CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-072

ADMINISTRATIVE DOCUMENTS

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: **ANDA 75072/000**
Stamp: **10-FEB-1997** Regulatory Due:
Applicant: **DURAMED PHARMS**
5040 LESTER RD
CINCINNATI, OH 45213

Priority: Org Code: **600**
Action Goal: District Goal: **10-APR-1998**
Brand Name:
Established Name: **VERAPAMIL HYDROCHLORIDE**
Generic Name:
Dosage Form: **EXT (EXTENDED-RELEASE TABLET**
Strength: **240 MG, 180 MG & 120 MG**

FDA Contacts: **T. AMES (HFD-617) 301-827-5849 , Project Manager**
J. SIMMONS (HFD-810) 301-594-2570 , Team Leader

Overall Recommendation:

ACCEPTABLE on 12-MAY-1999 by J. D AMBROGIO (HFD-324) 301-827-0062
WITHHOLD on 20-OCT-1997 by J. SINGER (HFC-240) 301-827-0066

Establishment:
DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **12-MAY-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **DRUG SUBSTANCE RELEASE TESTER**

Establishment: 2
CEUTICALS
DMF No:
AADA No:

Profile: **TTR** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **30-MAR-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **FINISHED DOSAGE MANUFACTURER**

Establishment:
DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **26-MAR-1999**
Decision: **ACCEPTABLE**

Responsibilities: **DRUG SUBSTANCE RELEASE TESTER**

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Reason: **BASED ON PROFILE**

Establishment:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **26-MAR-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

OGD APPROVAL ROUTING SUMMARY

ANDA # 75-072 Applicant Duramed

Drug Verapamil HCL ER Tablets USP Strength 120mg & 240 mg

APPROVAL ☒ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ OTHER ☐

REVIEWER:

1. Tim Ames, Project Manager, Branch 6
   Review Support Br

DRAFT RECEIPT
Date 5/6/99
Initials

FINAL ACTION
Date 5/19/99
Initials

Application Summary:

Original Rec'd date 10-FEB-1997
Date Acceptable for Filing same
Patent Certification (type) ~~I~~ II
Date of Office Bio Review 11-MAR-1999
Methods Val. Samples Pending Yes ☐ No ☒
30 Day Clock Start _____ End _____
Commitment Rcd. from Firm NA Yes ☐ No ☐
First Generic Yes ☐ No ☒

EER Status Pending ☐ Acceptable ☐ OAI ☒
Date of EER Status ~~withheld 20 OCT 97~~
Date Patent/Exclus.expires expired
Citizens Petition/Legal Case Yes ☐ No ☒
(If YES, attach email from PM to Pet. Coord. notifying of pending approval)
Pediatric Exclusivity Tracking System
Date checked 06-MAY-1999
Nothing Submitted ☒
Written request issued ☐
Study Submitted ☐

Previously reviewed and tentatively approved No ☐ Date _____
Previously reviewed and CGMP def./N/A Minor issued No ☐ Date _____
Comments: ER Product Ltr

Para II → all pats have expired

5/12/99

2. ~~Div. Dir.~~/Deputy (Acting) Dir. Date _____ Date 5/20/99
   Chemistry Div. I or II Initials _____ Initials
   Comments: CMC acceptable. EER is now OK.

The dissolution test for the 120 mg tablet does not match any of the 4 tests listed in USP. A copy of the approval letter needs to be sent to Compendial Operations Staff to initiate the appropriate change in the USP monograph. MSmela

3. Office Level Chem Review **(1st Generic Only)** Date _____ Date _____
   Chemistry Div. I or II Initials _____ Initials _____
   Comments:

4. Pat Beers Block Date 5/21/99 Date 5/24/99
   Supv., Review Support Branch Initials Initials
   RLD = 19152
   EER Status: Acceptable for all facilities as of May 12, 1999 (none OAI)

   Bioequivalence sites:
   Clinical site:
   Inspection needed: ☐ yes ☒ no
   Status: ☒ acceptable ☐ unacceptable ☐ pending
   Date of status: Based on firm's history (inspectional) See attached e-mail message re: inspectional history.
   Analytical site:
   Inspection needed: ☐ yes ☒ no
   Status: ☒ acceptable ☐ unacceptable ☐ pending
   Date of status: Based on firm's history (inspection)

   Labeling Status: labeling for the 100s & 500s contain BTS. & the 120 mg & 240 mg were found acceptable for approval 4/23/99.
   Bioequivalence office level sign off: Bioequivalence studies (fasting on 120 mg & 240 mg) and steady state (post prandial on 240 mg) were found acceptable for approval 3/11/99.
   Microbiology status:
   Patent Certification: No patents or pediatric exclusivity affect approval of this ANDA
   Controlled Correspondence/Cit.Pet: None
   Comments: CMC acceptable 5/20/99

REVIEWER: /S/

	DRAFT RECEIPT	FINAL ACTION
Supv. J Reg. Support Branch	Date 4/29/99 Initials 5/24/99	Date 4/29 Initials 5/24/99

Contains certification: Yes ☒ No ☐ Determ. of Involvement? Yes ☐ No ☐ N/A
(required by the GDEA if sub after 6/1/92)
Pediatric Exclusivity Tracking System
Patent/Exclusivity Certification: Yes ☒ No ☐ Date Checked May 24, 1999
If Para. IV Certification- did applicant Nonexempt Nothing Submitted ☒
Notify patent holder/NDA holder in a no unexpired patents or exclusivity Written request issued ☐
Timely manner: Yes ☐ No ☒ Study Submitted ☐
Was applicant sued w/in 45 days: Yes ☐ No ☒
Has case been settled: Yes ☐ No ☒
Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity: Yes ☐ No ☒
Comments: Office level BIO accepted/cleared 3/11/99 - DSI (OC) Clinical/Statistical Analyses do not need to be included. See Patty's section & E-mail attached. EER acceptable.

6. Robert L. West
Dir. Div. Labeling & Prog. Support
Date 5/24/99 Initials [illegible] Date 5/25/99 Initials [illegible]
Comments: RLD 19-152
No patent or exclusivity issues - multiple generics approved
180 mg strength withdrawn from application due to Bio issues in amendment dated 6/19/98
Labeling acceptable per approval summary dated 4/23/99 - Office Level Bio acceptable 3/11/9
fasting studies on 120mg + 240mg - steady-state study on the 240 mg (multi dose)
EER acceptable 5/12/99 (Verified in EES 5/25/99)

7. Gary Buehler
Deputy Director, OGD
Date _____ Initials _____ Date _____ Initials _____

Para.IV Patent Cert: Yes☐ No☐; Pending Legal Action:Yes☐ No☐; Petition:Yes☐ No☐
Comments:

8. Douglas L. Sporn
Director, OGD
Date 5/25/99 Initials [illegible] Date 5/25/99 Initials [illegible]
Comments:

Roger Williams, M.D.
Deputy Center Director for
Pharmaceutical Science
Date _____ Initials _____ Date _____ Initials _____
First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐

9. Project Manager
Review Support Branch
Date [illegible] Initials 5/20/99 Date _____ Initials _____

✓ No Records found.
_____ Pediatric Exclusivity Tracking System (check just prior to notification to firm)

Applicant notification:
11:02 A Time notified of approval by phone 11:37 Am Time approval letter faxed

FDA Notification:
5/26/99 Date e-mail message sent to "OGD approvals" account
5/26/99 Date Approval letter copied to"//cder/drugapp" directory

ANDA APPROVAL SUMMARY

AADA or ANDA NUMBER: 75-072

DRUG PRODUCT: Verapamil Hydrochloride Extended-release Tablets, 120 mg and 240 mg.

FIRM: Duramed Pharmaceuticals, Inc.

DOSAGE FORM: Extended-release Tablets **STRENGTH:** 120 mg and 240 mg.

CGMP STATEMENT/EER UPDATE STATUS: The EER is pending as of **4/22/99**, per EES. There is a recommendation to "withhold" approval of the ANDA due to significant CGMP deficiencies observed during an inspection of Consumer Product Testing Co. A copy of the compliance report dated **10/20/97**, is in Vol. 2.1 of this ANDA. In the **6/19/98**, amendment the applicant acknowledged that Consumer Product Testing Co. had CGMP deficiencies. Also, that Consumer Product Testing Co. has responded to the FDA comments and believes they are in compliance.

EER OK 5/12/99

BIO STUDY: The biostudies for the 120 mg and 240 mg dosage strengths are Acceptable per M. Makary, Ph.D. review dated **2/12/99**, and **2/25/99**, of the **1/13/99**, amendment.

METHODS VALIDATION -(DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):
..., since the products are covered by a compendium monograph. The methods are satisfactory-Pending Compendial Laison recommendation for dissolution testing to the USP.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?:
Container/closure: Yes, described below.

e ... .ve PS-22
l
s ... Each
(

LABELING:
FP labels in the **6/19/98**, amendment are satisfactory per A. Vezza review dated **10/1/98**. FP insert labeling with recommended revisions was requested in FAX dated **4/6/99**. Review within the Labeling Review Branch of the FP insert labeling in the **4/12/99**, amendment is pending.

Labeling OK 4/23/99

STERILIZATION VALIDATION (IF APPLICABLE): N/A

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS O.K.?):
Yes, the ds remains ADEQUATE on 7/17/97, in the context of this ANDA per ...is chemist. The 10/22/98, review concludes that the DMF remains ...ceptable for NDA 20-943.

Stability Protocol: Satisfactory.
Stability Data: Satisfactory in support of the proposed expiration dating

period of 24 mos. for the following lots:

Batch # 950301 for tablets of the 240 mg dosage strength was manufactured for the first biostudy by the original sponsor, Hallmark Pharmaceuticals, of this ANDA. In 1996, Duramed bought out Hallmark. Since the product logo was changed, another batch of the 240 mg strength was manufactured with the new logo. This batch of the 240 mg dosage strength with # 960703S was manufactured with the same process as that for batch # 950301. The theoretical batch size was tablets for batch # 950301, and 115,000 tablets for batch # 960703S. Batch # 960701S with a theoretical batch size of tablets of the 120 mg dosage strength was also manufactured for bioequivalence purposes.

For batch # 960701S of the 120 mg product, the tablets that were manufactured were filled into bottles of 100's and bottles of 500's.

For batch # 950301 of the 240 mg product, the tablets that were manufactured were filled into bottles of 100's and bottles of 500's.

The 2 dosage strengths can be manufactured from a common granulation. The proposed Master batch record for the preparation of of lubricated granulation equates to 120 mg tablets and 240 mg tablets.

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

The stability batches are the same as the BIO batches.

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

The manufacturing process for the proposed batch size is the same as that for the executed bio/stability batches.

Chemist: /S/ Robert C. Permisohn **DATE:** 5/19/99 April 22, 1999

Team Leader: /S/ Ubrani V. Venkataram, Ph.D. **DATE:** 5/18/99

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

ANDA Number: 75-072 Date of Submission: April 12, 1999

Applicant's Name: Duramed Pharmaceuticals, Inc.

Established Name: Verapamil Hydrochloride Extended-release Tablets USP, 120 mg and 240 mg

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APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: 100s and 500s (120 mg and 240 mg)
Satisfactory as of June 19, 1998 submission.

Professional Package Insert Labeling:
Satisfactory as of April 12, 1999 submission.

Revisions needed post-approval: None

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Isoptin® SR Tablets

NDA Number: 19-152

NDA Drug Name: Isoptin® SR (verapamil hydrochloride extended release) Tablets

NDA Firm: Knoll Pharmaceuticals

Date of Approval of NDA Insert and supplement #: 1/13/98 (S-023)

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: labels on file

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	

Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	X		
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in prin or lacking in prominence? (Name should be the most prominent information on the label.		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling (continued)	**Yes**	**No**	**N.A.**
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributed: statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			X
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been		X	

confirmed?			
Do any of the inactives differ in concentration for this route of administration? [Some of the inactives differ from the RLD].	X		
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FYR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.	X		
Patent/Exclusivity Issues?: FYR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD: (portions taken from previous review)

1. Labeling Model: Isoptin® SR (Knoll Laboratories; revised 9/97 and approved 1/13/98 - NDA 19-152/S-023).

2. The inactive ingredients are accurately listed in the DESCRIPTION section [Vol. B1.2, section VII].

3. Closure:

   100s & 500s - non CRC [Vol. B1.3 section XIII]

4. The firm's physical description of the tablets are accurate as seen in the HOW SUPPLIED section [Vol B1.3, section XIV].

5. Packaging:

   RLD - 100s & unit dose 100s
   ANDA - 100s & 500s

6. No patent or exclusivity.

7. Differences in the ANDA & RLD labeling:

The third paragraph under CLINICAL PHARMACOLOGY (Pharmacokinetics and Metabolism) is different from the RLD. See file folder for FTR dated 2/13/92.

In the OVERDOSAGE section the innovator uses the phrase "calcium solutions", we have asked generic firms to use "calcium injection".

8. Scoring:

RLD - 120 mg/unscored
240 mg/scored

ANDA - 120 mg/unscored
240 mg/scored

[Vol. B1.3, section XIV, p 32-0369]

9. Storage:

RLD - Store at 59° to 77°F (15° to 25°C) and protect from light and moisture.

ANDA - Store between 15° and 25°C (59° and 77°F). Protect from light and moisture.

10. Dispensing

RLD - Dispense in tight, light-resistant containers.

ANDA - Dispense in tight, light-resistant containers.

USP - Preserve in tight, light-resistant containers.

Date of Review: 4-20-99 Date of Submission: 4-12-99

Primary Reviewer: Adolph Vezza Date:

/S/ 4/23/99

Team Leader: Charlie Hoppes Date:

/S/ 4/23/99

cc:

:ap.1.DOC

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

ANDA Number: **75-072** Date of Submission: **June 19, 1998**

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

Established Name: **Verapamil Hydrochloride Extended-release Tablets USP, 120 mg, and 240 mg**

Labeling Deficiencies

INSERT

1. DESCRIPTION

   Penultimate paragraph - ... *in vitro* ... (*italics*)

2. CLINICAL PHARMACOLOGY

   Pharmacokinetics and Metabolism - Replace all the text from "In a random ..." up to and including "... of verapamil hydrochloride (immediate release)." with the following paragraph:

   In a randomized, single-dose, crossover study using healthy volunteers, administration of verapamil hydrochloride extended-release tablets with food produced lower peak concentrations, delayed time to peak, and lesser total absorption (AUC) , than when the product was administered to fasting subjects. Similar results were demonstrated for plasma norverapamil. Food thus produces decreased bioavailability (AUC) but a narrower peak-to-trough ratio. Good correlation of dose and response is not available, but controlled studies of extended-release verapamil have shown effectiveness of doses similar to the effective doses of immediate-release verapamil.

   In healthy man, orally ...

3. HOW SUPPLIED

   Relocate the symbol "Rx only" to immediately beneath the title of the insert.

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

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

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

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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

ANDA Number: **75-072** Date of Submission: **June 19, 1998**

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

Established Name: **Verapamil Hydrochloride Extended-release Tablets USP, 120 mg, and 240 mg**

Labeling Deficiencies

INSERT

1. DESCRIPTION

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   In healthy man, orally ...

3. HOW SUPPLIED

   Relocate the symbol "Rx only" to immediately beneath the title of the insert.

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

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

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

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling?

Container Labels: 100s and 500s (120 mg and 240 mg)
Satisfactory as of June 19, 1998 submission.

Professional Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Isoptin® SR Tablets

NDA Number: 19-152

NDA Drug Name: Isoptin® SR (verapamil hydrochloride extended-release) Tablets

NDA Firm: Knoll Pharmaceuticals

Date of Approval of NDA Insert and supplement #: 1/13/98 (S-023)

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: labels on file

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Applicant's Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	

	Yes	No	N.A.
Is this product a USP item? If so, USP supplement in which verification was assured.	X		
Is this name different than that used in the Orange Book?		X	
Error Prevention Analysis			
PROPRIETARY NAME - NONE		X	
PACKAGING -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR. [For package sizes see FTR.]			
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product? [See FTR for storage/dispensing recommendations]		x	
Are there any other safety concerns?		x	
LABELING			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Error Prevention Analysis:			
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	

	Yes	No	N.A.
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			X
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR [See FTR]			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration? [Some of the inactive ingredients differ from the RLD].	X		
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		x	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		x	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		x	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		x	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable) [pending]			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why. See FTR].	X		
Patent/Exclusivity Issues: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state. [See FTR].			

FOR THE RECORD: (portions taken from previous review)

1. Labeling Model: Isoptin® SR (Knoll Laboratories; revised Sept. 1997 and approved Jan. 13, 1998 - **NDA 19-152/S-023**).

2. The inactive ingredients listed in the DESCRIPTION section are consistent with the firm's components and composition statements. [Vol. B1.2, section VII]

3. Closure:

   100s & 500s - nonCRC
   [Vol. B.1.3 section XIII]

4. The firm's physical description/imprints of their tablets in the HOW SUPPLIED section is NOT consistent with their Controls/Finished Dosage Form reports.
   -The discrepancy is only with the 240 mg tablet. The firm's product specifications/batch reports indicate that the 240 mg tablet is debossed with "H240". However, the HOW SUPPLIED section indicates that the 240 mg tablet is debossed with "dp 482". [Vol. B1.3, section XIV] **The debossing "dp482" will be used for the 240 mg dosage strength. A batch of product with this debossing has been manufactured.**

5. Packaging:

   RLD - 100s & 100s unit dose
   ANDA - 100s & 500s

6. No patent or exclusivity

7. Difference in the ANDA & RLD labeling:

   - The comment under CLINICAL PHARMACOLOGY (Pharmacokinetics and Metabolism) contains text that differs from RLD. See file folder for FTR dated 2/13/92. Since a copy of the latest Isoptin SR insert labeling went with the previous labeling deficiencies the firm mistakenly rerevised this section to be like the innovator - this review directs them to change it back.

   - In the OVERDOSAGE section the innovator uses the phrase "calcium solutions", we have asked generic firms to use "calcium injection".

8. Scoring:

RLD - 120 mg/unscored
180 mg/scored
240 mg/scored

ANDA - 120 mg/unscored
180 mg/scored **(firm has withdrawn this strength)**
240 mg/scored

[Vol. B1.3, section XIV, p. 32-0369

9. Storage:

RLD - Store at 59° to 77°F (15° to 25°C) and protect from light and moisture.

ANDA - STORAGE: Store between 15° and 25°C (59° and 77°F) Protect from light and moisture.

10. Dispensing:

RLD - Dispense in tight, light-resistant containers.

ANDA - Dispense in tight, light-resistant containers.

USP - Preserve in tight, light-resistant containers

Date of Review: 10-1-98 Date of Submission: 6-19-98

Primary Reviewer: Adolph Vezza Date: 11/6/98

Team Leader: Charlie Hoppes /S/ Date: 11/9/98

/S/

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cc:

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

ANDA Number: **75-072** Date of Submission: **October 24, 1997**

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

Established Name: **Verapamil Hydrochloride Extended-release Tablets USP, 120 mg, 180 mg and 240 mg**

Labeling Deficiencies:

1. General Comment

   Replace the "CAUTION: Federal law..." statement with the symbol "Rx only" or "℞ only" on your labels and labeling. We refer you to the Guidance for Industry, "Implementation of Section 126, Elimination of Certain Labeling Requirements...", at the internet site, **http://www.fda.gov/cder/guidance/index.htm** for guidance.

2. CONTAINER

   We acknowledge your comments that the USP Drug Release Test for your 120 mg and 180 mg drug products is still pending. However, we encourage you to add "USP" following the established name. Information regarding pending release tests need only to appear in the DESCRIPTION section of the package insert. Delete the asterisk on the front panel and the corresponding statement on the side panel, "The *in-vitro* USP ...".

3. INSERT

   a. General Comments

      i. Due to changes in the approved labeling of the reference listed drug, Isoptin SR® (Knoll Pharmaceutical Company; Approved January 13, 1998 and revised September 1997), we ask that you revise your package insert labeling to be in accord with the enclosed insert labeling.

ii. A "mocked-up" copy of the most currently approved insert of the reference listed drug is included indicating further revisions to your insert labeling.

b. HOW SUPPLIED

i. The tablet imprint of your 240 mg tablet is not consistent with your finished dosage form information that you have submitted ["H240" versus "dp 482"]. Please revise and/or comment.

ii. Indicate whether or not the tablet is scored for each strength.

Please revise your container labels and insert labeling, as instructed above, and submit draft package insert labeling or final print if you prefer.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

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

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Attachment: Copy of Isoptin SR® insert labeling.

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

ANDA Number: **75-072** Date of Submission: **October 24, 1997**

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

Established Name: **Verapamil Hydrochloride Extended-release Tablets USP, 120 mg, 180 mg and 240 mg**

Labeling Deficiencies:

1. General Comment

   Replace the "CAUTION: Federal law..." statement with the symbol "Rx only" or "℞ only" on your labels and labeling. We refer you to the Guidance for Industry, "Implementation of Section 126, Elimination of Certain Labeling Requirements...", at the internet site, **http://www.fda.gov/cder/guidance/index.htm** for guidance.

2. CONTAINER

   We acknowledge your comments that the USP Drug Release Test for your 120 mg and 180 mg drug products is still pending. However, we encourage you to add "USP" following the established name. Information regarding pending release tests need only to appear in the DESCRIPTION section of the package insert. Delete the asterisk on the front panel and the corresponding statement on the side panel, "The *in-vitro* USP ...".

3. INSERT

   a. General Comments

      i. Due to changes in the approved labeling of the reference listed drug, Isoptin SR® (Knoll Pharmaceutical Company; Approved January 13, 1998 and revised September 1997), we ask that you revise your package insert labeling to be in accord with the enclosed insert labeling.

ii. A "mocked-up" copy of the most currently approved insert of the reference listed drug is included indicating further revisions to your insert labeling.

b. HOW SUPPLIED

i. The tablet imprint of your 240 mg tablet is not consistent with your finished dosage form information that you have submitted ["H240" versus "dp 482"]. Please revise and/or comment.

ii. Indicate whether or not the tablet is scored for each strength.

Please revise your container labels and insert labeling, as instructed above, and submit draft package insert labeling or final print if you prefer.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

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

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Attachment: Copy of Isoptin SR® insert labeling.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Applicant's Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured.	X		
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			
Error Prevention Analysis			
PROPRIETARY NAME - NONE			
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
PACKAGING -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR. [For package sizes see FTR.]			
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		x	
Does the package proposed have any safety and/or regulatory concerns?		x	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product? [See FTR for storage/dispensing recommendations]			
Are there any other safety concerns?		x	
LABELING			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths?		X	

Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		x	
Error Prevention Analysis: *LABELING* (Continued)	**Yes**	**No**	**N.A.**
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		x	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			X
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR [See FTR]			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		x	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration? [Some of the inactive ingredients differ from the RLD].	X		
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		x	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		x	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?	•	x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		x	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		x	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		x	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		x	
Does USP have labeling recommendations? If any, does ANDA meet them?		x	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container? [See NOTE TO THE CHEMIST]	x		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable) [pending]			

Insert labeling references a food effect or a no-effect? If so, was a food study done?	x		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why. See FTR].	x		
Patent/Exclusivity Issues: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state. [See FTR].			

NOTE TO THE PROJECT MANAGER

Please ensure that the "mocked-up" insert labeling of the reference listed drug (ISOPTIN® SR) is faxed along with the labeling deficiencies.

NOTES TO THE CHEMIST

1. Is the Drug Release test listed in the DESCRIPTION section accurate? **YES**

2. The firm's physical description/imprints of their 240 mg tablets in the HOW SUPPLIED section is NOT consistent with their Controls/Finished Dosage Form reports. The firm's product specifications/batch reports indicate that the 240 mg tablet is debossed with "H240". However, the HOW SUPPLIED section indicates that the 240 mg tablet is debossed with "dp 482". Which description is accurate? **The debossing "dp482" will be used for the 240 mg dosage strength. A batch of product with this debossing has been manufactured.**

3. The USP recommends storage of this drug product in a tight, light-resistant container. Are the firm's containers tight and light-resistant? **YES**

FOR THE RECORD: (portions taken from previous review)

1. Labeling Model: Isoptin® SR (Knoll Laboratories; revised Sept. 1997 and approved Jan. 13, 1998 - **NDA 19-152/S-023**).

2. The inactive ingredients listed in the DESCRIPTION section are consistent with the firm's components and composition statements. [Vol. B1.2, section VII]

3. Closure:

100s & 500s - nonCRC
[Vol. B.1.3 section XIII]

4. The firm's physical description/imprints of their tablets in the HOW SUPPLIED section is NOT consistent with their Controls/Finished Dosage Form reports.
-The discrepancy is only with the 240 mg tablet. The firm's product specifications/batch reports indicate that the 240 mg tablet is debossed with "H240". However, the HOW SUPPLIED section indicates that the 240 mg tablet is debossed with "dp 482". [Vol. B1.3, section XIV] **The debossing "dp482" will be used for the 240 mg dosage strength. A batch of product with this debossing has been manufactured.**

5. Packaging:

RLD - 100s & 100s unit dose
ANDA - 100s & 500s

6. No patent or exclusivity

7. Difference in the ANDA & RLD labeling:

- The comment under CLINICAL PHARMACOLOGY (Pharmacokinetics and Metabolism) contains text that differs from RLD. See file folder for FTR dated 2/12/92.

- In the OVERDOSAGE section the innovator uses the phrase "calcium solutions", we have asked generic firms to use "calcium injection".

8. Scoring:

RLD - 120 mg/unscored
180 mg/scored
240 mg/scored

ANDA - 120 mg/unscored
180 mg/scored (bisected)
240 mg/scored (bisected)

[Vol. B1.3, section XIV, p. 32-0369

9. Storage:

RLD - Store at 59° to 77°F (15° to 25°C) and protect from light and moisture.

ANDA - STORAGE: Store between 15° and 25°C (59° and 77°F)
Protect from light and moisture.

10. Dispensing:

RLD - Dispense in tight, light-resistant containers.

ANDA - Dispense in tight, light-resistant containers.

USP - Preserve in tight, light-resistant containers

C /S/ ite
Primary Reviewer
Jacqueline White, Pharm.D.

4/9/98
Date

/S/
Team Leader

4/9/98
Date

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cc:

75-072

TELECON MINUTES-

DATE: 8/25/97 Subject: ANDA 75-011, Verapamil

FIRM: KEN PHELPS, DURAMED PHARMACEUTICALS, INC 513-458-7325

Recorder: Nancy Chamberlin, Pharm.D., Project Manager NC

The firm wanted clarification of the August 18, 1997 incomplete letter. The discussion on the specific questions in the letter follows below:

#2 The firm felt that it had passed on the least squares means at 125 and why was the arithmetic means done? Ans. The least square mean exceeded the acceptable range of 80-125% so it failed. Because it failed the reviewer looked at the arithmetic means, which also failed. If one had passed then the study would have passed. From the FDA's viewpoint both failed and the study will have to be redone.

#3 The firm tried to explain that the last dose was at 144 hours and they sampled after that. Ans. However, it appeared to our reviewer that the sixth dose was at 120 hours and the blood sampling should be from 120 to 144 hours. The firm will clarify the times of doses and sampling, and maybe it is a type error.

#4 Ans. The firm had submitted mean values for the dissolution test. The reviewer needs the specific values for each tablet. The firm will try to provide this.

tel

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

ANDA Number: 75-072

Date of Submission: February 10, 1997

Applicant's Name: Duramed Pharmaceuticals, Inc.

Established Name: Verapamil Hydrochloride Extended-release Tablets USP, 120 mg, 180 mg and 240 mg

Labeling Deficiencies:

1. CONTAINER: 120 mg, 180 mg and 240 mg - 100 and 500s

   a. General Comments

      We note you have included "USP" in the established name in your insert labeling. We also encourage the inclusion of "USP" in the established name on your container labels. Please revise accordingly.

   b. Revise your storage statement to read, "Store between 15° and 25°C (59° and 77°F").

2. INSERT

   a. General Comments

      i. Revise your insert labeling to be in accord with the enclosed copy of the insert labeling of Calan® SR (G.D. Searle & Co.; revised April 11, 1994 and approved July 28, 1994).

      ii. For consistency, hyphenate "extended-release", throughout your insert labeling.

      iii. Please refer to the enclosed mocked-up copy of your draft insert labeling for further revisions.

iv. Verapamil Hydrochloride Extended-release Tablets, USP is the established name of this product. Delete "(ER) Oral" from the title and "(ER)" from the product name throughout your insert labeling.

b. DESCRIPTION

i. You may delete the text referring to the physical description of your drug products, since this information is listed in the HOW SUPPLIED section.

ii. Revise the molecular weight to be in accord with USP 23/NF 18.

M.W. = 491.07

c. CLINICAL PHARMACOLOGY (Pharmacokinetics and Metabolism)

Start a new paragraph with the sentence, "In a randomized, single-dose, study ..., and revise the paragraph to read as follows:

In a randomized, single-dose, crossover study using healthy volunteers, administration of verapamil hydrochloride extended-release tablets with food produced lower peak concentrations, delayed time to peak, and lesser total absorption (AUC), than when the product was administered to fasting subjects. Similar results were demonstrated for plasma norverapamil. Food thus produces decreased bioavailability (AUC) but a narrower peak-to-trough ratio. Good correlation of dose and response is not available, but controlled studies of extended-release verapamil have shown effectiveness of doses similar to the effective doses of immediate release verapamil.

d. OVERDOSAGE

In the second paragraph revise "calcium solutions" to read "calcium injections".

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

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

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

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Enclosures:
1. Reference listed drug package insert labeling
2. Mocked-up copy of ANDA 75-072 package insert labeling

Department of Health and Human Services
Public Health Service
Food and Drug Administration
ESTABLISHMENT EVALUATION REPORT
for March 07, 1997

Requestor's Name: **Division:** **Phone:**

Application: ANDA 75072
Brand Name:
Established Name: VERAPAMIL HYDROCHLORIDE
Strength: 240 MG, 180 MG & 120 MG **Dosage Form** EXT
Org Code: 600 **Priority:**

Sponsor: DURAMED PHARMS
Office:
Street: 5040 LESTER RD
City / State: CINCINNATI, OH 45213
Action Goal:

District Goal:

User Fee Goal:

Establishment: **Name:**

Responsibilities	Dmf No	Profile	Status	Date
DRUG SUBSTANCE RELEASE TESTER		NEC		

Establishment: **Name:**

Responsibilities	Dmf No	Profile	Status	Date
FINISHED DOSAGE MANUFACTURER		T		

Establishment: **Name:**

Responsibilities	Dmf No	Profile	Status	Date
DRUG SUBSTANCE RELEASE TESTER				

Establishment: **Name:**

Responsibilities	Dmf No	Profile	Status	Date
DRUG SUBSTANCE MANUFACTURER				

CSO	Date	Recommendation

ANDA CHECKLIST FOR COMPLETENESS and ACCEPTABILITY of the APPLICATION

AADA / ANDA # 75072 FIRM NAME Dunnared

DRUG NAME: Verapamil HCl

DOSAGE FORM: Extended-release Tablets USP, 120mg, 180mg, 240mg

Supervisory Chemist (Summers) Labeling Reviewer (Adolph Viggiano)

Random Assignment (Random II)

	YES	NO
Comments EC3 ✓ On Cards ✓		
Therapeutic Code 10|0300 ✓ Calcium channel Blockers	2|10|97 2|10|97	
Methods Validation Package (3 copies) (ND) Required for Non-USP drugs		
Cover Letter	✓	
Letter of Authorization	na	
U.S. Agent (If needed, Countersignature on 356h)	na	
DMF Referral(s)	✓	
356 Form - Completed /Original Signature ✓	✓	
Table of Contents	✓	
Listed Drug/Firm Isoptin SR Tablets	✓	
AADA Monograph	na	
Information to show proposed product is the same as the listed product: (i) (a) indications (ii) active ingredients(s) iii (a) route (b) dosage form (c) strength (iv) labeling – side by side comparison - insert:	✓	
Container:	✓	
Same Formulation? solid-oral dosage form	na	
Ophthalmics/Otics/Externals Parenterals	|	
Parenteral: Same Size Container / (strength/volume)	|	
Petition Required		✓
Debarment Certification (p. 32-0482)	✓	
List of Convictions	✓	
Third Copy Certification (w/ cover letter)	✓	
Patent Certification	✓ 2	
Use Patent Statement? Exclude Use in labeling / indications?		✓
Exclusivity Addressed	✓	

Five year exclusivity? If yes, cannot be filed until expiration of exclusivity or after 4 years if patent challenged.		✓
Labeling: 4 copies of draft (✓) or 12 copies of FPL ( )	✓	
Statement re Rx/OTC Status	356h ✓	
Components & Composition (Unit Composition)	✓	
Specifications and Tests for Active Ingredients and Dosage Form		
Source of Active Ingredient(s)	✓	
COA from Manufacturer of Active Ingredient(s)	✓	
Applicant COA	✓	
COA for finished product Q. 32-0373	✓	
Specifications and Tests for Inactive Ingredients		
Source of Inactive Ingredients Identified	✓	
Applicant COA for Inactive Ingredient	✓	
COA from Manufacturer of Inactive Ingredients	✓	
Manufacturing Controls	✓	
Batch Formulation	✓	
Master Production Batch Record for largest batch size intended for production (No more than 10x pilot batch)		
Certification of GMP	✓	
Description of Facilities	✓	
Address of Manufacturing Site for Production Batches	✓	
Manufacturing Procedures (Batch Records)		
Package entire test batch	✓	
Batch Number(s)	✓	
Mfg. Facility Akeelmann	✓	
If Sterile product: Aseptic Fill _____ Terminal Sterilization _____	na	
Stability Profile Including stability Data (Use of Stability Indication Method)		
3 months Accelerated Stability Data	✓	
Batch Number(s) Listed on Stability Records (Batch number(s) the same as the test batch	✓	
Sample Statement Plus Data	✓	
Bioavailability/Bioequivalence Study DISK Enclosed	✓	
In Vivo Study/Waiver Request		
Comparative Dissolution Data	✓	

Paragraph IV bio study acceptable for filing		
Date acceptable for filing		
Computer Disk Submitted		
Environmental Impact Analysis	✓	
Compliance Statement	✓	

Reviewing CSO / CST (/S/

Date 3/6/97

Recommendation **FILE** **REFUSE to FILE**

Supervisory Concurrence / Date 3/25/97

Duplicate copy sent to Bio:
(Hold if RF and send when acceptable)

Duplicate copy to HFD _____ **for Consult**

Type of Consult:

Micro Assignment:

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

ANDA Number: 75-072

Date of Submission: February 10, 1997

Applicant's Name: Duramed Pharmaceuticals, Inc.

Established Name: Verapamil Hydrochloride Extended-release Tablets USP, 120 mg, 180 mg and 240 mg

Labeling Deficiencies:

1. CONTAINER: 120 mg, 180 mg and 240 mg - 100 and 500s

   a. General Comments

      We note you have included "USP" in the established name in your insert labeling. We also encourage the inclusion of "USP" in the established name on your container labels. Please revise accordingly.

   b. Revise your storage statement to read, "Store between 15° and 25°C (59° and 77°F").

2. INSERT

   a. General Comments

      i. Revise your insert labeling to be in accord with the enclosed copy of the insert labeling of Calan® SR (G.D. Searle & Co.; revised April 11, 1994 and approved July 28, 1994).

      ii. For consistency, hyphenate "extended-release", throughout your insert labeling.

      iii. Please refer to the enclosed mocked-up copy of your draft insert labeling for further revisions.

iv. Verapamil Hydrochloride Extended-release Tablets, USP is the established name of this product. Delete "(ER) Oral" from the title and "(ER)" from the product name throughout your insert labeling.

b. DESCRIPTION

i. You may delete the text referring to the physical description of your drug products, since this information is listed in the HOW SUPPLIED section.

ii. Revise the molecular weight to be in accord with USP 23/NF 18.

M.W. = 491.07

c. CLINICAL PHARMACOLOGY (Pharmacokinetics and Metabolism)

Start a new paragraph with the sentence, "In a randomized, single-dose, study ..., and revise the paragraph to read as follows:

In a randomized, single-dose, crossover study using healthy volunteers, administration of verapamil hydrochloride extended-release tablets with food produced lower peak concentrations, delayed time to peak, and lesser total absorption (AUC), than when the product was administered to fasting subjects. Similar results were demonstrated for plasma norverapamil. Food thus produces decreased bioavailability (AUC) but a narrower peak-to-trough ratio. Good correlation of dose and response is not available, but controlled studies of extended-release verapamil have shown effectiveness of doses similar to the effective doses of immediate release verapamil.

d. OVERDOSAGE

In the second paragraph revise "calcium solutions" to read "calcium injections".

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

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

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

7-25-97

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Enclosures:
1. Reference listed drug package insert labeling
2. Mocked-up copy of ANDA 75-072 package insert labeling

NOTE TO THE CHEMIST

1. Are the Drug release tests listed in the DESCRIPTION section accurate?

2. The firm's physical description/imprints of their 240 mg tablets in the HOW SUPPLIED section is NOT consistent with their Controls/Finished Dosage Form reports.
The firm's product specifications/batch reports indicate that the 240 mg tablet is debossed with "H240". However, the HOW SUPPLIED section indicates that the 240 mg tablet is debossed with "dp 482".
Which description is accurate?

3. The USP recommends storage of this drug product in a tight, light-resistant container. Are the firm's containers tight and light-resistent?

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Applicant's Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured.	X		
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			
Error Prevention Analysis			
PROPRIETARY NAME			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
PACKAGING -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR. [For package sizes see FTR.]			
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		x	
Does the package proposed have any safety and/or regulatory concerns?		x	

If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product? [See FTR for storage/dispensing recommendations]			
Are there any other safety concerns?		x	
LABELING			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		x	
Error Prevention Analysis: *LABELING* (Continued)	**Yes**	**No**	**N.A.**
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		x	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			X
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR [See FTR]			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		x	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration? [Some of the inactive ingredients differ from the RLD].	X		

Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		x	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		x	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		x	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		x	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		x	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		x	
Does USP have labeling recommendations? If any, does ANDA meet them?		x	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container? [See NOTE TO THE CHEMIST]	x		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioeqivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable) [pending]			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	x		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why. [See FTR].	x		
Patent/Exclusivity Issues: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state. [See FTR].			

FOR THE RECORD:

1. Labeling Model: Calan® SR (G.D. Searle & Co.; revised April 11, 1997 and approved July 28, 1994).

2. The inactive ingredients listed in the DESCRIPTION section are consistent with the firm's components and composition statements.
[Vol. B1.2, section VII]

3. Closure:

100s & 500s - nonCRC
[Vol. B.1.3 section XIII]

4. The firm's physical description/imprints of their tablets in the HOW SUPPLIED section is NOT consistent with their Controls/Finished Dosage Form reports.
-The discrepancy is only with the 240 mg tablet. The firm's product specifications/batch reports indicate that the 240 mg tablet is debossed with "H240". However, the HOW SUPPLIED section indicates that the 240 mg tablet is debossed with "dp 482".
-See NOTE TO THE CHEMIST
[Vol. B1.3, section XIV]

5. Packaging:

RLD - 100s & 100s unit dose
ANDA - 100s & 500s

6. No patent or exclusivity

7. Difference in the ANDA & RLD labeling:

- The comment under CLINICAL PHARMACOLOGY (Pharmacokinetics and Metabolism) contains text that differs from RLD. See file folder for FTR dated 2/12/92.

- In the OVERDOSAGE section the innovator uses the phrase "calcium solutions", we have asked generic firms to use "calcium injection".

8. Scoring:

RLD - 120 mg/unscored
180 mg/scored
240 mg/scored

ANDA - 120 mg/unscored
180 mg/scored
240 mg/scored

9. Storage:

RLD - Store at 59° to 77°F (15° to 25°C) and protect from light and moisture.

ANDA - STORAGE: 59°- 77°F (15° - 25°C)
Protect from light and moisture.
[See comment under CONTAINER]

10. Dispensing:

RLD - Dispense in tight, light-resistant containers.

ANDA - Dispense in tight, light-resistant containers.

USP - Preserve in tight, light-resistant containers

/S/

Primary Reviewer
Jacqueline White, Pharm.D.

7/25/97
Date

/S/

Secondary Reviewer

7/25/97
Date

/S/

Team Leader
Labeling Review Branch

Date

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Endorsements: