform placebo.

As a second part of the PVC-suppression study, the sponsor performed an elaborate series of NONMEM analyses, attempting to express PVC frequency as a function of age and procainamide/NAPA concentrations. Of several models tested,‖ the best fit was an E_{max} model achieved with

$$\text{PVCs/hr} = K \bullet \text{age} \bullet [1 - C_{mean} / (\theta_2 + \theta_5 \bullet \text{age} + C_{mean})]$$

where the C_{mean} was that of procainamide; K was 2.50±0.54 for placebo, 4.98±1.90 for PROCAN SR, and 5.08±1.90 for PROCANBID; θ_2 was -3.92±3.98; and θ_5 was 0.13±0.12. Models using NAPA concentration and/or using other concentrations of procainamide (C_{max}, C_{min}) were no better than this one.

K here should be directly proportional to E_{max}, and the old and new formulations yield point estimates for K that are remarkably close to each other in comparison to their distance from the K of placebo. Nevertheless, the coefficients of variation of the various parameters are so large that it is impossible to read much into this coincidence. That the data's variation is substantially unexplained by the model is dramatically evident in the figure on the next page.

One striking result of this model is the apparent importance of age; the model-derived procainamide concentration for 50% inhibition of PVCs (I_{50}) rises from 0.11 μg/ml at age 31 to 6.2 μg/ml at age 78.

The modeling results confirm the impression that the serum concentrations of procainamide and NAPA are only loosely linked to the suppression of PVCs.

Conclusions

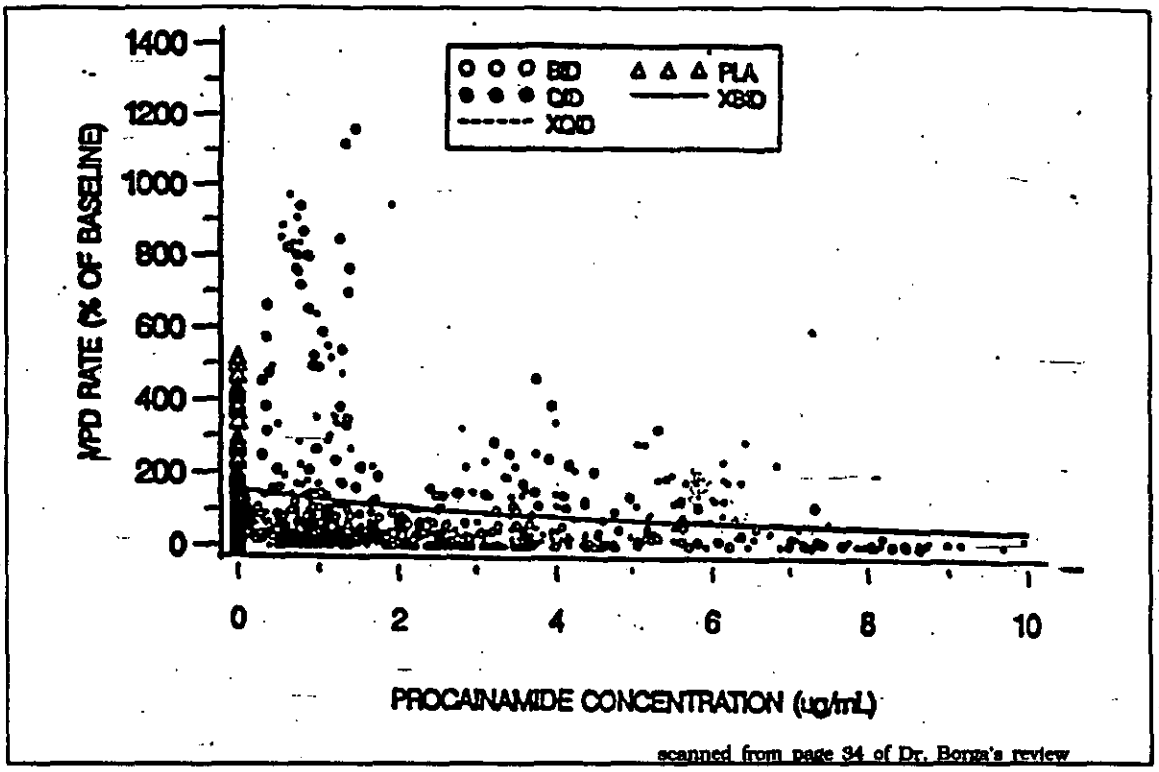
With this application, the sponsor proposes a new formulation of procainamide, recommended for twice-daily dosing. Compared¶ to a four-times-daily regimen of the older formulation of procainamide, the new formulation×regimen is "bioequivalent" to the old, although the concentration/time curve of the new formulation×regimen fluctuates somewhat more than that of the old formulation×regimen.

In a randomized trial using PVC suppression as the metric of activity, the sponsor attempted to show that the new and old formulation×regimens had similar dose-activity curves. Probably because the trial was underpowered, it

monotonicity and near-monotonicity is only as significant as monotonicity in a single analysis of a four-armed trial. The likelihood that 4 random numbers are given in increasing order is 1/(4!)=0.042.

‖ The modeling process is described on pages 27-28 of Dr. Borga's review, and the results of the various models are tabulated on (unnumbered) pages 36-45.

¶ Using a sensible adaptation of the serum-concentration standards that are usually imposed when two formulations are compared using the same dosing regimen for each.



could not distinguish the old formulation×regimen from placebo. On the other hand, the trial provided substantial evidence that the new formulation is pharmacologically active.

Modeling of the trial suggests that PVC suppression is linked only loosely to serum concentration of procainamide or of NAPA.

What Should We Do?

It's easy enough to argue that PROCANBID should not be approved. There is no approved twice-daily procainamide product, so PROCANBID could not, as a matter of law, be bioequivalent to anything. There have been no trials to show that PROCANBID is effective. In the one trial to show that the proposed regimen of PROCANBID was as active, on a mg/day basis, as the approved regimen of PROCAN SR, PROCAN SR was indistinguishable from placebo.

On the other hand, a case can be made for approval. PROCAN SR (and other formulations of procainamide) are approved, and the Division decided long ago that the current application would not justify reopening the question of whether procainamide (in some form) is safe and effective. When PROCANBID is administered according to its proposed regimen and PROCAN SR is administered according to its approved regimen, the serum concentration/time curves of procainamide (and of N-acetylprocainamide) are so close that they would, if they had arisen from formulations given according to the same regimen, be evidence of bioequivalence. The PVC-suppression trial may have been underpowered to

compare the activities of PROCANBIDand PROCAN SR, but it was adequate to show that the procainamide released by PROCANBID is biologically active, and that this activity increases with dose in a consistent manner.

Your call.

cc: NDA 20-545
HFD-110/RFenichel
HFD-110/GBunker
HFD-111/DWillard
HFD-426/CBorga

DF

Minutes of a Meeting
July 6, 1995

Application: NDA 20-545
Procanbid (extended-release procainamide) Tablets

Class: 3S

Sponsor: Parke-Davis Research

Purpose of Meeting: Mid-Review

Attending:

Robert Fenichel, Ph.D., M.D.	Group Leader/Medical, HFD-110
Gerald Bunker, M.D., Ph.D.	Medical Officer, HFD-110
J.V. Advani	Chemist, HFD-110
Olof Borga, Ph.D.	Biopharmaceutist. HFD-426
James Hung, Ph.D.	Statistician, HFD-713
Natalia Morgenstern	Supervisor, Project Management Team, HFD-111
Diana Willard	Consumer Safety Officer, HFD-111

Background: Parke-Davis Research submitted this application on December 21, 1995 for Procanbid (extended-release procainamide HCl) Tablets for twice daily use in the treatment of life-threatening ventricular arrhythmias. The original IND [ ] for Procainamide BID was filed by Parke-Davis on October 24, 1990. Procan SR is the Parke-Davis product for four times daily extended-release procainamide HCl (ANDAs 86-065, 87-510 and 88-489).

Meeting: Dr. Borga stated that Parke-Davis has submitted a number of bioavailability studies and one concentration/effect study for this NDA. The study designs are reasonable. Dr. Borga noted that a very weak concentration/effect relationship exists. He was unsure if any concentration/effect data are present in applications for other procainamide formulations. Other than the weakness of the concentration/effect data, he considers the application approvable. Dr. Borga is midway through his review for this NDA and foresees a completion date of August 18, 1995. The review will then go to Dr. Parekh for sign-off. Biopharm Day will be scheduled by mid-September.

Dr. Hung stated that the statistics employed to evaluate the data are complicated. He has requested and received supplemental information from the sponsor to aid in his review. The statistical review will be completed for forwarding to Dr. Chi for sign-off by August 11, 1995.

Dr. Bunker finished his review in April. He will amend his review with a graph he has located in published literature depicting the therapeutic range for procainamide.

Mr. Advani stated that an amendment to update the application with minor revisions in the CMC section will be submitted next week. The EER has not been returned from Compliance. He will contact Compliance to ensure that the District Office is aware that the Parke-Davis New Jersey

facility will be closed for two weeks in August.

/S/
Diana M. Willard

cc: NDA 20-545
HFD-110
HFD-111/DWillard
HFD-111/SBenton

Drafted: 7/10/95
RD: Fenichel 7/13/95
Bunker 7/13/95
Advani 7/13/95
Borga 7/13/95
Hung 7/13/9
Morgenstern 7/14/95

DW

Minutes of a Meeting
April 5, 1995

MAY - 4 1995

Application: NDA 20-545
Procanbid (extended-release procainamide) Tablets

Class: 3S

Sponsor: Parke-Davis Research

Purpose of Meeting: Discuss March 15, 1995 deficiency letter

Attending:

Parke-Davis:

Alexander Brankiewicz	Manager, Worldwide Regulatory Affairs
Russell Nesbitt, Ph.D.	Senior Director, Product Development/Quality Assurance
Sean Brennan, Ph.D.	Senior Director, Worldwide Regulatory Affairs

FDA:

Robert Wolters, Ph.D.	Supervisory Chemist, HFD-110
J.V. Advani, Ph.D.	Chemist, HFD-110
Diana Willard	Consumer Safety Officer, HFD-111

Background: Parke-Davis Research has submitted this application for Procanbid (extended-release procainamide HCl) Tablets for twice daily use in the treatment of life-threatening ventricular arrhythmias. The original IND [ ] for Procainamide BID was filed by Parke-Davis on October 24, 1990. Procan SR is the Parke-Davis product for four times daily extended-release procainamide HCl (ANDAs 86-065, 87-510 and 88-489).

Meeting: Dr. Brennan began by stating that Parke-Davis requested this meeting to discuss the March 15, 1995 deficiency letter, specifically Item number 4 (see attachment 1). Parke-Davis believes that the information requested in Item number 4 is available in the February 13, 1995 amendment to the NDA. Dr. Nesbitt proceeded to present overheads (see attachment 2) detailing the manufacturing process, the equipment used at both the [ ] manufacturing sites, and distinguishing features of the Procainamide BID formulation.

Tables showing typical Procanbid batches used in clinical studies and packaging data on Procanbid batches used in clinical studies were also provided. It was emphasized that clinical batches of Formulations -46, -46 A1, and -46 A2 (all 1000 mg) are considered equivalent. Clinical batches of -47, -47 A1, and -47 A2 (all 500 mg) are also considered equivalent. The sponsor stated that the only change proposed for the commercial product is the percentage of the overcoat. The overcoat will be going from % %. It was noted that all batches tested for stability are larger than % of commercial scale.

Dr. Advani noted that Parke-Davis needs to submit stability data of samples in blister packages from each of three different batches for each dosage strength. He asked what formulations would be used for the stability samples. Dr. Nesbitt said the although there were processing differences of scale and equipment used between the [ ] facilities, the products produced are considered bioequivalent. Mr. Brankiewicz said Parke-Davis now has twelve month stability data ready to submit. Dr. Advani stated that if the Division accepts that there is no difference between the batches manufactured at the two different facilities, the submission containing the twelve month stability data would be sufficient for the review of stability.

Dr. Wolters asked if the bottles for the two different sizes (60 and 100 tablets) were size proportional. Dr. Nesbitt replied that the bottles were size proportional and that the container and closures are made of the same material. Dr. Wolters said that the data for the different size containers could be pooled for the review of stability.

Dr. Brennan asked what type of information the Division was looking for in Item 6 as Parke-Davis understood this concern to be a Compliance issue. Dr. Wolters said we would like some general information including the type of equipment used in packaging, the environmental controls used during packaging and information on tests conducted (and the results of those tests) to ensure that the correct product and lots are packaged and correct lot numbers assigned.

/S/

Diana M. Willard

cc: NDA 20-545
HFD-110
HFD-111/DWillard
HFD-111/SBenton

Drafted: 4/25/95
RD: Wolters 5/1/95
Advani 4/26/95

DF

Minutes of a Filing Meeting
January 27, 1995

FEB 13 1995

Application: NDA 20-545
Procanbid (extended-release procainamide) Tablets

Class: 3S

Sponsor: Parke Davis Research

Application Date: December 21, 1994

Receipt Date: December 22, 1994

Related IND: [ ]

Attending:

Raymond Lipicky, M.D.	Division Director, HFD-110
Shaw Chen, M.D., Ph.D.	Group Leader/ Medical, HFD-110
Robert Fenichel, Ph.D., M.D.	Group Leader/ Medical, HFD-110
Abraham Karkowsky, M.D., Ph.D.	Group Leader/ Medical, HFD-110
Gerald Bunker, M.D., Ph.D.	Medical Officer, HFD-110
Maryann Gordon, M.D.	Medical Officer, HFD-110
Robert Wolters, Ph.D.	Supervisory Chemist, HFD-110
J.V. Advani, Ph.D.	Chemist, HFD-110
George Chi, Ph.D.	Supervisory Statistician, HFD-713
Lu Cui, Ph.D.	Statistician, HFD-713
Olof Borga, Ph.D.	Biopharmaceutist, HFD-426
Natalia Morgenstern	Supervisory Consumer Safety Officer, HFD-111
Diana Willard	Consumer Safety Officer, HFD-111

Background: Parke-Davis Research has submitted this application for Procanbid (extended-release procainamide HCl) Tablets for twice daily use in the treatment of life-threatening ventricular arrhythmias. The original IND[ ]for Procainamide BID was filed by Parke-Davis on October 24, 1990. Procan SR is the Parke-Davis product for four times daily extended-release procainamide HCl (ANDAs 86-065, 87-510 and 88-489).

Meeting: Dr. Bunker stated that this single, multi-center clinical study followed a double-blind, placebo-controlled, dose-response, formulation -crossover design. The lack of a washout period before the crossover may be a problem in that it creates the possibility of a carry-over effect. Dr. Advani reported that there are three facilities to inspect.

A brief discussion followed as to whether this is a 505 (b)(1) or 505 (b)(2) application. It was decided that this is a 505 (b)(1) application. (Federal Register notices of September 8, 1972 and September 17, 1976 are attached. These notices serve as documentation that

procainamide hydrochloride preparations have been generally recognized as safe and effective for use in the treatment of premature ventricular contractions and ventricular tachycardia, atrial fibrillation and paroxysmal atrial tachycardia.)

The reviewers gave the following estimates of the date their first reviews would be complete:

Discipline	Reviewer	Completion Date
Medical	Dr. Bunker	February 10, 1995
Chemistry	Dr. Advani	March 15, 1995
	Dr. Wolters	March 17, 1995
Pharmacology	Dr. DeFelice	January 27, 1995
Biopharmaceutics	Dr. Borga	August 18, 1995
Statistics	Dr. Cui	August 18, 1995

Dr. Lipicky will be the secondary medical reviewer and will sign-off on the application. He will work in parallel with the statistical reviewer and predicts his review will be completed by the end of August. Dr. Chi will be on leave the end of August, but will keep track of the statistical review so his sign-off will not delay the package.

A time line is attached.

Addendum: Dr. Parekh said her review will be completed mid-September. No date has been set for Biopharm day.

/S/

Diana M. Willard, CSO

cc: NDA 20-545
HFD-110
HFD-111/DWillard
HFD-111/SBenton

NDA FILING MEETING
APPLICATION SUMMARY

JAN 3 1 1995

Application: NDA 20-545
Procanbid (extended-release procainamide hydrochloride) Tablets

Class: 3S

Sponsor: Parke-Davis Research

Application Date: December 21, 1994

Receipt Date: December 22, 1994

Related IND: [ ]

BACKGROUND: Parke-Davis Research has submitted this application for Procanbid (extended-release procainamide HCl) Tablets for twice daily use in the treatment of life-threatening ventricular arrhythmias. The original IND [ ] for Procainamide BID was filed by Parke-Davis on October 24, 1990. Procan SR is the Parke-Davis product for four times daily extended-release procainamide HCl (ANDAs 86-065, 87-510 and 88-489).

MEETINGS WITH THE FIRM:

December 3, 1987	Discussion of whether a blood level to effect relationship exists for procainamide (pre-IND)
June 15, 1989	Discussion of proposed clinical development plan (pre-IND)
July 6, 1990	Discussion of clinical development (pre-IND)
December 19, 1991	Discussion of clinical development

ASSIGNED REVIEWERS:

Clinical:	Gerald Bunker, M.D., Ph.D.
Pharmacology:	Drs. DeFelice/Resnick
Chemistry:	J.V. Advani, Ph.D
Statistics:	Lu Cui, Ph.D.
Biopharmaceutics:	Olof Borga, Ph.D.

FILING ISSUES/COMMENTS:

Clinical: Please see attached handout for concerns raised by Dr. Bunker.

Pharmacology: No Item 5. (Nonclinical Pharmacology and Toxicology) was included in the NDA as agreed to at the December 19, 1991 meeting. Dr. Lipicky would like a statement from the Pharmacologist that states whether there were or were not any animal toxicology/reproduction data submitted and whether the proposed labeling is consistent with the currently approved labeling for procainamide. There should also be some comment reflecting the presence or absence of a problem regarding excipients and/or other components of the formulation. The Pharmacologist's review is attached.

Chemistry: none

Statistics: none

Biopharmaceutics: Dr. Borga made the observation that the sponsor did not use the formulation they plan to market in their food study.

OTHER ISSUES:

The question of whether or not this is a 505(b)(2) application has been raised. The application is not a complete application on its own as it contains no carcinogenicity data. In the Federal Registers of September 8, 1972 and September 17, 1976 (DESI 6320), there is documentation that procainamide hydrochloride preparations have been generally recognized as safe and effective for use in the treatment of premature ventricular contractions and ventricular tachycardia, atrial fibrillation and paroxysmal atrial tachycardia.

The tradname has beenapproved by the nomenclature committee

SUMMARY OF APPLICATION:

The application includes a complete Form FDA 356h, DMF authorization, patent information, a Debarment Statement and certification that a field copy of the CMC section has been provided to the District Office. An Environmental Assessment has been included in the submission. The sponsor is requesting three years exclusivity for Procanbid Tablets. The 39 volumes are well organized and, on its face, the application contains all of the components (except, as noted above, the nonclinical and pharmacology section) outlined in 21 CFR 314.50.

/S/

Diana M. Willard

cc: NDA 20-545
HFD-110

MEMO OF A TELECONFERENCE

Date: January 18, 1995

Application: NDA 20-545

Sponsor: Parke-Davis

Subject: Information request from Dr. Olof Borga

The sponsor was contacted requesting information that Dr. Borga would like before the January 27, 1995 filing meeting for this NDA.

/S/
Diana M. Willard

cc: original · file
HFD-110
HFD-111/DWillard