CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20943

ADMINISTRATIVE DOCUMENTS

Statistical Review not necessary

KDK

Minutes of a 30-Day Safety Meeting

OCT 31 1996

Date of Meeting: September 30, 1996

Application: IND
Verelan PM (verapamil HCl) Capsules

Sponsor: Elan Pharmaceutical Research Corporation

Subject: 30-Day Safety Meeting

Participants

Charles Ganley, M.D., HFD-110, Medical Team Leader
Isaac Hammond, M.D., Ph.D., HFD-110, Medical Officer
Charles Resnick, Ph.D., HFD-110, Pharmacology Team Leader
Kathleen Jongedyk, HFD-110, Chemist
David Roeder, HFD-110, Regulatory Health Project Manager

Background

The sponsor has reformulated their sustained release verapamil product (Verelan) to make it a delayed sustained release formulation. Their intent is to recommend the new formulation (Verelan PM) for evening dosing so that peak plasma levels will occur in the morning.

Meeting

Chemistry

Reviewer: Kathleen Jongedyk

The chemist noted that the sponsor had not set limits on the critical parameters of the manufacturing process. This and other deficiencies will be noted in her review and conveyed to the firm. Ms. Jongedyk did not have any safety concerns.

Pharmacology

Reviewer: Charles Resnick, Ph.D.

Dr. Resnick noted that there were no pharmacology data submitted to the IND and that none were necessary. He had no safety concerns.

Clinical

Reviewer: Isaac Hammond, M.D., Ph.D.

Although Dr. Hammond had no safety concerns, he noted that there were a number of deficiencies in the protocol, as outlined in the attachment. He recommended that these deficiencies be conveyed to the firm.

Conclusion

From the safety standpoint, the proposed studies may proceed; however, there are some clinical and chemistry issues that the sponsor should consider that could affect the approval of a future NDA.

Action Items

Mr. Roeder will ensure that the chemistry and clinical deficiencies are conveyed to the sponsor.

Addendum

After receiving Dr. Hammond's comments, the sponsor requested a teleconference with Drs. Hammond and Ganley to discuss several items on the deficiency list. This discussion occurred on October 4, 1996. The following agreements were reached:

Item #5: The sponsor can use ambulatory blood pressure measurements for the primary measurement of efficacy as long as they also take cuff measurements. The two measurements should be consistent and there should be a dose response.

Item #8: Dr. Hammond suggested that they take additional precautions to monitor pregnancy in the course of the study. Dr. Ganley suggested that they have patients contact the investigators if they miss their menstrual period.

Item # 9: The sponsor agreed to discontinue patients if their systolic pressure rises above 200 mm Hg. The sponsor agreed to comply with the other items in the list. They will follow up this discussion with a protocol amendment.

Minutes Preparer: David Roeder

Concurrence Chair: Charles Ganley, M.D.

dr/10-10-96/10-31-96

RD: KJongedyk/10-30-96
IHammond/10-30-96
CGanley/10-31-96

cc: IND [redacted]
HFD-110
HFD-110/CSO

PATENT INFORMATION

U.S. Patent No. 4,863,742 assigned to Elan Corporation, plc of Monksland, Athlone, County Westmeath, Republic of Ireland, the parent Company of the present Applicant, issued September 5, 1989 and expires June 19, 2007, claims the verapamil formulation referred to in the above-referenced application.

Respectfully submitted,

Marla J. Church
Corporate Patent Counsel

Paragraph II Certification

In accordance with the Federal Food, Drug, and Cosmetic Act, as amended September 24, 1984, Patent Certification is hereby provided for our New Drug Application for Verapamil PM (verapamil hydrochloride) Extended Release Capsules.

Elan hereby certifies that, in its opinion and to the best of its knowledge, U.S. Patent No. 3,261,859 held by Knoll A.G. Chemische Fabriken, Ludwigshafen Germany expired on July 19, 1983.

This certification is made in accordance with Section 505(j)(2)(A)(vii)(II) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.94(a)(12)(I)(A)(2).

Elan Pharmaceutical Research Corporation

Marla J. Church
Corporate Patent Counsel

DR

JUL 17 1997

Minutes of a Pre-NDA Meeting

Date: June 20, 1997

Application: IND
Verelan PM (verapamil HCl) Capsules

Sponsor: Elan

Subject: Pre-NDA

Participants

FDA

Shaw Chen, M.D., Ph.D., HFD-110, Medical Team Leader
Sughok Chun, M.D., HFD-110, Medical Officer
Robert Wolters, Ph.D., HFD-110, Chemistry Team Leader
Kun Jin, Ph.D., HFD-110, Statistician
David Roeder, HFD-110, Regulatory Health Project Manager

Sponsor

Sharon Hamm, Vice President, Regulatory and Medical Affairs
Roger W. Wiley, Director, North America Regulatory Affairs
Bobby Burt, Senior Director, Medical Affairs
Robert Haake, Statistician (Parexel)
David Smith, M.D., (Clinical Investigation Analysis)

Background

Elan is developing a delayed sustained release verapamil capsule under IND for the treatment of hypertension.

Meeting

Discussion Point #1: CMC -- Stability

Dr. Wolters said that the firm's proposal for a stability program is acceptable from the point of view of filing the NDA, but the expiry date would be dependent on the amount of stability data available at the time of approval.

Discussion Point #2: Presentation of Data in Individual Study Reports

The sponsor was given the attached comments from Drs. Ganley and Chun regarding the presentation of their data in the study reports. With regard to the tables that Dr. Ganley recommended they delete, Dr. Chen noted that they might include these tables in an appendix in case one of the primary reviewers would find them useful.

Discussion Point #3: Pooling of Data from Centers Based on Geographic Proximity

The sponsor proposed that data from centers with fewer than four patients per treatment arm be pooled with results from other centers, based primarily on geographic proximity. The FDA's concern was that this should have been specified in the protocol. The sponsor noted that it had been specified, although not in great detail. The FDA representatives agreed that, if prespecified, this proposal is acceptable. The results from the pooling should be consistent with the analysis using the model without the center effect term.

Discussion Point# 4: Efficacy Analysis Populations

The sponsor plans to define the efficacy analysis populations as follows: a) for Intent-to-treat, at least one dose of double-blind medication, and b) for efficacy evaluable, at least 7 days of double-blind medication. The FDA representatives agreed that this approach is acceptable.

Discussion Point #5: Criteria for Identifying Laboratory Values as Clinically Significant

The sponsor proposed criteria for identifying laboratory values as clinically significant. Dr. Chen noted that these criteria were not spelled out in the protocol, but it is not as critical that safety criteria be prospectively defined as it is for efficacy measures. He said that these values appeared to be acceptable but that it should be confirmed by Dr. Ganley.

Discussion Point #6: Format of Electronic Data

Dr. Jin stated that the statistical data sets could be submitted in SAS on a ZIP drive. He recommended that the sponsor speak with him before submitting any electronic data.

Mr. Roeder asked that they submit the biopharmaceutics data on an ASCI file.

Discussion Point #7: Pharmacology/Toxicology Section

Mr. Roeder noted that, since they were not adding any ingredients to the formulation, no additional preclinical data would be necessary. This application will be a 505(b)(2) NDA, however, and they will be required to identify a listed drug and submit a patent certification.

Minutes preparer: _____
David Roeder

Concurrence Chair: _____
Shaw Chen, M.D., Ph.D.

dr/7-2-97/7-15-97

RD: KJin/7-3-97
RWolters/7-17-97
SChun/7-9-97
SChen/7-9-97

cc: IND 51,459
HFD-110
HFD-110/CSO

ROEDER

JAN 26 1998

MEMORANDUM

Date: January 21, 1998

To: Henry J. Malinowski, Ph.D.
Mehul U. Mehta, Ph.D.

Through: Ameeta Parekh, Ph.D., Team Leader 1/26/98

From: Venkata Ramana S. Uppoor, Ph.D. 01/26/98

Subject: Filing meeting for NDA 20,943 for Verapamil PM (verapamil hydrochloride) extended release capsules, 100, 200, and 300 mg strengths, submitted on December 23, 1997 by Elan Pharmaceutical Research Corp., Gainesville, GA 30504

Verapamil PM extended release capsules contain a racemic mixture of verapamil hydrochloride, a calcium channel blocker, in three dosage strengths of 100, 200 and 300 mg. This is indicated for the management of essential hypertension. The proposed dose is 200 mg given once daily at bedtime. Verapamil PM extended release capsules use a proprietary CODAS (chronotherapeutic oral drug absorption system) technology. These multiparticulate pellet filled capsules provide for extended release of the drug in the gastrointestinal tract. The verapamil PM formulation has been designed to initiate the release of verapamil 4 - 5 hours after ingestion. This delay is introduced by the level of non-enteric release-controlling polymer applied to the drug loaded beads. The release-controlling polymer is a combination of water soluble and water insoluble polymers. As water from the g.i.t. comes in contact with the polymer coated beads, the water soluble polymer dissolves and the drug diffuses through the resulting pores in the coating. The water insoluble polymer continues to act as a barrier, maintaining the controlled release of the drug. This formulation has been developed based on chronotherapeutic principles, since the hypertensive patients need the highest level of protection (medication) during early morning hours.

This NDA (505(b)(2)) is submitted requesting approval of three strengths of Verapamil PM capsules for treatment of hypertension. These three strengths appear to contain the same bead blend in different quantities (formulation details not provided in item 6 of NDA). Two pivotal clinical trials have been conducted with this formulation to demonstrate safety and efficacy of this product.

PHARMACOKINETIC / BIOAVAILABILITY STUDIES

This NDA contains several clinical and pharmacokinetic studies. The PK studies conducted to characterize the biopharmaceutical characteristics of the product are listed below:

1. A single dose study in healthy volunteers to evaluate the bioavailability of Elan's Verapamil PM 200 mg formulation following night time dosing relative to Isoptin 80 mg tablet (Knoll pharmaceuticals) dosed three times daily at eight hourly intervals.
2. Single dose food effect study on verapamil PM 200 mg formulation.
3. A multiple dose study in healthy volunteers to evaluate the bioavailability of Elan's Verapamil PM 200 mg formulation following night time dosing relative to Isoptin 80 mg tablet (Knoll pharmaceuticals) dosed three times daily at eight hourly intervals.
4. Dose proportionality study using 100, 200 and 300 mg strengths of verapamil PM formulation.
5. IVIVC study to evaluate the effect of varying the in vitro dissolution of verapamil PM using very slow, slow, medium and fast 240 mg formulations along with immediate release 80 mg Isoptin tablet formulation.

The sponsor stated that the verapamil PM batches used in the biopharmaceutic, clinical studies and stability had the same qualitative composition. Minor changes which consist of imprinting on capsule have also been made during the product development. Analytical methods used and quality control data have been provided. Dissolution data has also been submitted.

COMMENTS

1. Details of formulation composition and dissolution method development have not been submitted in item 6 of this NDA. These need to be obtained from the chemist.
2. The sponsor did not provide any explanation regarding batches having 'same qualitative composition' and of any quantitative changes. After discussions with the chemist regarding changes in composition of the product, it was found out that during manufacturing of this product, the coating and associated heating process with shellac is performed until the beads meet the dissolution specifications for the product. This means that each batch may have slightly different composition. It is therefore extremely important to evaluate the correlation between dissolution and bioavailability (IVIVC) to determine if the dissolution method and specifications are meaningful.

RECOMMENDATION

The Human Pharmacokinetics and Bioavailability section of this NDA is organized, indexed, and paginated in a manner to initiate review. Hence, the submission is fileable from Clinical Pharmacology and Biopharmaceutics point of view.

CC list: HFD-110: NDA 20,943; Division file; CSO\Roeder; HFD-860: Venkata Ramana S. Uppoor; Patrick Marroum; HFD-340: Viswanathan; CDR\Barbara Murphy.

DF

JAN 23 1998

Memo to the File

Date: January 21, 1998

Application: NDA 20-943
Verelan PM (verapamil HCl) Capsules

Sponsor: Elan

Subject: Payment of User Fee

NDA 20-943 is a 505(b)(2) NDA for a new dosage form of verapamil. Elan was planning to pay a user fee for this application, but prior to its submission, and after my initial review of the application, I incorrectly advised Mr. Roger W. Wiley of Elan that this application was exempt from the fee requirement. Several days later, upon closer examination, I realized that a fee was required for this application. I contacted Mr. Wiley on January 13, 1998 and informed him that a user fee would be required. Elan submitted the fee immediately, and it was posted on January 16, 1998. The user fee goal date was not adjusted in this case because the applicant was acting on incorrect advice from the Agency.

[redacted]
David Roeder
Regulatory Health Project Manager

cc: NDA 20-943
HFD-110
HFD-110/CSO

FEB 4 1998

FILING SUMMARY

NDA Number and Drug Name: NDA 20-943
Verapamil PM (verapamil HCl) Capsules

Indication: Hypertension

Sponsor: Elan

Therapeutic Classification: 5S

Date of Application: December 23, 1997

Date of Receipt: December 29, 1997

User Fee Goal: December 29, 1998 (1 year)

User Fee Status: [X] Paid; [ ] Unpaid; [ ] Small Business Exception

If Unpaid, UN letter issued? [ ] YES; [ ] NO

Submission Complete As Required Under 21 CFR 314.50?
[X] YES; [ ] NO
If no, explain:

Patent Information Included? [X] YES; [ ] NO

Patent Certification? [X] YES; [ ] NO

If yes, what type? Paragraph II

Exclusivity Requested? [ ] YES; If yes, ____ years; [X] NO

Debarment Statement Included? [X] YES; [ ] NO

BACKGROUND

NDA 20-943 provides for a new formulation of verapamil for the treatment of hypertension that is intended to be dosed in the evening. It is a reformulation of Verelan in which the sponsor changed the ratio of fast-release to slow-release beads. They have a right of reference to the Verelan NDA. The NDA contains two pivotal clinical trials.

This NDA is a 505(b)(2) NDA since it does not contain animal pharmacology/toxicology data. The sponsor made the appropriate paragraph II patent certification, but they did name a specific product as the reference listed drug. They merely referred to the "well established pre-

clinical data from the immediate release products."

The dosage strengths are 100, 200 and 300 mg.

Assigned Reviewers:

DISCIPLINE	REVIEWER
Medical:	Sughok Chun, M.D.
Sec. Medical:	Charles Ganley, M.D.
Pharmacology:	Charles Resnick, Ph.D.
Chemist:	Kathleen Jongedyk
Env. Assessment:	N/A
Statistician:	Kooros Mahjoob, Ph.D.
Biopharmaceutist:	Patrick Marroum, Ph.D.
Microbiologist:	N/A
DSI:	
Project Manager:	David Roeder

Did firm request categorical exclusion for environmental assessment?
☐ YES; ☒ NO

EIR package transmitted? ☒ YES; ☐ NO

Trade Name Review Requested? ☐ YES; ☒ NO

The applicant has not proposed a trade name yet

DSI - There is precedent for not inspecting the clinical sites for 505(b)(2) application such as this that are only for a new formulation of an already-approved drug. A decision will have to be made at the filing meeting regarding the need for a DSI audit.

REGULATORY REQUIREMENTS/ORGANIZATION - Acceptable

David Roeder
Project Manager, HFD-110

To: Kasturi Srinivasachar, Ph.D.

From: Dan Boring, Ph.D.

Re; LNC opinion about "Controlled Onset"

The LNC evaluates additional labeling statements on a case-by-case basis. If these statements present an opportunity for confusion or are exaggerated, misleading and inaccurate, the LNC will object.

"Controlled onset" was evaluated as an unofficial dosage form modifier. The LNC does not believe that this term adds more clarification or meaning to the label than extended release alone. However, if it is used, it must be distinctly separated from the established name and not give the appearance of being the established name for this product.

Additionally, the LNC believes that the label should contain "bedtime dosing" or equivalent in the usual dose section to reinforce the importance of bedtime dosing to the efficacy of this drug. In fact, the LNC usually objects to medical abbreviations appearing in trademarks, but made an exception in the original case of COVERA-HS to allow "HS" to emphasize bedtime dosing.

Dan Boring, R.Ph., Ph.D.
Chair, CDER Labeling and Nomenclature Committee

CC: NDA 20-931
HFD-110
HFD-110/DRoeder

NOV 16 1998

MEMORANDUM

Date: 16 Nov. 1998

From: K. Srinivasachar, Ph.D., Chemistry Team Leader, HFD-110

To: NDA 20-943, Verapamil Hydrochloride Extended Release Capsules

Subject: Updated stability information and labeling issues

Stability:

The Amendment of Nov. 9, 1998 provides additional stability data in support of the firm's proposed 24 month expiration date for this product under storage at controlled room temperature (25° C). Data up to the 18 month time point are available. The stability studies have been carried out at 25°C (ambient humidity) and at ICH conditions (25°C/60 % RH, 30°C/60 % RH and 40°C/75 % RH). One batch of each strength (100, 200 and 300 mg) has been stored in either the trade package (bottles) or in the blister packages described in the NDA. These studies are extensions of previously reported data (see chemistry reviews #1, 2, and 3 for this NDA by K. Jongedyk).

At 25°C and ambient humidity the data show an acceptable stability profile after 18 months for both packaging configurations. All parameters tested (appearance, assay, related compounds and dissolution) remained within specified limits.
The same 3 batches were stored at ICH conditions and the results are reported up to the 18 month time point.
At 25°C/ 60 % RH all results are within specifications for product stored in bottles or in blister packages after 18 months. There seems to be no increase in related compounds with time. Most of the dissolution results are within the specifications at the L1 stage of testing. The general trend is that the 100 mg strength is somewhat less stable than the other strengths.
At 40°C/ 75 % RH there are dissolution failures as early as 3 months-- most of the problem is at the 24 hr time point where values less than the specified % are encountered. The firm has used the 30°C/ 60 % RH test station as back-up in these cases. Results are also available at the 18 month time point at this intermediate storage condition. All dissolution results were within specifications at 30°C/60 % RH at 18 months (although stage 2 testing was needed for some batches) except for one batch of the 100 mg strength in the blister package configuration. This batch did not comply with the specifications at the 18 month time point but was within the limits at 12 months.

An expiration date of 24 months can be granted based on the data submitted for the 200 and 300 mg strengths of drug product; however, because of the dissolution failure for the 100 mg strength after 18 months' storage at 30°C /60 % RH, an expiration date of 18 months is

recommended for this strength.

Labeling:

The Labeling and Nomenclature Committee was consulted regarding the use of the term "controlled onset", as a dosage form modifier, in the package insert and on the container labels. There is precedent for the use of this term since Searle's Covera HS has the same modifier. The L & N Committee found the use of this term acceptable provided it was well separated from the established name. The Committee also recommended "bedtime dosing" on the labels –see attached memo from Dan Boring, R.Ph., Ph.D.

The L & N Committee was also consulted regarding the use of the "CODAS" delivery system in the package insert. The Committee suggested that this was acceptable if this proprietary name was its own; otherwise this would be misleading advertisement.

The firm proposed other tradenames for the product even though Circelan had been found acceptable. These names, listed below, were submitted to the L & N Committee for evaluation:
Verelan PM
Verelan HS
Verelan NT and Verelan SE
The order of preference was Verelan PM followed by Verelan HS; if neither was acceptable the other 2 were requested to be considered. The Committee's recommendations are attached. Both Verelan PM and HS were found acceptable.

Conclusions and Recommendations: An expiration date of 24 months for the 200 and 300 mg strengths and 18 months for the 100 mg strength of drug product can be granted for storage at controlled room temperature (25°C). The recommendations of the Labeling and Nomenclature Committee should be forwarded to the HFD-110 Division Director for his concurrence and the firm notified accordingly.

CC:
Orig. NDA 20-943
HFD-110/ Div. File NDA 20-943
HFD-110/ K. Srinivasaehar/Project Manager/Jongedyk

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION Public Health Service
Division of Cardio-Renal Drug Products

Memorandum

DATE : NOV 13 1998

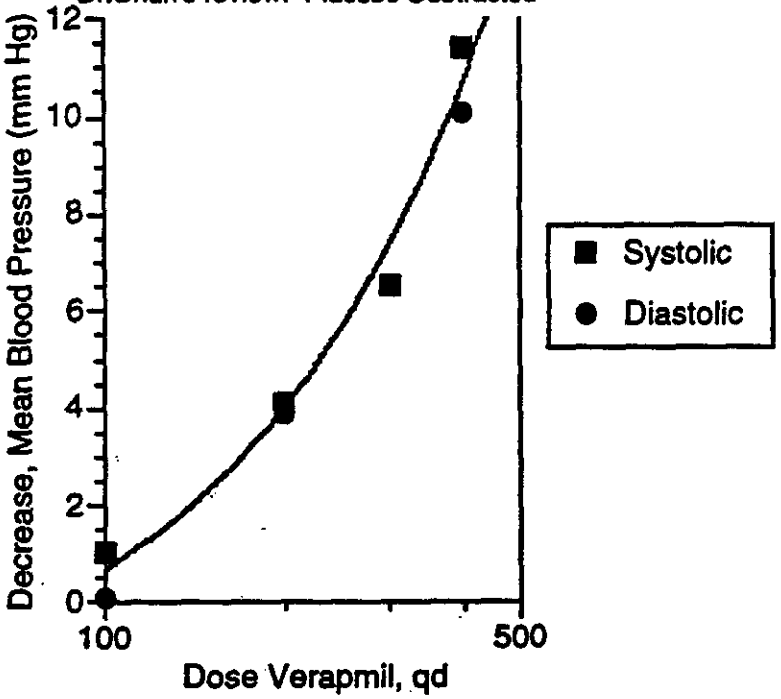
FROM : Director, Division of Cardio-Renal Drug Products, HFD-110

SUBJECT: NDA 20-~~934~~ 943, Circelan capsules, Verapamil PM, Elan Pharmaceutical Research Corporation

TO : NDA 20-~~934~~ 943 File

Verapamil, a calcium channel blocker, has been approved as an antihypertensive since 1982 (as an immediate release tablet) with the first controlled release formulation for the same indication being approved in 1986. The first controlled release formulation of verapamil that had a delayed onset of absorption (designed to taken at bedtime with the peak plasma concentrations achieved in the morning of the next day) was a Searle product marketed under the trade name Covera-HS. Covera-HS is a solid oral dosage form (tablet) that must be ingested whole and unchewed. The Elan product, this NDA, is the second formulation that has the same pharmacokinetic design features (e.g., delayed onset but then sustained absorption), but is a capsule consisting of verapamil loaded beads that are each coated with a combination of water soluble and water insoluble polymers. The polymers coating the beads are what give the absorption characteristics. Consequently, the capsule can be disassembled and its contents ingested in some other fashion (e.g., sprinkled on food). I find no documentation of the sprinkle on food within those studies reviewed in the NDA.

Study VER-0596-002-US, Table 02-2,
Dr.Chun's review. Placebo Subtracted



Elan has submitted the results of 2 multicenter, placebo-controlled clinical trials (VER-0596-001-US and VER-0596-002-US) that involved a total of 415 randomized patients (117 randomized to placebo, 298 to verapamil) who had mild to moderate hypertension. Standard casual, seated, cuff blood pressure measurements were made at trough (measured between 6 P.M. and 10 P.M.) and form the principal data that constitute a basis for approval.

All patients also had Ambulatory Blood Pressure Measurements, which provided results that were entirely consistent with those of evening cuff blood pressure measurements. The dose ranges studied were between 100 and 400 mg administered once-a-day, at bedtime. Compared to placebo, each dosage arm (from 100 to 400 mg) had statistically significant ($p<0.001$, by one analysis or another) decreases in blood pressure by the end of 8 weeks of double-blind therapy. The above figure shows seated, cuff blood pressure at trough; the 300 mg dosage arm produced essentially the same change and therefore 2 symbols for that data point do not show. Note that linear fit line drawn for systolic and diastolic blood pressures superimpose.

There were no adverse effect surprises. More patients discontinued from the placebo arms than from the verapamil arms. Headache and constipation were the major treatment emergent adverse effects. There was one death, a patient who was taking 300 mg verapamil. The only dose related change noted was that of the duration of the PR Interval.

The delayed absorption is clearly defined by plasma concentration vs time plots. Peak plasma concentrations occur about 12 hours after ingestion and plasma concentrations do not start to rise until about 4 hours after ingestion. The sponsor in-vitro/in-vivo correlation (IVIVC)studies (4 batches with different dissolution characteristics. The results clearly show that the sponsor's ideas relevant to what the rate limiting steps are related to the formulations characteristics are well founded. However, the results do not quite meet the quantitative expectation of the FDA guidance document on IVIVC. Therefore the Division of Biopharmaceutics will not agree to future waivers of bioavailablity (e.g., substituting dissolution for bioavailability should there be manufacturing changes).

The package insert is identical to that of Covera-HS, except for those sections that deal specifically with the Elan product.

A marked-up version of the package insert can be sent to the sponsor, along with an approvable letter. Sprinkling on food should not be allowd at this juncture.

cc: N 20-943
HFD-110
HFD-110/DRoeder

RHPM Package Overview

Date of Overview:	July 17, 1998
Application:	NDA 20-943 Circelan (verapamil HCl) Capsules 100, 200 and 300 mg
Applicant:	Elan Pharmaceuticals Research Corporation
Date of Application:	December 23, 1997
Date of Receipt:	December 29, 1997
User Fee Goal:	December 29, 1998

Background

NDA 20-943 provides for a new formulation of verapamil for the treatment of hypertension that is intended to be dosed in the evening. it is a reformulation of Verelan in which the sponsor changed the ratio of fast-release to slow-release beads. They have a right of reference to the Verelan NDA. The NDA contains two pivotal trials.

This NDA is a 505(b)(2) application since it does not contain animal pharmacology/toxicology data. The sponsor made the appropriate paragraph II patent certification.

Chemistry

Reviewer: Kathleen Jongedyk

The chemistry review is not finished yet.

Pharmacology

Reviewer: Charles Resnick, Ph.D.

Dr. Resnick has recommended that the sponsor recalculate the animal/human dose ratios in the sections of the package insert concerning animal studies.

Biopharmaceutics

Reviewer: Nakissa Sadrieh, Ph.D.

The Biopharmaceutics review is in draft. The reviewer recommended approval; however, she did recommend revised dissolution specifications and package insert revisions.

Statistics

A statistics review was not necessary

Clinical

Reviewer: Sughok Chun, M.D.

The reviewer recommends approval.

DSI

DSI audits were not necessary.

_____

David Roeder
Regulatory Health Project Manager

dr/7-17-98

cc: NDA 20-943
HFD-110
HFD-110/DRoeder

Dhreden

NOV 25 1998

RHPM Package Overview

Application: NDA 20-943
Verelan PM (verapamil HCl) Extended-Release Capsules

Applicant: Elan Pharmaceutical Research Corp.

Letter Date: December 23, 1997

Receipt Date: December 29, 1997

Chemistry

Reviewer: Kathleen Jongedyk

All CMC reviews are complete. The following issues have been resolved and are mentioned in the approval letter:

- The expiry date is 18 months for the 100 mg capsule and 24 months for the 200 and 300 mg capcules.
- The sponsor's proposed dissolution specifications are acceptable, but the in vivo/in vitro correlation was not properly validated, so it cannot be used to support a waiver of bioequivalence studies for future manufacturing changes.
- The methods have not been validated, and the firm is being asked to cooperate to resolve any problems that might arise.
- The applicant is reminded that the approval of this NDA does not imply that changes can be made to NDA 19-614 without notifying the Agency.

The facility inspections are complete.

The Tradename has been found to be acceptable.

Pharmacology/Toxicology

Reviewer: Charles Resnick, Ph.D.

Dr. Resnick recommended that adjustments be made to the labeling regarding the multiples of human dose in the animal studies. These changes have been made.

Biopharmaceutics

Reviewer: Nakissa Sadrieh, Ph.D.

Labeling changes recommended by the reviewer have been made.

Clinical

Reviewer: Sughok Chun, M.D.

The clinical reviewer recommended approval.

Statistical

A statistical review was not necessary.

Division Director's Memo

Dr. Lipicky recommends approval. His labeling recommendations have been incorporated.

David Roeder
Regulatory Health Project Manager

dr/11-24-98

cc: NDA 20-943
HFD-110
HFD-110/DRoeder

DEBARMENT CERTIFICATION

In accordance with Section 306(k)(1) of the Act (21 U.S.C. 335a (k)(1), Elan Pharmaceutical Research Corporation did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) [Section 306(a) or(b)], in connection with this application.

In addition, in accordance with Section 306(k)(2) of the Act 21 U.S.C. 335a (k)(2), neither Elan Pharmaceutical Research Corporation or any affiliated persons responsible for the development or submission of this application has had any convictions as described in Section 306(a) and (b) of the Act within the last five years of the date of this application.

Note: Elan was contacted by FDA, Division of Cardio-Renal, and was made aware of an investigator, Robert Fiddes, M.D. (Whittier, CA – Site 107), relative to his activities on other investigational studies. As a result of this information, the data on Dr. Fiddes' seven patients; five on active drug and two on placebo, were deleted from the primary data analysis.

Roger Wayne Wiley, R.Ph.

December 22, 1997
Date

Director, North America Regulatory Affairs
Title

000035