

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

40136

ADMINISTRATIVE DOCUMENTS

RECORD OF TELEPHONE CONVERSATION

DATE: March 13, 1997

PRODUCT NAME: Hydralazine HCl Injection

ANDA/AADA NUMBER: 40-136

FIRM NAME: Luitpold Pharmaceuticals Inc.

**NAME AND TITLE OF PERSON WITH
WHOM CONVERSATION WAS HELD:**

Robert Anderson, Drug Regulatory Affairs, Luitpold

PARTICIPANT(S) TELEPHONE:

Melissa Maust, Review Chemist, Branch I, Chemistry, OGD, CDER, FDA
Dr. Vilayat Sayeed, Team Leader, Branch I, Chemistry, OGD, CDER, FDA
James Wilson III, Project Manager, Branch I, Chemistry, OGD, CDER, FDA

MINUTES OF CONVERSATION:

We asked about the internal alert specification for finished product. Mr. Anderson explained that this spec is used as a benchmark so that any total impurities above % generates a full GMP investigation along with a historical review of the product. Ms. Maust asked why the finished product impurity spec was set at % when the data on the exhibit batch did not support the spec? We asked Luitpold to reduce the specification based on twelve month stability data collected.

The USP allows 1% impurities for the drug substance. We would like Luitpold to identify the impurities rather than the retention times. We asked if the individual limit on impurities is still %? Mr. Anderson stated that the limits have not changed.

NAME OF OGD REPRESENTATIVE:

Melissa Maust, Review Chemist, Branch I, Chemistry, OGD, CDER, FDA

SIGNATURE OF OGD REPRESENTATIVE:

MS 4-2-97

DIVISION/BRANCH: Office of Generic Drugs Division I, Branch 1.

MINUTES PREPARED BY:

James Wilson III, Project Manager, Branch I, Chemistry, OGD, CDER, FDA

RECORD OF TELEPHONE CONVERSATION

DATE: February 13, 1997

PRODUCT NAME: Hydralazine HCl Injection

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MINUTES OF CONVERSATION:

We responded to questions from our last deficiency letter as clarifications. For tests and specifications related to impurities we asked for data to support the stated specifications. Expiration dating can be extended post-approval with data from three post-approval lots of finished product. The data shows a drop in pH after one year, please explain. We require sterility and endotoxin testing at the end of the expiration dating in the inverted position. We discussed vendor qualification batch to batch for stoppers until the vendor is qualified in our 1/15/97 teleconference. We would like a commitment to test for stopper extractables for the first three lots and then annually thereafter. We asked that these responses be submitted as a telephone amendment.

NAME OF OGD REPRESENTATIVE:

Melissa Maust, Review Chemist, Branch I, Chemistry, OGD, CDER, FDA

SIGNATURE OF OGD REPRESENTATIVE:

MS 4297

DIVISION/BRANCH: Office of Generic Drugs Division I, Branch 1.

MINUTES PREPARED BY:

James Wilson III, Project Manager, Branch I, Chemistry, OGD, CDER, FDA

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

Date of Review: July 5, 1996

ANDA Number: 40-136

Review Cycle: #2

Date of Submission: June 21, 1996

Applicant's Name [as seen on 356(h)]: Luitpold Pharmaceuticals,
Inc.

Manufacturer's Name (If different than applicant):

Proprietary Name: None

Established Name: Hydralazine Hydrochloride Injection, USP
(20 mg/mL)

Reviewer: C. Park

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

A. Do you have 12 Final Printed Labels and Labeling? Yes

CONTAINER LABELS: Satisfactory in final print as of 6/21/96
submission

CARTON LABELING: Satisfactory in final print as of 6/21/96
submission

PACKAGE INSERT LABELING: Satisfactory in final print as of
6/21/96 submission

C. BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Apresoline Hydrochloride
Injection, USP by Ciba-Geigy, ltd.

NDA Number: 08-303

NDA Drug Name: Apresoline Hydrochloride Injection, USP

NDA Firm: Ciba-Geigy, ltd.

Date of Approval of NDA Insert and supplement #: Approved 12/22/86 (SLR/059 According to Mr. William Hall in the DDIR this is the latest labeling revision for Apresoline® Injection).

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: CFR, USP and side-by-side comparison

Basis of Approval for the Carton Labeling: CFR, USP and side-by-side comparison

Other Comments: (revisions needed post-approval)

CARTON: At first revision - Bold the statement "For emergency use - only in patients unable to take oral medication".

INSERT: At first revision - Replace the hyphens in the DOSAGE AND ADMINISTRATION section with the word "to" (e.g. 20 to 40mg...).

REVIEW OF PROFESSIONAL LABELING CHECKLIST

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			
<i>PROPRIETARY NAME</i>			
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	
<i>PACKAGING</i> -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA for this drug product? 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 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	
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 (p. #) in the FTR			x
Is the scoring configuration different than the RLD? -			
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			
Inactive Ingredients: (FTR: List p. # 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?		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?		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: 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.			

NOTES/QUESTIONS TO THE CHEMIST:

FOR THE RECORD:

1. Model for package insert: Apresoline®, Ciba, rev.4/86, approved 12/22/86 (SLR/059). According to the Orange book and COMIS system both Apresoline HCL Injection and Tablet have same NDA #08303. I have checked with Mr. William Hall in DDIR to find out what is the latest labeling revision was made. The labeling approved 12/22/96 is the latest one for the injection to his best knowledge.
2. No patents or exclusivities exist.
3. The innovator carton labeling is labeled as follows:
For emergency use - only in patients unable to take oral medication.

Neither the applicant nor the only approved generic (Solopak's ANDA 88-517) retained this statement on the carton labeling. No FTR regarding this statement could be found. After discussion with the Acting Branch Chief it was decided that this statement could guide the use of this product and therefore that it should be requested for the applicant and in a letter to an annual report for the approved ANDA.

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

Date of Review: 4/4/96 Date of Submission: 2/17/95

Primary Reviewer: Charlie Hoppes

Secondary Reviewer: John Grace

ANDA Number: 40-136

Review Cycle: 1

Applicant's Name [as seen on 356(h)]: Luitpold Pharmaceuticals,
Inc.

Established Name: Hydralazine Hydrochloride Injection USP,
20 mg/mL

LABELING DEFICIENCIES, WHICH ARE TO BE INCORPORATED WITH THE
CHEMISTRY COMMENTS TO THE FIRM:

[NOTE: These deficiencies can be located on the x-drive as
detailed in notes from Ted Sherwood regarding the New X-Drive]

A. CHEMISTRY DEFICIENCIES

B. LABELING DEFICIENCIES

1. GENERAL COMMENT:

Revise your storage recommendation to appear as
follows:

Store between 15°-30°C (59°-86°F)

2. CONTAINER

See General Comment.

3. CARTON

- a. Include the following statement as seen on the carton labeling of the listed drug:

For emergency use - only in patients unable to take oral medication.

- b. We encourage the inclusion of a pH range as seen in your package insert labeling (DESCRIPTION).

4. INSERT

a. DESCRIPTION

- i. First paragraph, last line, "...Hydrazinophthalazine...", (capital "H").
- ii. Include the molecular formula of hydralazine hydrochloride, " $C_8H_8N_4 \cdot HCl$ ".

b. PRECAUTIONS

- i. Revise to read "hydralazine", rather than throughout this section with the following exceptions:

- Second paragraph in the Laboratory Tests subsection (should read "hydralazine hydrochloride").
- In the Pediatric Use subsection.

ii. Pediatric Use

...in pediatric patients have...

c. HOW SUPPLIED

See General Comment.

Please revise your labels and labeling, as instructed above, and submit final print labeling. 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. Please note that we

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

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

Do you have 12 Final Printed Labels and Labeling? Yes No
If no, list why:

Container Labels:

Carton Labeling:

Unit Dose Blister Label:

Unit Dose Carton Label:

Professional Package Insert Labeling:

Patient Package Insert Labeling:

Auxiliary Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? Yes No

What is the RLD on the 356(h) form:

NDA Number:

NDA Drug Name:

NDA Firm:

Date of Approval of NDA Insert and supplement #:

Has this been verified by the MIS system for the NDA?
Yes No

Was this approval based upon an OGD labeling guidance?
 Yes No

If yes, give date of labeling guidance:

Basis of Approval for the Container Labels:

Basis of Approval for the Carton Labeling:

Other Comments:

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?			X
Error Prevention Analysis			
<i>PROPRIETARY NAME</i>			
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?			
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?			
<i>PACKAGING</i> -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.		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	

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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.	?		
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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	

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Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
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4. The applicant did not include the statement regarding inspection for particulate matter, on carton labeling as does the innovator. The statement does not appear on carton labeling of the only approved ANDA. It also

