CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 73-479

Name: Sterile Pentamidine Isethionate, 300 mg/vial

Sponsor: Abbott Laboratories

Approval Date: June 30, 1992

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 73-479

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 73-479

APPROVAL LETTER

ANDA 73-479

JUN 30 1992

Abbott Laboratories
Hospital Products Division
Attention: Frederick A. Gustafson
One Abbott Park Road
Abbott Park, IL 60064-3500

Dear Sir:

Reference is made to your abbreviated new drug application dated September 12, 1989, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Sterile Pentamidine Isethionate, 300 mg/vial.

Reference is also made to your amendments dated May 11 and 15, 1992.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence agrees that the information submitted by Abbott Laboratories demonstrates that Sterile Pentamidine Isethionate, 300 mg/vial, falls under 21 CFR Section 320.22 (c)(2) of the Bioavailability/Bioequivalence Regulations. The waiver of in-vivo bioequivalence study requirements for 300 mg/vial injection of the test product is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test injectable formulation to be bioequivalent to Pentam® 300, 300 mg/vial, manufactured by LyphoMed, Inc.

Any significant change in the conditions outlined in this abbreviated application requires an approved supplemental application before the change may be made, except for changes made in conformance with other provisions of Section 314.70 of the Regulations.

Postmarketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80 and 314.81 of the Regulations.

This administration should be advised of any change in the marketing status of this drug.

For Initial Campaigns: We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your immediate advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form,

not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

For Subsequent Campaigns: We call your attention to Section 314.81(b)(3) of the Regulations which requires that materials for any subsequent advertising or promotional campaign, at the time of their initial use, be submitted to our Division of Drug Marketing, Advertising and Communications (HFD-240) with a completed Form FD-2253.

Sincerely yours,

6/30/92

Roger L. Williams, M.D.
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA #43-479
DUP/Division File
HFC-130/JAllen
HFD-19
HFD-82
HFD-600 Reading File
HFD-638/KShah 6/4-5-92 Stephen Sherken 6/5/92
HFD-634/MSmela/SSherken/06/02/92
HFD-634/VVashio/06/04/92
R/D initialed by MSmela MSmela 6/5/92 pending Micro consult & EER ← Noted Revised Claims
cls/06/05/92/d:43-479.LTR
F/T by cls/06/05/92
Approval

R.A. Jewssi 6/23/92

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 73-479

APPROVED LABELING

RAO4279-R4-Rev. Sept., 1991

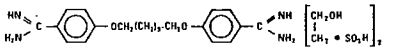
Sterile Pentamidine Isethionate

Fliptop Vial

DESCRIPTION

Sterile Pentamidine Isethionate, an antiprotozoal agent, is a nonpyrogenic, lyophilized product. After reconstitution, it should be administered by intramuscular or intravenous (I.M. or I.V.) routes (see DOSAGE AND ADMINISTRATION).

Pentamidine isethionate is a white, crystalline powder soluble in water and glycerin and insoluble in ether, acetone, and chloroform. It is chemically designated as 4,4'-diamidinodiphenoxypentane di (β-hydroxyethanesulfonate) with the following structural formula:



$C_{23}H_{36}N_4O_{10}S_2$ 592.68

Each vial contains:

Pentamidine isethionate ..... 300 mg

May contain sodium hydroxide and/or hydrochloric acid for pH adjustment. Headspace nitrogen gassed.

CLINICAL PHARMACOLOGY

Pentamidine isethionate, an aromatic diamidine, is known to have activity against *Pneumocystis carinii.*

The mode of action of pentamidine is not fully understood. *In vitro* studies with mammalian tissues and the protozoan *Crithidia oncopelti* indicate that the drug interferes with nuclear metabolism producing inhibition of the synthesis of DNA, RNA, phospholipids and proteins.

Little is known about the drug's pharmacokinetics. Preliminary studies have shown that in seven patients treated with daily I.M. doses of pentamidine at 4 mg/kg for 10 to 12 days, plasma concentrations were between 0.3 and 0.5 mcg/mL. The levels did not appreciably change with time after injection or from day to day. Higher plasma levels were encountered in patients with an elevated BUN. The patients continued to excrete decreasing amounts of pentamidine in urine up to six to eight weeks after cessation of the treatment.

Tissue distribution has been studied in mice given a single intraperitoneal injection of pentamidine at 10 mg/kg. The concentration in the kidneys was the highest followed by that in the liver. In mice, pentamidine was excreted unchanged, primarily via the kidneys with some elimination in the feces. The ratio of amounts excreted in the urine and feces (4:1) was constant over the period of study.

INDICATIONS AND USAGE

Sterile pentamidine isethionate is indicated for the treatment of pneumonia due to *Pneumocystis carinii.*

CONTRAINDICATIONS

Once the diagnosis of *Pneumocystis carinii* pneumonia has been firmly established, there are no absolute contraindications to the use of pentamidine isethionate.

WARNINGS

Fatalities due to severe hypotension, hypoglycemia and cardiac arrhythmias have been reported in patients treated with pentamidine isethionate, both by the I.M. and I.V. routes. Severe hypotension may result after a single dose (see PRECAUTIONS). The administration of the drug should, therefore, be limited to the patients in whom *Pneumocystis carinii* has been demonstrated. Patients should be closely monitored for the development of serious adverse reactions (see PRECAUTIONS and ADVERSE REACTIONS).

JUN 30 1992

APPROVED

PRECAUTIONS

General

Pentamidine isethionate should be used with caution in patients with hypertension, hypotension, hypoglycemia, hyperglycemia, hypocalcemia, leukopenia, thrombocytopenia, anemia, and hepatic or renal dysfunction.

Patients may develop sudden, severe hypotension after a single dose of pentamidine isethionate, whether given I.V. or I.M. Therefore, patients receiving the drug should be lying down and the blood pressure should be monitored closely during administration of the drug and several times thereafter until the blood pressure is stable. Equipment for emergency resuscitation should be readily available. If pentamidine isethionate is administered I.V., it should be infused over a period of 60 minutes.

Pentamidine isethionate-induced hypoglycemia has been associated with pancreatic islet cell necrosis and inappropriately high plasma insulin concentrations. Hyperglycemia and diabetes mellitus, with or without preceding hypoglycemia, have also occurred, sometimes several months after therapy with pentamidine isethionate. Therefore, blood glucose levels should be monitored daily during therapy with pentamidine isethionate, and several times thereafter.

Laboratory Tests

The following tests should be carried out before, during and after therapy:

a) Daily blood urea nitrogen and serum creatinine determinations.
b) Daily blood glucose determinations.
c) Complete blood count and platelet count.
d) Liver function tests, including bilirubin, alkaline phosphatase, AST (SGOT), and ALT (SGPT).
e) Serum calcium determinations.
f) Electrocardiograms at regular intervals.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been conducted to evaluate the potential of pentamidine isethionate as a

carcinogen, mutagen, or cause of impaired fertility.

Pregnancy Category C

Animal reproduction studies have not been conducted with pentamidine isethionate. It is also not known whether pentamidine isethionate can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Pentamidine isethionate should be given to a pregnant woman only if clearly needed.

ADVERSE REACTIONS

CAUTION: Fatalities due to severe hypotension, hypoglycemia and cardiac arrhythmias have been reported in patients treated with pentamidine isethionate, both by the I.M. and I.V. routes. The administration of the drug should, therefore, be limited to the patients in whom *Pneumocystis carinii* has been demonstrated.

Of 424 patients treated with pentamidine isethionate, 244 (57.5%) developed some adverse reaction. Most of the patients had the acquired immunodeficiency syndrome (AIDS). In the following table, "Severe" refers to life-threatening reactions or reactions that required immediate corrective measures and led to discontinuation of pentamidine isethionate.

Adverse Reactions	Number	%
Severe		
Leukopenia (<1000/mm³)	12	2.8
Hypoglycemia (<25 mg/dL)	10	2.4
Thrombocytopenia (<20,000/mm³)	7	1.7
Hypotension (<60 mm Hg systolic)	4	0.9
Acute renal failure (serum creatinine >6 mg/dL)	2	0.5
Hypocalcemia	1	0.2
Stevens-Johnson syndrome	1	0.2
Ventricular tachycardia	1	0.2
Total number of patients with severe effects*	37	8.7
Moderate		
Elevated serum creatinine (2.4 to 6.0 mg/dL)	98	23.1
Sterile abscess, pain, or induration at the site of I.M. injection	47	11.1
Elevated liver function tests	37	8.7
Leukopenia	32	7.5
Nausea, anorexia	25	5.9
Hypotension	17	4.0
Fever	15	3.5
Hypoglycemia	15	3.5
Rash	14	3.3
Bad taste in mouth	7	1.7
Confusion/hallucinations	7	1.7
Anemia	5	1.2
Neuralgia	4	0.9
Thrombocytopenia	4	0.9
Hyperkalemia	3	0.7
Phlebitis	3	0.7
Dizziness (without hypotension)	2	0.5
Other moderate adverse reactions**	5	1.2
Total number of patients with moderate adverse reactions*	207	48.8

* Patient total may not equal sum of reactions, since some patients had more than one reaction.

**Each of the following moderate adverse reactions was reported in one patient: Hypocalcemia, abnormal ST segment of electrocardiogram, bronchospasm, diarrhea, and hyperglycemia.

DOSAGE AND ADMINISTRATION

Pentamidine isethionate should be administered I.M. or I.V. only. The recommended regimen for adults and children is 4 mg/kg once a day for 14 days. The benefits and risks of therapy with pentamidine isethionate for more than 14 days are not well defined.

Intramuscular Injection

The contents of one vial (300 mg) should be dissolved in 3 mL of Sterile Water for Injection. The calculated daily dose should then be withdrawn and administered by deep I.M. injection.

Intravenous Injection

The contents of one vial should first be dissolved in 3 to 5 mL of Sterile Water for Injection or Dextrose Injection 5%. The calculated dose of pentamidine isethionate should then be withdrawn and diluted further in 50 to 250 mL of Dextrose Injection 5%. **The diluted I.V. solutions containing pentamidine isethionate should be infused over a period of 60 minutes.**

Aseptic technique should be employed in preparation of all solutions. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

Stability: Intravenous infusion solutions of pentamidine isethionate at 1 mg and 2.5 mg/mL prepared in Dextrose Injection 5% are stable at room temperature for up to 24 hours.

HOW SUPPLIED

Sterile Pentamidine Isethionate is a sterile, lyophilized powder supplied in a single-dose, fliptop vial containing 300 mg of pentamidine isethionate packaged in individual cartons (List 4548).

Store the dry product at controlled room temperature 15° to 30°C (59° to 86°F). Protect the dry product and reconstituted solution from light.

Discard unused portions.

Caution: Federal (USA) law prohibits dispensing without prescription.

Printed in USA

ABBOTT LABORATORIES, NORTH CHICAGO, IL60064, USA

ORIG

FOR IM or IV USE
Each vial contains Pentamidine Isethionate 300 mg. Reconstitute vial contents with Sterile Water for Injection, USP or Dextrose Injection 5%, USP only as directed in package insert. USUAL DOSAGE: See package insert. Store the dry product at controlled room temperature 15° to 30°C (59° to 86°F). Protect the dry product and reconstituted solution from light. Retain in carton until time of use. Caution: Federal (USA) law prohibits dispensing without prescription.

RAO4277-2/R3-9/91

Exp.

Lot

Reconstituted on _____

at _____ AM. PM.

Abbott Laboratories
North Chicago, IL60064, USA

APPROVED

NDC 0074-4548-01
Sterile lyophilized powder

Sterile Pentamidine Isethionate 300 mg

For IM or IV Use
Single Dose Vial
Discard unused portion.

JUN 30 1992

NDC 0074-4548-01

Single-dose
Fliptop Vial
Sterile Lyophilized Powder

Sterile
Pentamidine
Isethionate
300 mg

Store the dry product at controlled room temperature 15° to 30°C (59° to 86°F).

Protect the dry product and reconstituted product from light. Retain in carton until time of use.

Caution: Federal (USA) law prohibits dispensing without prescription.

Exp. JUN 30 1992

Lot APPROVED

RAO4278-27R4-9/91

Printed in USA

NDC 0074-4548-01

Single-dose Fliptop Vial
Sterile Lyophilized Powder

Sterile Pentamidine Isethionate 300 mg

For IM or IV Use

Single-dose Vial, discard unused portion.

ABBOTT LABS, N. CHGO, IL60064, USA

Each vial contains: Pentamidine isethionate 300 mg.
May contain sodium hydroxide and/or hydrochloric acid for pH adjustment. Headspace nitrogen gassed.

USUAL DOSAGE:
Recommended regimen for adults and children is 4 mg/kg once a day for 14 days. The benefits and risks of therapy with pentamidine isethionate for more than 14 days are not well defined.

RECONSTITUTION AND ADMINISTRATION:
Intramuscular Injection: The contents of 1 vial (300 mg) should be dissolved in 3 mL of Sterile Water for Injection, USP. The calculated daily dose should then be withdrawn and administered by deep intramuscular injection.
Intravenous Injection: The contents of 1 vial should first be dissolved in 3 to 5 mL of Sterile Water for Injection, USP or Dextrose Injection 5%, USP only. The calculated dose of pentamidine isethionate should then be withdrawn and diluted further in 50 to 250 mL of Dextrose Injection 5%, USP. **The diluted intravenous solutions containing pentamidine isethionate should be infused over a period of 60 minutes.**
For additional information, see package insert.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 73-479

LABELING REVIEW(S)

REVIEW OF PROFESSIONAL LABELING

ANDA

DRAFT - Container Labels, Carton and Package Insert Labeling

DATE OF REVIEW: 2/2/90

ANDA #: 73-479 NAME OF FIRM: Abbott Laboratories

NAME OF DRUG:

Generic: Sterile Pentamidine Isethionate, 300 mg

DATE OF SUBMISSION: 9/12/89

COMMENTS:

Container: Not Satisfactory

A. Add "Discard unused portion." This should be linked with "Single Dose Vial".

B. Add:

Reconstituted on _____ at _____ AM PM.

C. Reconstitution information

Relocate "5%" so it appears between "Injection" and "USP". [Refer to USP XXII, p. 1472 if you have questions.]

D. Storage Recommendations

1) Store the dry...(Add "the".)
2) Protect the dry...(Add "the".)

Carton: Not Satisfactory

A. See comments A., C. and D. under Container.

B. ADMINISTRATION

1) Revise to read RECONSTITUTION AND ADMINISTRATION.

2) Intravenous Injection

a) We prefer:

i) 3 to 5 (rather than 3-5)
ii) 50 to 250 (rather than 50-250)

b) Sentence 2 - ...dextrose injection 5%.

c) The final sentence should appear in bold print.

d) See comment C under Container.

Insert: Not Satisfactory

A. DESCRIPTION

Paragraph 2, line 1 - Place a comma (,) after "white."

B. PRECAUTIONS

1) Paragraph 2 should appear in bold print. The quality of the xerox prevents us from determining if this has been done.

2) Laboratory Tests, item d - tests (plural)

C. ADVERSE REACTIONS

The section heading and first two paragraphs are missing.

D. DOSAGE AND ADMINISTRATION

1) See comments B. 2. c. and d. under Carton.

2) It is not necessary to include "USP" in this section.

E. HOW SUPPLIED

1) Line 1

a) Place a comma (,) after "sterile" and "single-dose."

b) ...300 mg of pentamidine isethionate.

c) Please indicate the carton size in this section.

F. The requirements of 21 CFR 201.56(e) must be met.

RECOMMENDATIONS:

1. Inform the firm of the above comments.

2. Request the firm revise their labels and labeling, then prepare and submit draft copy for our review and comment.

3. Chemist

   A. As we interpret it lyophilized means freeze-dried. Is this product actually freeze-dried? Is the innovator's product actually freeze-dried?

   Yes. Both are lyophilized.

   B. Please see the final paragraph in the DOSAGE AND ADMINISTRATION section. The firm needs to submit data to support this claim.

   Data was submitted on 4/12/90

   C. Please double check the structural formula. It agrees with USAN but not with the innovator's labeling.

   Both are correct A.

4. FOR THE RECORD

   A. This product is covered by orphan drug exclusivity until 10/16/91.

   B. We note that the LyphoMed labeling does not provide information on storage or stability of the reconstituted product before it is either further diluted or administered IM. The Handbook of Injectable Drugs (Trissel) does provide some information. We have sent a consult to HFD-530 seeking their input into this issue.

Yana Mille

Yana Mille

cc: HFD-630
Y. Mille 2/8/90
YMille/TPoux
ms: 2/7/90 (4048m)
DUP
2/8/90

REVIEW OF PROFESSIONAL LABELING

Original Amendment

DRAFT - Container Labels, Carton and Package Insert Labeling

DATE OF REVIEW: July 15, 1991

ANDA #:73-479

NAME OF FIRM: Abbott Laboratories

NAME OF DRUG: Generic: Sterile Pentamidine Isethionate, 300 mg

DATE OF SUBMISSION: September 4, 1990

COMMENTS:

A. General Comment -

We would like to take this opportunity to direct your attention to USP XXII, General Notices, p 4, Added Substances, paragraph 3. If applicable, we recommend you meet the USP requirements at this time. We believe the required information should appear on the container labels (if there is space) and on the carton and package insert labeling as part of the "Each vial contains" statement.

B. Container: Not Satisfactory (Single Dose Vial)

1. USUAL DOSAGE

DOSAGE rather than DOSE

2. We encourage you to include the following statement after the "Protect...light" statement:

Retain in carton until time of use.

3. Delete the periods in "IM", "IV" and after "Use".

C. Carton: —— Not Satisfactory

1. Refer to comment 2. under Container.

2. USUAL DOSAGE rather than DOSAGE
(add USUAL)

3. The statement "Discard unused portion" should be linked with "Single Dose Vial".

4. Delete the periods in IM, IV and after "Use".

D. Insert: Not Satisfactory

1. INDICATIONS AND USAGE, Line 1 should read:

Sterile pentamidine isethionate...

(It is not necessary to capitalize the first letter of each word in the established name).

2. Please include a revision date.

RECOMMENDATIONS:

Inform the firm of the above comments.

Request the firm revise their container labels, carton and package insert labeling, then prepare and submit twelve final printed copy.

FOR THE RECORD:

a. The labeling is based on the insert labeling for PENTAM, revised 4/87.

b. PENTAM has exclusivity until 10/16/91.

K. Shah

K Shah 7/17/91

cc;
ANDA #73-479 Jerry Phillips 7/17/91
HFD-638/JPhillips
HFD-638/KShah
kt (hab) 73479.REVL
HAB

REVIEW OF PROFESSIONAL LABELING

Orig. Amendment

FPL - Container Labels, Carton and Insert Labeling

DATE OF REVIEW: November 13, 1991

ANDA #: 73-479

NAME OF FIRM: Abbott Laboratories

NAME OF DRUG: Generic: Sterile Pentamidine Isethionate, 300 mg

DATE OF SUBMISSION: October 15, 1991

COMMENTS:

Container: Satisfactory for 300 mg

Carton: Satisfactory for 1 x 300 mg

Insert: Satisfactory

RECOMMENDATIONS:

1. From a labeling viewpoint this application is satisfactory for approval.

2 FOR THE RECORD:

The firm has submitted final printed carton and insert labeling which includes the following "new" information which does not appear on the container label:

> "May contain sodium hydroxide and/or hydrochloric acid for pH adjustment. Headspace nitrogen gassed".

While we prefer all labels and labeling be consistent, in this case the amount of space on the labels is limited. Therefore, we will not require this information appear on the container label.

However, the labeling reflects the pH is adjusted with the "NaOH **and/or** HCl" while the manufacturing directions (see p. 5 of October 15, 1991 submission) indicate **"either** HCl **or** NaOH". We believe this must be corrected either by revising the manufacturing directions or the labeling.

We will ask for the chemists input on this issue. If labeling must be revised we can inform them at the time of the first annual report.

3. Chemist

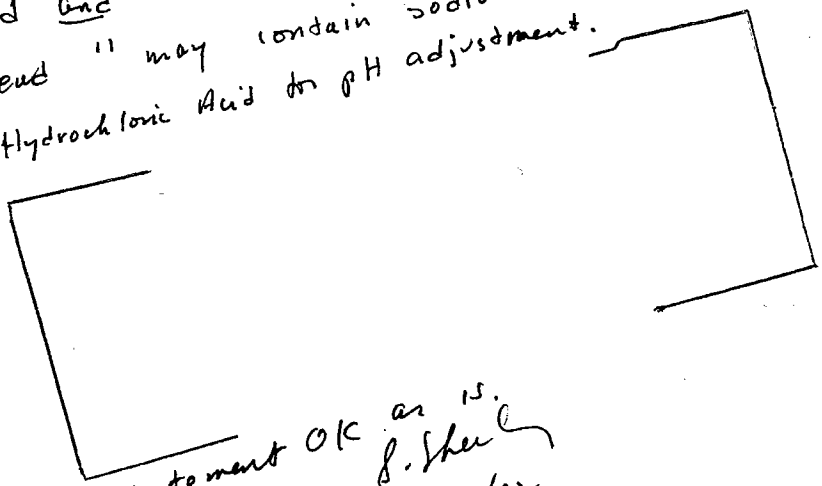
IMPORTANT - See FOR THE RECORD.

K. Shah

cc: ANDA 73-479
HFD-638/Shah/YMille
HFC-130/JAllen
bcw/11-25-91/73479lab.rev
labeling review

KSh 11-26-91
ymille 11/26/91

Please have the firm delete the word ~~and~~ in the labeling. It should read "may contain sodium hydroxide & hydrochloric Acid for pH adjustment.



pH statement OK as is.
L. Shen
3/14/92

Abbott

LABELING WORKSHEET

ANDA #: 73-479 ANDA#: _____ ANDA#: _____
PRODUCT NAME: Sterile Pentamidine Isethionate, 300 mg
NDA HOLDER(S): Lyphomed (PENTAM 300)
NDA NUMBER(S): 19-264

LABELING OF THE LISTED DRUG

DATE NOTED:	FIRM:	NDA#:	APPROVAL DATE:	REV. DATE:
	Lyphomed	19-264	4-9-87	4-87

CONTAINER LABELS:
APPROVED COPY ON FILE? ✓ Y ___ N ___ COMMENT
USP CONTAINER/CLOSURE REQUIREMENTS: ø not USP
OTHER KEY ISSUES: ø "Protect from light" on innovator
- Innovator packaged in clear vials
NaOH and/or HCl vs NaOH or HCl - See FOR THE RECORD attached to the review

INSERT LABELING:
PATENT ISSUES: ø
EXCLUSIVITY ISSUES: ø
BIO ISSUES: ø
OTHER KEY ISSUES: ø

SUMMARY FOR APPLICATION APPROVAL:
CONTAINER LABELS: Satisfactory in FPL as of 10-15-91 submission
CARTONING: Satisfactory in FPL as of 10-15-91 submission
LABELING COMMENT/FURTHER REVISION: Satisfactory in FPL as of 10-15-91 submission

DATE: 11-13-91
REVIEWER: Khyati Shah
SUPERVISOR: Aparna Mitra 11/14/91

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 73-479

CHEMISTRY REVIEW(S)

1. CHEMIST'S REVIEW NO. 1

2. ANDA #: 73-479

3. NAME AND ADDRESS OF APPLICANT:

Abbott Laboratories

Abbott Park, IL 60064-3500

7. NONPROPRIETARY NAME:

Pentamidine Isethionate

9. AMENDMENTS AND OTHER DATES:

DOA - 9/12/89; DAFF - 10/16/89; Amend - 1/10/90; ONC - 1/24/90;

ONC - 4/12/90

10. PHARMACOLOGICAL CATEGORY:

Treatment of pneumonia due

to pneumocystii carinii

(Aids related drug)

11. Rx or OTC:

Rx

12. RELATED IND/NDA/DMF(s):

DMF 3023

13. DOSAGE FORM:

Dry sterile powder

Sterile Pentamidine Isethionate

14. POTENCY:

300 mg/vial

15. CHEMICAL NAME AND STRUCTURE:
4, 4" - diamidine - diphenoxypentane di (ß-hydroxyethane sulfonate)
$C_{23}H_{36}N_4O_{10}S_2$ MW = 592.68

17. COMMENTS:
The application was incomplete when submitted. However, in a later addition to the application, a complete batch record and three-month stability data at 40°C was included. Information missing on many sections because of references to two DMFs where the authorization to review was missing. Labeling needs correction. Samples will be sent to St. Louis and District for validation.

18. CONCLUSIONS AND RECOMMENDATIONS:
Not approvable

19. REVIEWER: Stephen Sherken
DATE COMPLETED: 5/25/90

20. COMPONENTS AND COMPOSITION:

Stephen Sherken Retired 7/25/94
7/21/90

APPEARS THIS WAY
ON ORIGINAL

Redacted 6 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #1

h) [redacted]

i) [redacted]

30. CONTROL NUMBERS
Information found in DMF 3023 (see Section 25).

31. SAMPLES AND RESULTS
Samples will be sent to St. Louis for the drug substance and a field lab for the finished product.

32. LABELING
Reviewed by Y. Mille, 2/2/90.

33. ESTABLISHMENT INSPECTION
EI of 1/18/90 remains outstanding.

34. RECALLS
Environmental impact statement satisfactory for an ANDA.

35. BIOEQUIVALENCY STATUS
Bio Waiver granted on 3/30/90, and the product coded AP. No letter sent, however, Bio has recommended that Abbott be informed of the results.

1. CHEMIST'S REVIEW NO. 2

2. ANDA # 73-479

3. NAME AND ADDRESS OF APPLICANT

Abbott Labs
Abbott Park, Ill. 60064-3500

4. LEGAL BASIS for ANDA SUBMISSION

Generic Drug

5. SUPPLEMENT(s)

N/A

6. NAME OF DRUG

N/A

7. NONPROPRIETARY NAME

Sterile Pentamidine Isethionate

8. SUPPLEMENT(s) PROVIDE(s) FOR N/A

9. AMENDMENTS AND OTHER DATES

DOA 9/12/89; Amend 1/10/90; ONC 1/24/90; ONC 4/12/90; NA 7/31/90; ONC 8/8/90; Amend 8/22/90 Amend 8/30/90; Amend 9/4/90.

10. PHARMACOLOGICAL CATEGORY

Treatment of pneumonia due to pneumocystii carnii. (An Aids Related Drug).

11. HOW DISPENSED

Rx

12. RELATED IND/NDA/DMF(s)

DMF-8176 is Abbott's DMF type II for the drug substance. It will be reviewed separately.

DMF-3023 is Abbott's DMF type I for the manufacturing facility of the finished product. It is for their Pharmaceutical Products Division in Abbott Park, Ill. It is where the final product is to be manufactured. It will not be reviewed.

DMF-1617 is Abbott's DMF type I for the manufacturing of PI drug substance. It is for their Chemical and Agricultural Division in North Chicago Ill. This is where the drug substance will be manufactured. It will not be reviewed.

Authorization to review all three DMFs provided.

13. DOSAGE FORM

Lyophilized dry powder

14. POTENCY

300 mg/vial (— % overage)
Will question reason for overage.

15. CHEMICAL NAME AND STRUCTURE

Remains satisfactory.

16. RECORDS AND REPORTS

N/A

17. COMMENTS

Most questions answered satisfatorily, however some clarifications still needed. Analytical methods found acceptable and assay is stability indicating. Bio waver granted, labeling need minor revision. Probibly OK next time around. Stability data satisfactory. Since this drug is a cure for an Aid related desease I propose to remove it from the first in, first review criteria and handle it as quickly as possible. Abbott is [redacted]. Dr. Cooney's group will have to review for sterility assurance since product is [redacted]. PENTAM (Lyphomed) has exclusivity until 10/16/91.

18. CONCLUSIONS AND RECOMMENDATIONS

Not approvable

19. REVIEWER

Stephen Sherken

Stephen Sherken

DATE COMPLETED

7/23/91

Related 7/24/91

Redacted 4 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #2

36. FI/FR Yes

CHEMREVNOS

cls/07/19/91/d:73-479.REV

APPEARS THIS WAY
ON ORIGINAL

1. CHEMIST'S REVIEW NO. 3

2. ANDA # 73-479

3. NAME AND ADDRESS OF APPLICANT

Abbott Labs
Abbott Park, Ill. 60064-3500

4. LEGAL BASIS for ANDA SUBMISSION

Generic Drug

5. SUPPLEMENT(s)

N/A

6. NAME OF DRUG

N/A

7. NONPROPRIETARY NAME

Sterile Pentamidine Isethionate

8. SUPPLEMENT(s) PROVIDE(s) FOR N/A

9. AMENDMENTS AND OTHER DATES

DOA 9/12/89; Amend 1/10/90; ONC 1/24/90; ONC 4/12/90; NA 7/31/90; ONC 8/8/90; Amend 8/22/90 Amend 8/30/90; Amend 9/4/90; NA 8/22/91; Amend 8/30/90; *Amend (minor) 10/15/91; Micro NA (Cooney) 2/7/92.

10. PHARMACOLOGICAL CATEGORY

Treatment of pneumonia due to pneumocystii carnii. (An Aids Related Drug).

11. HOW DISPENSED

Rx

12. RELATED IND/NDA/DMF(s)

DMF-8176 is Abbott's DMF type II for the drug substance. Found deficient. Will review response separately.

DMF-3023 is Abbott's DMF type I for the manufacturing facility of the finished product. It is for their Pharmaceutical Products Division in Abbott Park, Ill. It is where the final product is to be manufactured. It will not be reviewed.

DMF-1617 is Abbott's DMF type I for the manufacturing of PI drug substance. It is for their Chemical and Agricultural Division in North Chicago Ill. This is where the drug substance will be manufactured. It will not be reviewed.

DMF-[redacted].
Information in application is sufficient.

Authorization to review all four DMFs provided.

13. DOSAGE FORM

Lyophilized dry powder

14. POTENCY

300 mg/vial ([redacted]% overage) Will question reason for overage.

The reason provided for the [redacted]% overage was to [redacted]. This allows a delivery of 100 mg/ml of solution. Additionally, the overage is in general agreement with USP XXII Injections <1> in which solution overages are recommended for vial injectables. The overage of NDS has been adequately justified.

15. CHEMICAL NAME AND STRUCTURE

Remains satisfactory.

16. RECORDS AND REPORTS

N/A

17. COMMENTS

Dr. Cooney has several questions about the [redacted] validation process. DMF is deficient. One minor problem with labeling.

18. CONCLUSIONS AND RECOMMENDATIONS

Not approvable (minor amendment) due to DMF and Micro deficiencies.

19. REVIEWER

Stephen Sherken

Stephen Sherken

DATE COMPLETED

3/20/92

cc: ANDA 73-479
73-479/Division File
73-479/Dup
HFD-634/SSherken

M Smela 3/20/92

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information from

CHEMISTRY REVIEW #3

33. ESTABLISHMENT INSPECTION

EIR of 1/8/90 remains outstanding. Abbott at Abbott Park, Ill. is not ————————————————.

34. BIOAVAILABILITY

Bio waver granted on 3/30/90. No letter sent.

35 ENVIRONMENTAL

Remains satisfactory.

36. FI/FR No. March of 92 was the first month that this amendment to the application was flagged as "P". Previously it wasn't.

APPEARS THIS WAY
ON ORIGINAL

DMF CHECKLIST FOR ANDA/AADA # 73-479

DMF #	DMF SUBJECT/HOLDER	ACTION CODE	RESULT OF REVIEW	DATE REVIEW COMPLETED	COMMENTS
8176	II Abbott	3	DEF		~~DEF~~ Amendment to Deficiency letter is outstanding
3023	I Abbott	2			
1617	I Abbott	2			
—	II —	4			

ACTION CODES: (1) DMF Reviewed. Other codes indicate why the DMF was not reviewed, as follows:

(2) Type 1 DMF;
(3) Reviewed previously and no revision since last review;
(4) Sufficient information in application;
(5) Authority to reference not granted;
(6) DMF not available;
(7) Other (explain under "Comments").

PAGE 1 OF 1

Stephen Sherba
Reviewer

Stephen Sherba
Signature

3/20/92
Date

1. CHEMIST'S REVIEW NO. 4

2. ANDA # 73-479

3. NAME AND ADDRESS OF APPLICANT

Abbott Labs
Abbott Park, Ill. 60064-3500

4. LEGAL BASIS for ANDA SUBMISSION

Generic Drug

5. SUPPLEMENT(s)

N/A

6. NAME OF DRUG

N/A

7. NONPROPRIETARY NAME

Sterile Pentamidine Isethionate

8. SUPPLEMENT(s) PROVIDE(s) FOR N/A

9. AMENDMENTS AND OTHER DATES

DOA 9/12/89; Amend 1/10/90; ONC 1/24/90; ONC 4/12/90; NA 7/31/90; ONC 8/8/90; Amend 8/22/90 Amend 8/30/90; Amend 9/4/90; NA 8/22/91; Amend 8/30/90; Amend (minor) 10/15/91; Micro NA (Cooney) 2/7/92; NA 3/23/92 (minor); *Amend 5/11/92 *Micro Amend 5/15/92

*subject of this review.

10. PHARMACOLOGICAL CATEGORY

Treatment of pneumonia due to pneumocystii carnii. (An Aids Related Drug).

11. HOW DISPENSED

Rx

12. RELATED IND/NDA/DMF(s)

DMF-8176 is Abbott's DMF type II for the drug substance. It was reviewed on 5/29/92 and found satisfactory. Abbott decided to submit the two amendments sent to the DMF dated 3/2/92 and 4/3/92. The review of 5/29/92 is found in DMF-8176 and a copy of it will be attached to the 4th review of this application as an Addendum.

DMF-3023 is Abbott's DMF type I for the manufacturing facility of the finished product. It is for their Pharmaceutical Products Division in Abbott Park, Ill. It is where the final product is to be manufactured. It will not be reviewed.

DMF-1617 is Abbott's DMF type I for the manufacturing of PI drug substance. It is for their Chemical and Agricultural Division in North Chicago Ill. This is where the drug substance will be manufactured. It will not be reviewed.

DMF-[redacted].

Information in application is sufficient.

DMF- ——————————— type III for their ——————————— It is used in the ———————————. Information in jacket is sufficient. (See amendment dated May 11, 1992, page 19).
Authorization to review all five DMFs provided.

13. DOSAGE FORM

Lyophilized dry powder

14. POTENCY

300 mg/vial (— % overage)

15. CHEMICAL NAME AND STRUCTURE

Remains satisfactory.

16. RECORDS AND REPORTS

N/A

17. COMMENTS

A response to Abbott's DMF-8176 was placed in the 5/11/92 amendment in its entirety. It is identified as attachment I and II. This information was reviewed in DMF-8176 and found satisfactory on 5/29/92 by Mr. S.Sherken. A review of attachments I & II is provided as an addendum to this review. The container closure system and additional stability data were found to be satisfactory.

18. CONCLUSIONS AND RECOMMENDATIONS

Approval for chemistry, labeling and bio. Pending for sterility assurance and satisfactory pre-approval inspection.

19. REVIEWER — DATE COMPLETED

Stephen Sherken — 6/5/92

Stephen Sherken

cc: ANDA 73-479
73-479/Division File
HFD-634/SSherken

M Smela 6/5/92

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CHEMISTRY REVIEW #4

DMF CHECKLIST FOR ANDA/AADA # 73-479

DMF #	DMF SUBJECT/HOLDER	ACTION CODE	RESULT OF REVIEW	DATE REVIEW COMPLETED	COMMENTS
8176	II - Abbott	1	Satisfactory	5/29/92	Info also in ANDA. It was satisfactory
3023	I Abbott	2	—	—	Pharmaceutical Products Division
1617	I Abbott	2	—	—	Chemical & Agricultural Division
—	III —	4	—	—	—
—	III —	4	—	—	—

ACTION CODES: (1) DMF Reviewed. Other codes indicate why the DMF was not reviewed, as follows:

(2) Type 1 DMF;
(3) Reviewed previously and no revision since last review;
(4) Sufficient information in application;
(5) Authority to reference not granted;
(6) DMF not available;
(7) Other (explain under "Comments").

PAGE 1 OF 1

Stephen Shaka
Reviewer

Stephen Shaka
Signature

6/2/92
Date

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 73-479

BIOEQUIVALENCE REVIEW(S)

Pentamidine Ise
300 mg/vial
NDA# 73-479
Reviewer: M. Chen

bbott Laboratories
bbott Park, Il.
Submission Date:
Sept. 12, 1989

MAR 30 1990

Waiver Request for A Bioavailability Study

The firm has requested a waiver of in vivo bioavailability study requirements for its Sterile Pentamidine Isethionate, 300 mg/vial. The intended routes of administration for the proposed drug are i.v. and i.m. The formulation comparison between Abbott's product and the innovator LyphoMed's product, Pentam[R] 300 (Sterile Pentamidine Isethionate), is shown below.

Ingredient/Vial	LyphoMed	Abbott
Pentamidine Isethionate	300 mg	300 mg

Recommendation:

1. The Division of Bioequivalence agrees that the information submitted by Abbott Laboratories demonstrates that Sterile Pentamidine Isethionate, 300 mg/vial, falls under 21 CFR Section 320.22 (c)(2) of Bioavailability/ Bioequivalence Regulations. The waiver of in vivo bioequivalence study requirements for 300 mg/vial injection of the test product is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test injectable formulation to be bioequivalent to Pentam[R] 300, 300 mg/vial, manufactured by LyphoMed, Inc.

2. Therapeutic Equivalence Recommendation:

   The Division of Bioequivalence recommends that THE TEST PRODUCT SHOULD BE CODED AP IN TE THERAPEUTIC EQUIVALENCE LIST.

The firm should be informed of the recommendations.

Mei-Ling Chen

Mei-Ling Chen, Ph.D.
Division of Bioequivalence
Review Branch 2

RD INITIATED FPELSOR
FT INITIATED FPELSOR F. Pelsor

Concur: Charles M Ise Date: 3/29/90
C.M. Ise, Ph.D.
Deputy Director, Division of Bioequivalence

MChen/if/3/28/90/Wang #9083f

cc: NDA# 73-479 original, HFD-630, HFD-600 (Burlington, Hare), HFD-22 (Hooton), HFD-655 (Pelsor, Chen), Drug file

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

73-479

MICROBIOLOGY REVIEW(S)

Consultative Review to HFD-632
Division of Medical Imaging, Surgical and Dental Drug Products
Microbiologist's Review No. 1
October 3, 1991

A. 1. **Application Number:** ANDA 73-479

Applicant: Abbott Laboratories
Abbott Park, IL 60064-3500

2. **Product Name:** Pentamidine Isethionate for Injection

3. **Dosage Form:** Lyophilized; Single Dose Fliptop Vial

4. **Method of Sterilization:** ———— /Lyophilization

5. **Pharmacological Category and/or Principle Indication:** Anti-protozoal

6. **Drug Priority Classification:** Generic

B. 1. **Initial Submission:** Unknown

2. **Amendments:** September 4, 1990 (Subject of this Review)
Received for Review: 7/22/91

3. **Supporting Documents:** DMF 1617 - Abbott

C. **Remarks:**
The 9/4/90 Amendment is submitted in response to an Agency letter of July 31, 1990. Item #7 of that letter requested information concerning the ———— of the drug product including validation information. The request, as reproduced by Abbott is as follows:

> If adequate justification can be provided for ———— , then provide sterility validation of the ———— and lyophilization processes for Sterile Pentamidine Isethionate to include a complete description of the microbiological monitoring and control procedures, and sterilization processes used for this product. Specifications and data should be supplied. Information and data concerning qualification/validation of the process should also be included. Such validation should be for Sterile Pentamidine at the facility of manufacture (e.g., media fill validation data for the fill lines to be used for Sterile Pentamidine).

This application has not been previously reviewed by HFD-160 microbiologists.

The response to this question is contained in Exhibit XI, pp. 3-527 through 3-530. The consult requests review of these pages.

Although the results of —— media fill runs are given, there is substantially no other information included for review except very general and brief comments. The application cannot therefore be recommended for approval on the basis of sterility assurance. The

applicant needs to submit a complete validation package. An outline of the material which should be submitted is included below in the "Draft of letter to Applicant".

D. **Conclusions:** The application is not recommended for approval on the basis of sterility assurance. See "Remarks" above and "Draft of Letter to Applicant" below.

Peter H Cooney 10/3/91

Peter H. Cooney, PhD
Supervisory Microbiologist, HFD-160

10/10/91

cc: ANDA 73-479
HFD-160/Consult File/Cooney
HFD-632/Vashio/Rickman

APPEARS THIS WAY
ON ORIGINAL

Draft of Letter to Applicant

The information concerning the ———— processing of the subject drug product included in your September 4, 1990 Amendment is insufficient. The application therefore remains not approvable. The following outline covers the type of information that should be included in the ANDA file and which is necessary for review of the sterilization of the subject ———— drug product.

The information may be supplied directly to the file, or may be supplied by reference to a DMF or to another application. Exact references should be provided (e.g., dates, pages, etc.).

1. A brief description of the building and facilities including, for example, the number of filling areas and layout of critical and control areas, a brief description of the water systems, air-handling, etc. A floor plan is often helpful for this purpose.

2. A brief description of the overall manufacturing operation including, for example, material flow, filling, capping, ——— assembly, etc.

3. A description of the sterilization processes used for containers, closures, equipment, components, etc. A description of the validation of these processes should be provided including, for example, heat distribution/penetration summaries, biological studies (biological indicators and endotoxin), routine monitoring procedures, etc. Validation information for other types of sterilization processes should also be included. Information and data demonstrating distribution and penetration of the sterilant and efficacy of each process should be submitted.

4. Summaries of recent media fill validation methods and results for the same container/closure type and size class that is to be used for the product. All media fill results obtained, including failures, should be supplied. These data should be obtained using the same filling line(s) that are to be used for the product in question. The following details should be included with the data for each media fill run described:

a. Identification of filling room used. Relate this to the floor plan provided in number 1 above.
b. Container/closure type and size.
c. Volume filled.
d. Type of media filled.
e. Number of units filled.
f. Number of units incubated.

g. Number of units positive.
h. Incubation time and temperature for each group of units incubated and whether any group of units is subjected to two different temperatures during the incubation.
i. Date of media fill.
j. Procedures used to simulate any steps of a normal production fill. This might include, for example, mock lyophilization or substitution of vial headspace gas.
k. Microbiological monitoring data obtained during the media fill run.

5. A description of the disposition of product made after a failed media fill. Include descriptions of investigations, reviews, and how decisions are made to reject or release product.

6. A description of sterility testing methods and release criteria. Methods should include the protocol for the selection of representative units from the filling line during production.

7. Information concerning methods and results of container/closure integrity testing for both initial validation and the procedures used for the stability protocol.

8. A description of the microbiological monitoring program used during routine production and media fills. Include the frequency of monitoring, type of monitoring, sites monitored, alert and action level specifications, and precise descriptions of the actions taken when specifications are exceeded. These descriptions should include air, surface, personnel, and water monitoring programs. Descriptions of the bioburden monitoring program should also be provided, including specifications.

9. Evidence should be provided that there are formal, written procedures describing the above elements and that these procedures are followed.

Consultative Review to HFD-632
Division of Medical Imaging, Surgical and Dental Drug Products
Microbiologist's Review No. 1
June 10, 1992

A. 1. **Application Number:** ANDA 73-479

Applicant: Abbott Laboratories
Abbott Park, IL 60064-3500

2. **Product Name:** Pentamidine Isethionate for Injection

3. **Dosage Form:** Lyophilized; Single Dose Fliptop Vial

4. **Method of Sterilization:** ———————/Lyophilization

5. **Pharmacological Category and/or Principle Indication:** Anti-protozoal

6. **Drug Priority Classification:** Generic

B. 1. **Initial Submission:** Unknown

2. **Amendments:** September 4, 1990 (Subject of Review #1)
May 15, 1992 (Subject of this Review)

3. **Supporting Documents:** DMF 1617 - Abbott

C. **Remarks:**
This Amendment is submitted in response to the Administration's letter of February 7, 1992. The deficiencies were provided in Microbiologist's Review No. 1 (dated October 3, 1991) of this application. The deficiencies resulted from the fact that the applicant provided almost no information concerning the ———— process for the subject drug product, even though the Administration's letter of July 31, 1990 requested this information. See "E. Review Notes" below for comments on the applicant's responses to the February 7, 1992 letter.

D. **Conclusions:** The application is now recommended for approval on the basis of sterility assurance. See "Remarks" above and "Review Notes" below.

Peter H Cooney 6/10/92
Peter H. Cooney, PhD
Supervisory Microbiologist, HFD-160
WAC 6/11/92

cc: ANDA 73-479
HFD-160/Consult File
HFD-160/Cooney
HFD-632/Vashio
HFD-630/Rickman

JUN 17 1992

Redacted 5 page(s)

of trade secret and/or

confidential commercial

information from

6/10/1992 MICROBIOLOGY REVIEW

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 73-479

ADMINISTRATIVE DOCUMENTS

MEMORANDUM OF TELEPHONE CONVERSATION

January 17, 1990

between

FDA - Division of Generic Drugs	and	Abbott Laboratories, Inc.
David Rosen D Rosen		Frederick Gustafson

Re: ANDA for Sterile Pentamidine Isethionate

I called Mr Gustafson regarding the filing of this application. I noted that the innovator product was afforded 5 years of exclusivity as it was a new chemical entity approved after September 24, 1984. The excluvity expired on Oct 16. 1989, thus that is the date the ANDA was eligible for filing. I noted that the application did not contain any batch records or stability data. Mr. Gustafson looked into the matter and later called to inform me that a batch had recently been manufactured and that initial and one month accelerated stability data would be available next week. Mr. Gustafson stated that he would send in the data as well as a commitment to provide additional accelerated stability data when it became available. I informed him that we would file this ANDA, however, urged him to submit complete ANDAs (all three months of accelerated stability data) in the future.

RECORD OF TELEPHONE CONVERSATION/MEETING

DATE: 7 May 92

NDA NUMBER: 73479

IND NUMBER:

TELECON/MEETING

INITIATED BY: ☐ APPLICANT/SPONSOR ☒ FDA

MADE: ☐ BY TELEPHONE ☐ IN PERSON

PRODUCT NAME: Pentamidine ~~Dat~~ Isethionate

FIRM NAME: Abbott Labs.

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD: Dave Cusic

TELEPHONE NO.: 708 937 3216

Reference is made to Minor NA letter issued 3/23/92.

Phone call was made to firm Regarding response. The amendment should be submitted in the next few weeks.

DMF 8176 update was submitted 4/2/92 and should be on file.

SIGNATURE: Washco PSO

DIVISION: OGD

FORM FD 2587 (11/77)

ORIGINAL IND/NDA

U. S. GOVERNMENT PRINTING OFFICE-1984-432-976/7126

Memorandum of Telephone Conversation
between

David Guzek, Abbot Labs.
and
RA Jerussi, HFD-600

Subject: ANDA 73-479, Sterile Pentamidine Isethionate, 300mg/vial.

First Call: June 23, 1992. I called to speak to Fred Gustafson but in his absence spoke to Mr. Guzek. I pointed out that I had three questions about the application: 1. Abbott uses a ——— test for impurities in the active ingredient but have used a —— test which seems more sensitive than the —— one on —— lots. Why not use the latter in stead of the ——? 2. ——— and another ——— ——— are tested for and firm has found no ——— when tested. However, ——— may be used as ——— ———. Has the firm tested for it when it was used in ———? 3. ——— is tested for in the drug product as a degradent. Is it really a degradent since it is used in the ———? We agreed to a conference call on June 24 at 11 AM EST to answer these questions. I also agreed to fax Guzek a CDC publication about impurities in this drug from JOAC, 1986.

Second Call: June 24, 1992. A the arranged time Abbott phoned via a conference call. Present for Abbott were Fred Gustafson, David Guzek, David Riley (Chem. Devel. Section), Cathy McFarland (Dept. Mgr. Chem), Don Dieball (Section Mgr. Anal.), Jose Joseph(Hos. Products Div), David Cunningham (Chemist HPD). We went over the three questions posed the day before by me.

1. It was pointed out by the Abbott people that the —— assay method for the NDS is a ——— test. Abbott is using a —— test which is stability indicating and which J. Joseph said is the CDC method (from the AOAC publication). It is capable of ——— and they did indeed use it on — lots. However, Dave Cunningham said they use the——— test for release since they do not think it an insensitive test and that it is quicker than the——— test for impurities. They claim that the latter takes — minutes to run and they would have to do it in ———. We finally agreed that over the next 6 to 12 months the firm would send in to my attention the results of the —— test on the batches of NDS that they made during that time. since they will not apply the —— impurity test to every batch of NDA, they will wait until they have at least a batch which was done using both methods.

2. Dave Riley discussed the ——— issue. He said that ——— ——— was really an alternative ——— and that they no longer plan to use it as an alternative. Rather they have used ——— and have tested for it and have not found it. This issue was left as it is in the application.

3. Dave Riley also addressed this issue. He said that the major source of the ——————— is as a ——————— but that it can also come from degradation of the NDS. J. Joseph said that they did test for it in the drug. I said that they did for the drug product but not for the NDS and shouldn't it be there since it is a ———————. They informed me that it is tested for in the bulk with a limit of -%, code 14547. I apparently had missed this in the application.

We concluded by Mr. Gustafson agreeing to send in by fax a letter of this date agreeing with #1.

RA Jenssi 9/25/92
RA Jenssi

cc:
ANDA 73-479 Orig.
" " Dup/Div. File
M. Smela, HFD-600
S. Sherken, "

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Memorandum

DATE: 1-18-90

TO : Division of Manufacturing & Product Quality (HFN-320)

FROM: Division of Generic Drugs HFN- 230

Requester's Name Margo Bennett Phone 443-0193

ESTABLISHMENT EVALUATION REQUEST

Sterile Product XX Non Sterile Product

Application and Supplement No. 73-479

Brand Name *(if any)*

Establishment Name, Dosage Form and Strength Sterile Pentamidine Isethionate, 300 mg

Profile Class Code: svp

Priority Classification: *(See SMG BD-4820.3)*

Applicant's Name: Abbott Laboratories

Address: One Abbott Park Road D-389 AP30, Abbott Park, IL 60064-3500

Facilities to be Evaluated: *(Name, full Address, DMF No., and responsibility)*

For HFN-320 Use
Status & Date of Inspection:

1. applicant manuf nds and finished dosage form DMF 3023 at Abbott Chemical and
2. Agricultural Products Div. 14th and Sheridan Rd, N Chicago, IL 60064
3.
4.
5.

Other Information or Special Requests:

****

For HFN-320 Use Only: Date Received

CGMP Compliance Status of Facilities Evaluated:

CSO: Date Completed

Distribution: Original and First Copy: HFN-320
Remaining Copies: Requesting Office Use

FORM FDA 3274 (6/86)

DEPARTMENT OF HEALTH & HUMAN SERVICES 2937 Public Health Service

EER for approval

Memorandum

Date 5/13/92

From Division of Chemistry I

Requestor's Name Stephen Shaker/DDoleski

HFD- 634/632

Phone 295-8370 / 8315

Subject ESTABLISHMENT EVALUATION REQUEST

To Division of Manufacturing & Product Quality (HFD-320)

Sterile Product ✓ Non Sterile Product _____

Application and Supplement No. 73479

Brand Name *(if any)* _____

Establishment Name, Dosage Form and Strength Sterile Pentamidine Isethionate, 300 mg/vial Profile Class Code: _____

Priority Classification: EER for approval *(See SMG BD-4820.3)*

Applicant's Name: Abbott Labs, Hospital Products Division

Address: One Abbott Park Road, Abbott Park IL 60064-3500

Facilities to be Evaluated: *(Name, full Address, DMF No., and responsibility)*

For HFD 320 Use
Status & Date of Inspection:

7768 (1.) Abbott Labs - Pharmaceutical Products Division — AC 6/1/92
One Abbott Park, Abbott Park, ILL 60064-3500
Mfg of finished product - Testing & Stability
DMF I - 3023 (SVP)

7769 (2) Abbott - Chemical & Agricultural Products Division — AC-4/23/90
1401 Sheridan Road, W. Chicago, ILL. 60064-4000
Mfg of drug substance (CRU) DMFs I 1617 & II 8176

Other Information or Special Requests: EER for approval.

****

For HFD-320 Use Only:

Date Received: 5/14/92

CGMP Compliance Status of Facilities Evaluated: Acceptable

CSO: Melissa Garcia Date Completed: 6/30/92

Distribution: Original and First Copy: HFD-320
Remaining Copies: Requesting Office Use

FORM FDA 3274 (3/90)

NOTICE OF APPROVAL
NEW DRUG APPLICATION OR SUPPLEMENT

NDA NUMBER: 73-479

DATE APPROVAL LETTER ISSUED:

TO: Press Relations Staff (HFI-40)

FROM:
- [x] Bureau of Drugs
- [ ] Bureau of Veterinary Medicine

ATTENTION

Forward original of this form for publication only after approval letter has been issued and the date of approval has been entered above.

TYPE OF APPLICATION
- [ ] ORIGINAL NDA
- [ ] SUPPLEMENT TO NDA
- [x] ABBREVIATED ORIGINAL NDA
- [ ] SUPPLEMENT TO ANDA

CATEGORY
- [x] HUMAN
- [ ] VETERINARY

TRADE NAME (or other designated name) AND ESTABLISHED OR NONPROPRIETARY NAME (if any) OF DRUG:

Sterile Pentamidine Isethionate

DOSAGE FORM: Sterile Lyophilized Powder

HOW DISPENSED
- [x] RX
- [ ] OTC

ACTIVE INGREDIENT(S) (as declared on label. List by established or nonproprietary name(s) and include amount(s). If amount is declared on label.)

Pentamidine Isethionate, 300 mg/vial.

NAME OF APPLICANT (Include City and State)

Abbott Laboratories.
Abbott Park, IL. 60064-3500

PRINCIPAL INDICATION OR PHARMACOLOGICAL CATEGORY

Anti-protozoal

COMPLETE FOR VETERINARY ONLY

ANIMAL SPECIES FOR WHICH APPROVED

COMPLETE FOR SUPPLEMENT ONLY

CHANGE APPROVED TO PROVIDE FOR

FORM PREPARED BY

NAME: Stephen Sherba — DATE: 6/2/92

FORM APPROVED BY

NAME: Michael Smith (pending Micro + EER) — DATE: 6/4/92

FORM FDA 1642 (2/75) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED.

ANDA Approval Summary

ANDA Number	Applicant Name	Established Name of Drug	Dosage Form	Strength	Container size(s)
479	Abbott Laboratories	Sterile Pentamidine Isethionate	Sterile Lyophilized Powder	300mg/vial	15cc vial

	Date Found Satisfactory	Comment
Labeling	11/13/91	by K. Shah.
Chemistry, Manufacturing, and Controls		CHEM & MFG OK - Sterility assurance under review by HFD-160
GMP's		
EER Pending Manufacturer – Finished Dosage Form		
Outside Facilities	None	
Manufacturer(s) – Active Ingredient(s)		

Stephen Sherba — Chemist Reviewer — 6/2/92 — Date

Michael Smolin (Pending Micro + EER) — Branch Chief — 6/4/92 — Date

Petition Required	✓ No / Yes	
Listed Drug Information 505(j)(2)(A)	10/16/89	orig. fin. sub dated 9/25/89
Patent Certification 505(j)(2)(B)	PI 10/16/89	" " " " "
Date Patent/Exclusivity Expires (if applicable)	Exclusivity exp 10/16/91	

Bioequivalence Section

Dissolution Required?	✓ No / Yes : DB / DGD	Injectable product
In vivo study(s) required?	✓ No / Yes	
Study(s) Found Acceptable		
Waiver Request Granted	OK per bio review dated 3/30/90	
Total Bioequivalence Requirement Met	3/30/90	

Robert Rolbert — Administrative Reviewer — 6/8/92 — Date

Approved _____

Disapproved _____

Director, Division of Generic Drugs — Date

Comments:

479A

ANDA ACTION LETTER ROUTING RECORD

ANDA # 73-479
AADA #
Drug STERILE PENTAMIDINE ISETHIONATE
Dosage Form STERILE PWD FOR INJ
Strength 300mg/VIAL
Applicant ABBOTT LABS
Manufacturing Site(s) applicant @ N. Chicago
Proposed Action (AP) AE

Original Rec'd Date 9/25/89 (accepted for fil 10/16/8
Amendment Date(s) 1/10/90, 8/22/90, 9/1990
Chemistry Reviewer S. Sherkin 8/30/9
Supervisor M. Smela AM 10/15/9
Bio Reviewer M. Chen 5/11/92
Supervisor F. Pelsor AM 5/19/92
Patent Certification Para IV

REVIEWER:	RECEIPT	ACTION
1. R. Pollock, M.S Chief, Program Support Staff. Comments: Patent & exclusivity adequately addressed EER pending EER acceptable 6/30/92 Micro consult ~~pending~~ acceptable 6/24/92	Date 6/8/92 Initials RP	Date 6/8/92 Initials RP
2. S. Dighe, Ph.D. Director, Bioequivalence Comments: The test product is an injection (i.v. & i.m) and has the same formulation as the listed drug, Lyphomed's, Pentam®, 300 mg/vial. It has the same concentration in the same solvent as the listed product. Waiver of in vivo B/E study is appropriate and granted	Date 6/8/92 Initials SD	Date 6/16/92 Initials SD
3. K. Johnson, M.S. Applicants approvable Associate Director Office of Generic Drugs Comments: Labeling is ~~is~~ satisfactory.	Date 6-1-92 Initials KJ	Date 6-1-92 Initials KJ
4. Director of Chem. I ~~or II~~ Office of Generic Drugs Comments: Except for micro consult & EER the chem section is satisfactory	Date 6/11/92 Initials RRC	Date 6/11/92 Initials RRC
5. R. Jerussi, Ph.D. Office Level OGD Review (if necessary) Yes X No__ Comments: First approval, OK to approve. See Memo of 6/24/92 & attach Letter need new date of 6/24/92 on it	Date 6/12/92 Initials RJ	Date 6/23/92 Initials
6. Office Level Bio Review Comments: Waiver appropriately granted	Date 6/26/92 Initials MP	Date Initials
7. R. Williams, M.D. Director Office of Generic Drugs Comments:	Date Initials	Date 6/29/92 Initials

LETTER SIGNED: Roger L. Williams
(Date) 6/30/92

(revision date 12-16-91)
(C:Forms)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 73-479

CORRESPONDENCE

ABBOTT

505 J 2A
Info is Acceptable
NEE
exclusivity
Expired
10/16/89
DVR

Hospital Products Division

Abbott Laboratories
One Abbott Park Road
Abbott Park, Illinois 60064-3500

September 12, 1989

CENTER FOR DRUGS AND BIOLOGICS, HFN #230
Attn: DOCUMENT CONTROL ROOM #17B-20
5600 Fishers Lane
Rockville, Maryland 20857

ATTENTION: Mr. Richard Terselic
Acting Director, Division of Generic Drugs

RE: Sterile Pentamidine Isethionate
ORIGINAL ABBREVIATED NEW DRUG APPLICATION

Abbott Laboratories hereby submits an abbreviated new drug application for Sterile Pentamidine Isethionate in accordance with Section 505(j) of the Federal Food, Drug and Cosmetic Act. This dosage form will be manufactured at Abbott Laboratories' North Chicago, Illinois manufacturing facility and be supplied as a sterile, nonpyrogenic lyophilized powder as follows:

List Number	Product	Size/Container
4548	Sterile Pentamidine Isethionate 300 mg	15 mL Fliptop Vial

As discussed in a meeting on June 10, 1986 with representatives of the Generic Drug Division, Abbott Laboratories will produce one (1) production lot of Sterile Pentamidine Isethionate in Fliptop Vials at our North Chicago, Illinois production facility and submit the results of 1 month 40°C, 2 months 40°C and 3 months 40°C accelerated stability testing, along with the appropriate production batch records by January 1990. It is Abbott Laboratories' understanding that this abbreviated new drug application will be reviewed and approved, with the approval being made effective on or after October 16, 1991. Abbott Laboratories hereby certifies it will not engage in the commerical use or sale of this new drug product prior to the October 16, 1991 orphan drug exclusivity expiration date.

Please refer to the accompanying Table of Contents for the data supporting this submission. Also appended is information required by Section 505(j)(2)(A) of the Food, Drug and Cosmetic Act.

Sincerely,

ABBOTT LABORATORIES

Frederick A. Gustafson

Frederick A. Gustafson
Director
Regulatory Affairs
Hospital Products Division

DTG/kd
2208f/1
Attachments

APPEARS THIS WAY
ON ORIGINAL

ABBOTT

Hospital Products Division
Abbott Laboratories
One Abbott Park Road
Abbott Park, Illinois 60064-3500

73-479

AMENDMENT

January 10, 1990

CENTER FOR DRUGS AND BIOLOGICS, HFD #230
Attn: DOCUMENT CONTROL ROOM #17B-45
5600 Fishers Lane
Rockville, Maryland 20857

ATTENTION: Mr. Richard Terselic
Acting Director

Re: Pentamidine Isethionate for Injection

Abbott Laboratories hereby amends the above-referenced ANDA application of September 12, 1989 to include changes to the bulk drug Pentamidine Isethionate, Abbott Drug Code 14547.

The changes to the bulk drug code are fully described in Abbott Laboratories, Chemical and Agricultural Products Division's (CAPD) update to Master File 8176 dated January 4, 1990. These changes are summarized as follows:

o

o

Appended in support of these changes are:

Exhibit I: Revised Drug Code 14547 for Pentamidine Isethionate

Exhibit II: Validation of the Assay for ——— in Pentamidine Isethionate

ORIGINAL

Reference is also made to the aforementioned update to Master File 8176 for a complete description of the changes to Abbott Drug Code 14547.

We trust that this information is complete.

Sincerely,

ABBOTT LABORATORIES

Frederick A. Gustafson

Frederick A. Gustafson
Director,
Regulatory Affairs
Hospital Products Division
(708) 937-3213

DTG/dg
janfda.dtg/p12

attachment

JAN 24 1990

ANDA 73-479

Abbott Laboratories
Attention: Mr. Frederick A. Gustafson
One Abbott Park Road
Abbott Park, IL 60064-3500

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for the following:

NAME OF DRUG: Sterile Pentamidine Isethionate, 300 mg

DATE OF APPLICATION: September 12, 1989

DATE OF RECEIPT: September 25, 1989

DATE ACCEPTABLE FOR FILING: October 16, 1989

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Sincerely yours,

Peter L. Johnson for 1-24-90

Acting Director
Division of Generic Drugs
Center for Drug Evaluation and Research

cc:
DUP HFN-630
Pollock/Patel 1/23/90
bb/1-22-90
Ack 2769b/p. 9 received 1/23/90

ABBOTT

Hospital Products Division
Abbott Laboratories
One Abbott Park Road
Abbott Park, Illinois 60064-3500

73-479

January 24, 1990

~~AMENDMENT~~
ORIG NEW CORRES

CENTER FOR DRUGS AND BIOLOGICS, HFD #230
Attn: DOCUMENT CONTROL ROOM #17B-45
5600 Fishers Lane
Rockville, Maryland 20857

ATTENTION: Mr. Richard Terselic
Acting Director

Re: Pentamidine Isethionate for Injection, 90P-0023/CP

Abbott Laboratories hereby amends the above-referenced ANDA application of September 12, 1989 to provide additional information as requested in the January 17, 1990 telephone conversation between Mr. David Rosen of the Administration and Mr. Frederick Gustafson of Abbott Laboratories. As requested, appended are the following:

- Initial and one (1) month at 40°C assays for the subject drug product manufactured in the proposed Pharmaceutical Products Division, North Chicago, Illinois production facility
- Certificate of Analysis
- Production work order associated with the production of the subject drug lot

We trust that this information is complete.

Sincerely,

ABBOTT LABORATORIES

Frederick A. Gustafson

Frederick A. Gustafson
Director,
Regulatory Affairs
Hospital Products Division
(708) 937-3213

DTG/dg
janfda.dtg/18

attachment

RECEIVED
JAN 25 1990
GENERIC DRUGS

ORIGINAL

ABBOTT

Hospital Products Division

Abbott Laboratories
One Abbott Park Road
Abbott Park, Illinois 60064-3500

April 12, 1990

CENTER FOR DRUGS AND BIOLOGICS, HFD #230
Attn: DOCUMENT CONTROL ROOM #17B-45
5600 Fishers Lane
Rockville, Maryland 20857

ATTENTION: Mr. Richard Terselic
Acting Director

Re: ANDA 73-479 Pentamidine Isethionate for Injection

Abbott Laboratories hereby amends the above-referenced ANDA application of September 12, 1989 to provide: (1) the results of three (3) months at 40°C stability on the subject drug and (2) the results of twenty-four (24) hour compatibility studies with 5% Dextrose Injection, USP. Based on the results of these data, the ———— month expiration dating and the labeled 24 hour drug compatibility in 5% Dextrose Injection, USP are supported.

A Certificate of Analysis and the production work order associated with the manufacture of the subject drug lot in the proposed Pharmaceutical Products Division's, North Chicago, Illinois production facility were previously submitted on January 24, 1990.

We trust that this information is complete.

Sincerely,

ABBOTT LABORATORIES

Frederick A. Gustafson
Director,
Regulatory Affairs
Hospital Products Division
(708) 937-3213

DTG/dg
aprfda.dtg/8

attachment

ANDA 73-479

JUL 31 1990

Abbott Laboratories
Hospital Products Division
Attention: Mr. Frederick A. Gustafson
One Abbott Park Road
Abbott Park, IL 60064-3500

Dear Sir:

Please refer to your abbreviated new drug application dated September 12, 1989, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Sterile Pentamidine Isethionate, 300 mg/vial.

We also refer to your correspondence and amendment dated January 10 and 24, 1990, and April 12, 1990.

The application is deficient and therefore not approvable under Section 505 of the Act for the following reasons:

1.

2.

3.

4.

Redacted 1 page(s)

of trade secret and/or

confidential commercial

information from

7/31/1990 FDA LETTER

16. [redacted]

17.

18.

19. Further, our review of the submitted labels and package insert labeling identified the following: [label review]

20. LABEL REVIEW:

COMMENTS:

Container: Not Satisfactory

A. Add "Discard unused portion." This should be linked with "Single Dose Vial."

B. Add:

Reconstituted on _____ at _____ AM PM.

C. Reconstitution information

Relocate "5%" so it appears between "Injection" and "USP." [Refer to USP XXII, p. 1472 if you have questions.]

APPEARS THIS WAY
ON ORIGINAL

D. Storage Recommendations

1) Store the dry . . . (Add "the".)
2) Protect the dry . . . (Add "the".)

Carton: Not Satisfactory

A. See comments A., C. and D. under Container.

B. ADMINISTRATION

1) Revise to read RECONSTITUTION AND ADMINISTRATION.

2) Intravenous Injection

a) We prefer:

i) 3 to 5 (rather than 3-5)
ii) 50 to 250 (rather than 50-250)

b) Sentence 2 - . . . dextrose injection 5%.

c) The final sentence should appear in bold print.

d) See comment C. under Container

Insert: Not Satisfactory

A. DESCRIPTION

Paragraph 2, line 1 - Place a comma (,) after "white."

B. PRECAUTIONS

1) Paragraph 2 should appear in bold print. The quality of the xerox prevents us from determining if this has been done.

2) Laboratory Tests, item d - tests (plural).

C. ADVERSE REACTIONS

The section heading and first two paragraphs are missing.

D. DOSAGE AND ADMINISTRATION

1) See comments B. 2. c. and d. under Carton.

2) It is not necessary to include "USP" in this section.

E. HOW SUPPLIED

1) Line 1

a) Place a comma (,) after "sterile" and "single-dose."

b) . . . 300 mg of pentamidine isethionate.

c) Please indicate the carton size in this section.

F. The requirements of 21 CFR 201.56(e) must be met.

The file is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application, or if you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

Robert A. Jaeger for 7/30/90

Acting Director
Division of Generic Drugs
Center for Drug Evaluation and Research

cc:

HFD-634

HFD-634/Sherken/5/25/90

Sherken/Patel/ef/6/18/90

final type/mlb/7-18-90

Wang #3193F

J. Sherken 7/21/90

Rec'd 7/27/90

R/D: YMille/5/25/90 4/ Mille 7/25/90

RHassall/5/29/90

RPatel/5/29/90

NOT APPROVABLE

ANDA 73-479

JUL 31 1990

Abbott Laboratories
Hospital Products Divison
Attention: Mr. Frederick A. Gustafson
One Abbott Park Road
Abbott Park, IL 60064-3500

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Sterile Pentamidine Isethionate, 300 mg/vial.

In order for our laboratory to validate your submitted methodology, send the following materials to the address below:

Materials to be sent:

1. Finished dosage form - Send three times the amount needed to perform the required testing. Identify the lot number of the material sent.

2. A Certificate of Analysis for the lot sent.

3. Internal and Reference standards - Send three times the amount necessary to perform the required testing. (If you do not send the standard and the District doesn't have it, the analysis will be delayed).

4. Impurity Standards - send samples of standards for any impurities for which you test the dosage form.

5. Representative chromatograms and/or spectra (if applicable).

6. Copy of the method of analysis if the drug product is not compendial.

7. A Material Safety Data Sheet (OSHA Form 174) or equivalent information.

Address: Food and Drug Administration
Detroit District Laboratory
Attention: Mr. Felix Schneider, HFR-MA-200
1450 E. Jefferson Ave.
Detroit, MI 48207

These materials must be sent within 30 days of receipt of this letter. If you cannot send these materials by this date, please notify the above by letter. Send copies of all correspondence regarding the samples requested to the ANDA.

We recommend that you send the samples by registered mail/return receipt requested.

Sincerely yours,

Robert A. Jennings 7/30/90

Acting Director
Division of Generic Drugs
Center for Drug Evaluation and Research

cc:
ANDA 73-479
ANDA DUP S. Sherken 7/24/90
HFD-634/Sherken/5/25/90
Sherken/Patel/mlb/7/20/90
Wang #3192F
Samples to District

Rec'd 7/25/90

JUL 31 1990

ANDA 73-479

Abbott Laboratories
Hospital Products Divison
Attention: Mr. Frederick A. Gustafson
One Abbott Park Road
Abbott Park, IL 60064-3500

Dear Sir:

Reference is made to your abbreviated new drug application pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Sterile Pentamidine Isethionate, 300 mg/vial.

In order for our laboratory to ascertain that your bulk drug conforms to USP (if not USP, then appropriate) requirements, send the following materials to the address below:

Materials to be sent:

1. Pentamidine Isethionate — Drug Substance — Abbott — Manufacturer

   Send three times the amount needed to perform all USP testing. Package the material in a tight, moisture-free container sealed in an outer container. Identify the manufacturer, the manufacturer's address, DMF number and lot number of the bulk sent.

2. A Certificate of Analysis (either yours or the manufacturer's) for the lot sent.

3. Standards - Reference, Impurity, and Internal - Send three times the amount required by the USP. [If you do not send the standard and St. Louis doesn't have it, the analysis will be delayed].

4. Copies of representative chromatograms and/or spectra (if applicable.)

5. Copy of the method of analysis if the drug substance is not compendial.

6. A Material Safety Data Sheet (OSHA Form 174) or equivalent information.

Address:

FDA/Division of Drug Analysis
Attention: Chief, Drug Monitoring Branch
1114 Market Street, Room 1002
St. Louis, MO 63101

These materials must be sent within 30 days of receipt of this letter. If you cannot send these materials by this date, please notify the Drug Monitoring Branch by letter. If you fail to send the requested materials, or properly notify the Drug Monitoring Branch Chief of any delay, this submission should be withdrawn. Send copies of all correspondence regarding the samples requested to the ANDA.

We recommend that you send the samples by registered mail/return receipt requested.

Sincerely yours,

Robert A. Jemusi for
7/30/90

Acting Director
Division of Generic Drugs
Center for Drug Evaluation and Research

cc:
ANDA 73-479 L. Sherken 9/21/90
ANDA DUP
HFD-634/Sherken/5/25/90
Sherken/Patel/ef/6/18/90 Revised 7/27/90
Wang #3192F
Samples to St. Louis

ORIG

ABBOTT

Hospital Products Division

Abbott Laboratories
One Abbott Park Road
Abbott Park, Illinois 60064-3500

August 8, 1990

NAE Pollard, CSO 9/17/90

CENTER FOR DRUGS AND BIOLOGICS, HFD #230
Attn: DOCUMENT CONTROL ROOM #17B-45
5600 Fishers Lane
Rockville, Maryland 20857

ATTENTION: Mr. Richard Terselic
Acting Director

RE: ANDA 73-479 Pentamidine Isethionate for Injection

Abbott Laboratories hereby amends the above referenced new drug application to notify the FDA of our intent to file an amendment in response to the Administration's letter of July 31, 1990.

The filing of this amendment is anticipated on or before January 31, 1991.

Sincerely,

ABBOTT LABORATORIES

Frederick A. Gustafson cmk

Frederick A. Gustafson
Director,
Regulatory Affairs
Hospital Products Division
(708) 937-3213

DTG/cmk
augf-dtg/1

ORIG

ABBOTT

Hospital Products Division

Abbott Laboratories
One Abbott Park Road
Abbott Park, Illinois 60064-3500

August 22, 1990

CENTER FOR DRUGS AND BIOLOGICS, HFD #230
Attn: DOCUMENT CONTROL ROOM #17B-45
5600 Fishers Lane
Rockville, Maryland 20857

NDA ORIG AMENDMENT
AC

ATTENTION: Mr. Richard Terselic
Acting Director

RE: ANDA 73-479 Sterile Pentamidine Isethionate, 300 mg/mL

Abbott Laboratories hereby submits additional information in response to the Administration's letter of July 31, 1990 regarding the above subject drug. The following additional information was requested:

Request: "1. Finished dosage form - Send three times the amount needed to perform the required testing. Identify the lot number of the material set."

Response: The following samples have been submitted under separate cover to the Detroit District Laboratory:

Item	Description	Quantity
1	Sterile Pentamidine Isethionate Lot 34-864 AR	90 vials

Request: "2. A Certificate of Analysis for the lot sent."

Response; Appended in Exhibit I is a Certificate of Analysis for Sterile Pentamidine Isethionate, Lot 34-864 AR.

Request: "3. Internal and Reference Standards - Send three times the amount necessary to perform the required testing."

Response: The following samples have been submitted under separate cover to the Detroit District Laboratory:

Item	Description	Quantity
1	Abbott Pentamidine Isethionate Reference Standard	1 gram
2	[redacted]	2 gram
3	[redacted]	2 gram

Request: "4. Impurity Standards - send samples of standards for any impurities for which you test the dosage form."

Response: There are no impurity standards.

Request: "5. Representative chromatograms and/or spectra (if applicable)."

Response: Appended in Exhibit II are the [redacted] spectra associated with Pentamidine Isethionate ARS Lot 35289-157 and Sterile Pentamidine, Lot 34-864-AR.

Request: "6. Copy of the method of analysis if the drug product is not compendial."

Response: Appended in Exhibit III is the standard control procedure used in the testing of the finished drug product Sterile Pentamidine Isethionate.

Request: "7. A Material Safety Data Sheet (OSHA Form 174) or equivalent information."

Response: Appended in Exhibit IV is a material safety data sheet for pentamidine isethionate.

We trust that this information is completed.

Sincerely,

ABBOTT LABORATORIES

Frederick A. Gustafson
Director,
Regulatory Affairs
Hospital Products Division
(708) 937-3213

DTG/dg
attachment

augfda.dtg/45-7

cc: Mr. Felix Schneider, HFR-MA-260
Food and Drug Administration
Detroit District Laboratory
1450 E. Jefferson Ave.
Detroit, MI 48207

ABBOTT

Hospital Products Division

Abbott Laboratories
One Abbott Park Road
Abbott Park, Illinois 60064-3500

RIC

NDA ORIG AMENDMENT
AC

August 30, 1990

CENTER FOR DRUGS AND BIOLOGICS, HFD #230
Attn: DOCUMENT CONTROL ROOM #17B-45
5600 Fishers Lane
Rockville, Maryland 20857

ATTENTION: Mr. Richard Terselic
Acting Director

Re: ANDA 73-479 Sterile Pentamidine Isethionate, 300 mg/mL

Abbott Laboratories hereby submits additional information in response to the Administration's letter of July 31, 1990 regarding the above subject drug. The following additional information was requested:

Request: " Materials to be sent:

1. Pentamidine Isethionate — Abbott

Drug Substance — Manufacturer

Send three times the amount needed to perform all USP testing. Package ..... Identify the manufacturer, the manufacturer's address, DMF number and lot number of the bulk sent."

Response: The following samples have been submitted under separate cover to the St. Louis District Laboratory:

Item	Description	Quantity
1	Pentamidine Isethionate Lot 35-764 CE	15 grams

Manufacturer: Abbott Laboratories
Chemical Agricultural Products Division
N. Chicago, Illinois 60064

DMF 8176

RECEIVED

Request: "2. A Certificate of Analysis for the lot sent."

Response; Appended in Exhibit I is a Certificate of Analysis for Pentamidine Isethionate, Lot 35-764 CE.

Request: "3. Standards - Reference, Impurity and Internal - Send three times the amount required by the USP."

Response: The following samples have been submitted under separate cover to the St. Louis District Laboratory:

Item	Description	Quantity
1	Abbott Pentamidine Isethionate Reference Standard Lot 35289-157	2 x 500 mg

Request: "4. Copies of representative chromatograms and/or spectra (if applicable)."

Response: Appended in Exhibit II are the chromatograms/spectra associated with Pentamidine Isethionate ARS Lot 35289-157 and Pentamidine Isethionate, Lot 35-764 CE.

Request: "5. Copy of the method of analysis if the drug product is not compendial."

Response: Appended in Exhibit III is the standard control procedure used in the testing of the bulk drug product Pentamidine Isethionate.

The subject Standard Control Procedure (SCP) 14547 has been updated to widen the —— assay range from between —— and —— % to —— and ——% anhydrous to reflect the precision of the assay.

Request: "6. A Material Safety Data Sheet (OSHA Form 174) or equivalent information."

Response: Appended in Exhibit IV is a material safety data sheet for pentamidine isethionate.

We trust that this information is completed.

Sincerely,

ABBOTT LABORATORIES

Frederick A. Gustafson
Director,
Regulatory Affairs
Hospital Products Division
(708) 937-3213

DTG/dg
attachment

augfda.dtg/49-51

cc: Food and Drug Administration
Division of Drug Analysis
Attention: Chief, Drug Monitoring Brance
1114 Market Street, Room 1002
St. Louis, MO 63101

ABBOTT

Hospital Products Division

Abbott Laboratories
One Abbott Park Road
Abbott Park, Illinois 60064-3500

September 4, 1990

NDA ORIG AMENDMENT
(AC)

CENTER FOR DRUGS AND BIOLOGICS, HFD #230
Attn: DOCUMENT CONTROL ROOM #17B-45
5600 Fishers Lane
Rockville, Maryland 20857

ATTENTION: Mr. Richard Terselic
Acting Director

Re: ANDA 73-479 Pentamidine Isethionate for Injection

Abbott Laboratories hereby submits additional information as requested in the Administration's letter of July 31, 1990 regarding the above subject drug. The following information was requested:

Request: "1. [redacted]

Response: Appended in Exhibit I are revised [redacted] incorporating the Administration's requests.

Request: "2. [redacted]

Response: Appended in Exhibit II is a [redacted]

RECEIVED
1990
GENERIC DRUGS

Redacted 5 page(s)

of trade secret and/or

confidential commercial

information from

9/4/1990 ABBOTT LETTER

Request: "19. Further, our review of the submitted labels and package insert labeling identified the following: [label review]

Request: "20. LABEL REVIEW:

Container: Not Satisfactory"

Response: Appended in Exhibit XIX is revised draft labeling for the container label incorporating the Administration's requests.

Request: "Carton: Not Satisfactory"

Response: Appended in Exhibit XX is revised draft labeling for the carton label incorporating the Administration's requests.

Request: "Insert: Not Satisfactory"

Response: Appended in Exhibit XXI is revised draft labeling for the package insert. Regarding the revision date of the labeling, the information is prominently displayed above and to the right of the drug name Sterile Pentamidine Isethionate.

We trust that this information is completed.

Sincerely,

ABBOTT LABORATORIES

Frederick A. Gustafson
Director,
Regulatory Affairs
Hospital Products Division
(708) 937-3213

DTG/dg
attachment

pentad.doc

ANDA 73-479

Abbott Laboratories
Hospital Products Division
Attention: Mr. Frederick A. Gustafson
One Abbott Park Road
D-389, AP30
Abbott Park, Illinois 60064-3500

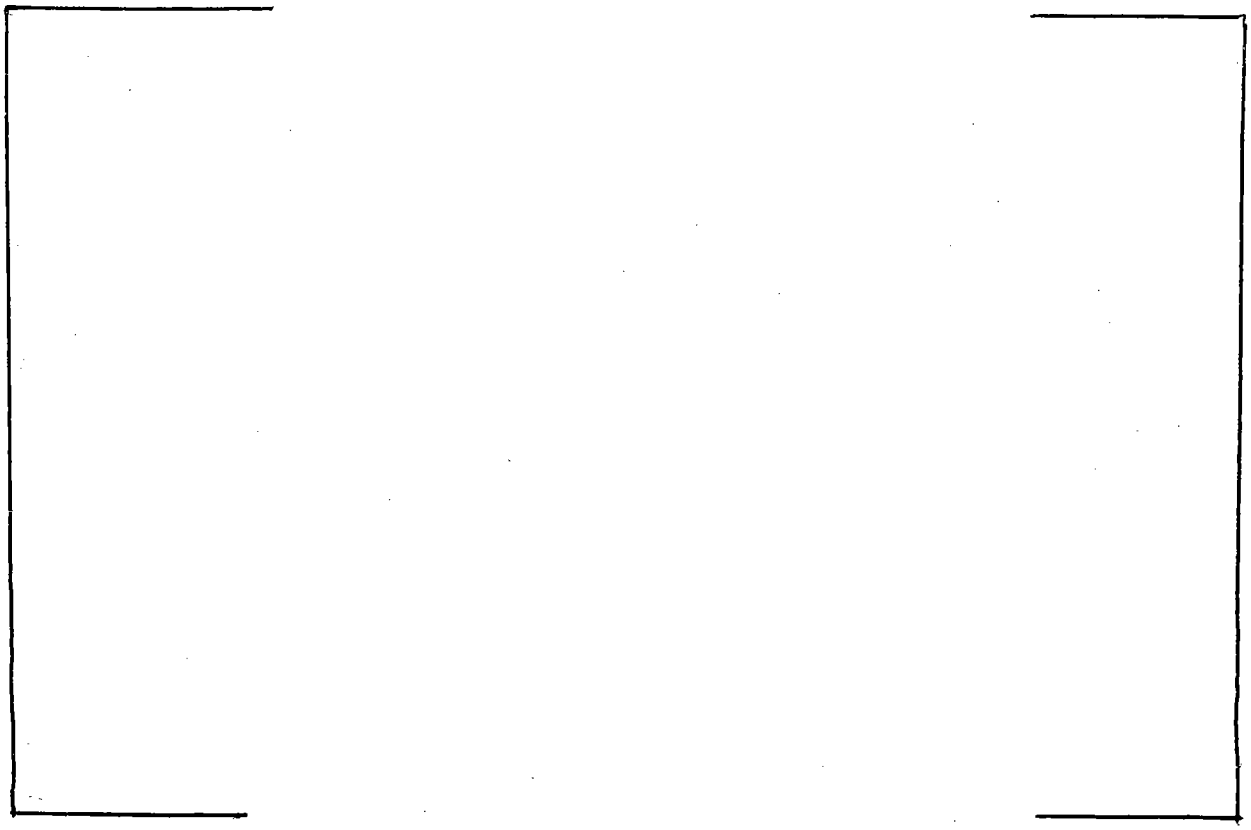
AUG 22 '991

Dear Sir:

Please refer to your abbreviated new drug application dated September 12, 1989, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Sterile Pentamidine Isethionate, 300 mg/vial

Reference is also made to your communications dated August 8, August 22, August 30, and September 4, 1990, amending this application.

The application is deficient and therefore not approvable under Section 505 of the Act for the following reasons:



8 Regarding the labeling, we have the following comments:

COMMENTS:

A. General Comment -

We would like to take this opportunity to direct your attention to USP XXII, General Notices, p 4, Added Substances, paragraph 3. If applicable, we recommend you meet the USP requirements at this time. We believe the required information should appear on the container labels (if there is space) and on the carton and package insert labeling as part of the "Each vial contains" statement.

B. Container: Not Satisfactory (Single Dose Vial)

1. USUAL DOSAGE

DOSAGE rather than DOSE

2. We encourage you to include the following statement after the "Protect...light" statement:

Retain in carton until time of use.

3. Delete the periods in "IM", "IV" and after "Use".

C. Carton: ——— Not Satisfactory

1. Refer to comment 2. under Container.

2. USUAL DOSAGE rather than DOSAGE (add USUAL)

3. The statement "Discard unused portion" should be linked with "Single Dose Vial".

4. Delete the periods in IM, IV and after "Use".

D. Insert: Not Satisfactory

1. INDICATIONS AND USAGE, Line 1 should read:

Sterile pentamidine isethionate...

(It is not necessary to capitalize the first letter of each word in the established name).

2. Please include a revision date.

Please revise your container labels, carton and package insert labeling, then prepare and submit twelve final printed copies.

The file is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a minor amendment and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

Robert A. Jenner 8/21/91

Acting Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA #73-479
DUP/Division File
HFC-130/JAllen
HFD-600 Reading File 8-20-91
HFD-638/KShah KShah Stephen Sherken 8/20/91
HFD-634/RPatel/SSherken/07/18/91
HFD-634/VVashio/07/22/91 Washio 8/21/91
R/D initialed by RPatel
cls/07/19/91/d:73-479.LTR
F/T by cls/07/23/91
Not Approvable

3/1

Called Tom Willard ORIG 4/1
and notified him of the
incorrect ANDA # 11/1/91
upstairs

Hospital Products Division

Abbot Laboratories
One Abott Park Road
Abbot Park, Illinois 60064-3500

Aust 28, 1991

CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS, HFD #630
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

ATTENTION: Roger Williams, M.D.
Director

ANDA 73-479 Sterile Pentamidine Isethionate, 300 mg Vial

Abbott Laboratories hereby amends the above referenced new drug application to notify the FDA of our intent to file an amendment in response to the Administrations's letter of August 22, 1991.

The filing of this amendment is anticipated on or before February 22, 1992.

Sincerely,

ABBOTT LABORATORIES

Frederick A. Gustafson /slz

Frederick A. Gustafson
Director,
Regulatory Affairs
Hospital Products Division
(708) 937-3213

DTG/slz
ackfda.doc/8

5 NOV 91

ABBOTT

Hospital Products Division

Abbott Laboratories
One Abbott Park Road
Abbott Park, Illinois 60064-3500

FPL container and carton and PI labeling is satisfactory
K Sw 11-13-91
yz 11/14/91

October 15, 1991

CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS, HFD #630
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

NDA ORIG AMENDMENT
AM FPL

ATTENTION: Roger Williams, M.D.
Director

Re: ANDA 73-479 Sterile Pentamidine Isethionate, 300 mg/vial

Abbott Laboratories hereby amends the above referenced Abbreviated New Drug Application in response to the Administration's letter of August 22, 1991. The following additional information was requested:

Request: "1. [redacted]

Response: [redacted]

Request: "2. [redacted]

Redacted 2 page(s)

of trade secret and/or

confidential commercial

information from

10/15/1991 ABBOTT LETTER

We trust that this information is complete.

Sincerely,

ABBOTT LABORATORIES

Frederick A. Gustafson
Director,
Regulatory Affairs
Hospital Products Division
(708) 937-3213

DTG/dg
attachment
9-91.fda/

APPEARS THIS WAY
ON ORIGINAL

ANDA 73-479

Abbott Laboratories
Hospital Products Division
Attention: Frederick A. Gustafson
One Abbott Park Road
D-389, AP30
Abbott Park, IL 60064-3500

FEB 7 1992

Dear Sir:

Please refer to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Sterile Pentamidine Isethionate, 300 mg/vial.

Reference is also made to sterilization process employed in the manufacture of the subject drug product. The sterilization data dated September 4, 1990 has been reviewed by the Division of Medical Imaging, Surgical and Dental Drug Products, HFD-160, and they have the following comments:

> The following outline covers the type of information that should be included in the ANDA file, and which is necessary for review of the sterilization of the subject ——————— drug product.

The information may be supplied directly to the file, or may be supplied by reference to a DMF or to another application. Exact references should be provided (e.g., dates, pages, etc.).

1. A brief description of the of the building and facilities including, for example, the number of filling areas, layout of critical and control areas, a brief description of water systems, air-handling, etc. A floor plan is often helpful for this purpose.

2. A brief description of the overall manufacturing operation including, for example, material flow, filling, capping, ——— assembly, etc.

3. A description of the sterilization process used for containers, closures, equipment, components, etc. A description of the validation of these processes should be provided including for example, heat distribution/penetration summaries, biological studies (biological indicators and endotoxin), routine monitoring procedures, etc. Validation information for other types of sterilization processes should also be included. Information and data demonstrating distribution and penetration of the sterilant and efficacy of each process should be submitted.

4. Summaries of recent media fill validation methods and results for the same container/closure type and size class that is to be used for the product. All media fill results obtained, including failure, should be supplied. These data should be obtained using the same filling line(s) that are to be used for the product in question. The following details should be included with the data for each media fill run described:

   A. Identification of filling room used. Relate this to the floor plan provided in number 1 above.
   B. Container/closure type and size.
   C. Volume filled.
   D. Type of media filled.
   E. Number of units filled.
   F. Number of units incubated.
   G. Number of units positive.
   H. Incubation time and temperature for each group of units incubated and whether any group of units is subjected to two different temperatures during the incubation.
   I. Date of media fill.
   J. Procedures used to simulate any steps of a normal production fill. This might include, for example, mock lyophilization or substitution of vial headspace gas.
   K. Microbiological monitoring data obtained during the media fill run.

5. A description of the disposition of product made after a failed media fill. Include descriptions of investigations, reviews, and how decisions are made to reject or release product.

6. A description of sterility testing methods and release criteria. Methods should include the protocol for the selection of representative units from the filling line during production.

7. Information concerning methods and results of container/closure integrity testing for both initial validation and the procedures used for the stability protocol.

8. A description of the microbiological monitoring program used during routine production and media fills. Include the frequency of monitoring, type of monitoring, sites monitor, alert and action level specifications, and precise descriptions of the actions taken when specifications are exceeded. These descriptions should include air, surface, personnel, and water monitoring programs. Descriptions of the bioburden monitoring program should also be provided, including specifications.

9. Evidence should be provided that there are formal, written procedures describing the above elements and that these procedures are followed.

The methods used to assure sterility for this drug product was not sufficiently addressed. Please provide responses to clarify these issues. The application is therefore not acceptable on the basis of sterility assurance.

Sincerely yours,

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA #73-479
DUP/Division File
HFC-130/JAllen
HFD-600/Reading File
HFD-82 (if w/d, AP, or R/F letter)
HFD-632/RPollock/2-5-92
R/D initialed by GJohnston
bcw/2-5-92/73479hfd.160
F/T by bcw/2-5-92
HFD-160 review

ANDA 73-479

MAY 23 1992

Abbott Laboratories
Hospital Products Division
Attention: Mr. Frederick A. Gustafson
One Abbott Park Road
Abbott Park, IL 60064-3500

Dear Sir:

Please refer to your abbreviated new drug application dated September 12, 1989 , submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Sterile Pentamidine Isethionate, 300 mg/vial.

Reference is also made to your communication dated October 15, 1991, amending this application.

The application is deficient and therefore not approvable under Section 505 of the Act for the following reasons:

1. Please respond to our deficiency letter of February 7, 1992. It will be reviewd by a qualified microbiologist within the Division of Medical Imaging, Surgical and Dental Drug Products (HFD-160). Any further deficiencies will be sent in a separate letter.

2. A deficiency letter was also sent to DMF-8176. Any further deficiencies found in the amendment to that deficiency letter will be sent to the appropriate person in Abbott who is responsible for it.

3. [redacted]

4. Please provide all stability data, including room temperature data of lot 34-486-AR, accrued to date.

The file is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. Your response to this letter will be considered a MINOR AMENDMENT and should be plainly marked as such in your cover letter. Please note that if the microbiology consult is not received prior to completion of the

chemistry and/or labeling review of your amendment, issuance of our subsequent action letter may be delayed. Further, should a major deficiency be cited in the microbiology consult response, the subsequent not-approvable letter will request that the reply be declared a major amendment. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

RKPatel 3/23/92

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA #73-479
DUP/Division File
HFC-130/JAllen
HFD-600 Reading File 3.19.92
HFD-638/KShah Stephen Sherken 3/19/92
HFD-634/MSmela/SSherken/03/17/92
HFD-634/VVashio/03/18/92 Washio 3/20/92
R/D initialed by MSmela
cls/03/18/92/d:73-479.LTR M Smela 3/20/92
F/T by cls/03/19/92
Not Approvable

ABBOTT

Hospital Products Division

NDA ORIG AMENDMENT

N/AM

no labeling in this submission per conversation dated 11-13-91 KSh 5-19-92

Abbott Laboratories
One Abbott Park Road
Abbott Park, Illinois 60064-3500

May 11, 1992

RECEIVED

MAY 13 1992

GENERIC DRUGS

CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS, HFD #630
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

ATTENTION: Roger Williams, M.D.
Director

Re: ANDA 73-479 Sterile Pentamidine Isethionate, 300mg/vial
MINOR AMENDMENT

Abbott Laboratories hereby submits a MINOR AMENDMENT to provide additional information as requested in the Administration's letter of March 23, 1992. The following additional information was requested:

Request: "1. Please respond to our deficiency letter of February 7, 1992. It will be reviewed by a qualified microbiologist within the Division of Medical Imaging, Surgical and Dental Drug Products (HFD-160). Any further deficiencies will be sent in a separate letter."

Response: The response to the Administration's February 7, 1992 letter will be submitted under separate cover.

Request: "2. A deficiency letter was also sent to DMF-8176. Any further deficiencies found in the amendment to that deficiency letter will be sent to the appropriate person in Abbott who is responsible for it."

Response: As requested in the deficiency letter submitted to Abbott Laboratories Chemical and Agricultural Products Division, the holder of the DMF for the bulk drug, we are providing in Attachment I their response to the Administration's 12/30/91 deficiency letter and in Attachment II an updated DMF 8176 Pentamidine Isethionate.

Request: "3. [redacted] [redacted]

W okay

15 days

Response: [redacted]

Request: "4. Please provide all stability data, including room temperature data of lot 34-486-AR, accrued to date."

Response: Appended in Attachment IV are updated stability data through 24 months at room temperature. Based on the stability data contained herein, Abbott Laboratories requests a product expiration dating of twenty-four (24) months.

We trust that this information is complete.

Sincerely,

ABBOTT LABORATORIES

Frederick A. Gustafson

Frederick A. Gustafson
Director,
Regulatory Affairs
Hospital Products Division
(708) 937-3213

DTG/dg
attachment
5-92fda.dtg

ABBOTT

Hospital Products Division

Abbott Laboratories
One Abbott Park Road
Abbott Park, Illinois 60064-3500

Orig

5.

NDA ORIG AMENDMENT

RECEIVED

MAY 19 1992

GENERIC DRUGS

May 15, 1992

CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS, HFD #630
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

ATTENTION: Roger Williams, M.D.
Director

Re: ANDA 73-479 Sterile Pentamidine Isethionate, 300mg/vial

Abbott Laboratories hereby submits additional information in response to the Administration's letter of February 7, 1992. The following additional information was requested:

Request: "1. A brief description of the building and facilities including, for example, the number of filling areas, layout of critical and control areas, a brief description of water systems, air-handling, etc. A floor plan is often helpful for this purpose.

Request: "2. A brief description of the overall manufacturing operation including, for example, material flow, filling, capping, ——— assembly, etc."

Response:

[redacted]

Request: "3. A description of the sterilization process used for containers, closures, equipment, components, etc. A description of the validation of these processes should be provided including for example, heat distribution/penetration summaries, biological studies (biological indicators and endotoxin), routine monitoring procedures, etc. Validation information for other types of sterilization processes should also be included. Information and data demonstrating distribution and penetration of the sterilant and efficacy of each process should be submitted."

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information from

5/15/1992 ABBOTT LETTER

Request: "9. Evidence should be provided that there are formal, written procedures describing the above elements and that these procedures are followed."

Response: [redacted]

We trust that this information is complete.

Sincerely,

ABBOTT LABORATORIES

Frederick A. Gustafson

Frederick A. Gustafson
Director,
Regulatory Affairs
Hospital Products Division
(708) 937-3213

DTG/dg
attachment
5-92fda.dtg/29

ABBOTT

Hospital Products Division

Abbott Laboratories
One Abbott Park Road
Abbott Park, Illinois 60064-3500

orig

4.1

June 24, 1992

CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS, HFD #630
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

ORIG NEW CORRES

ATTENTION: Roger Williams, M.D.
Director

Re: ANDA 73-479 Sterile Pentamidine Isethionate, 300mg/vial

As discussed in the June 24, 1992 telephone conversation between Dr. Robert Jerussi of the Administration and representatives of Abbott Laboratories, Abbott Laboratories hereby commits to provide within six (6) to twelve (12) months, the results of related substances as determined by — and — from one (1) or more new batches of the new drug substance.

We trust that this information is complete.

Sincerely,

ABBOTT LABORATORIES

Frederick A. Gustafson

Frederick A. Gustafson
Director,
Regulatory Affairs
Hospital Products Division
(708) 937-3213

DTg/dg
6-92fda.dtg

RECEIVED

JUN 2 5 1992

GENERIC DRUGS