CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-305

Chemistry Review(s)

NDA 21-305

Kit for the Preparation of
Sodium Iodide I-131 Capsules and Solution, USP

1000 mCi/mL
(Concentrated NaI –131 Solution USP)

250 mCi/vial and 500 mCi/vial

Therapeutic – for Oral Administration

DRAXIMAGE , Inc.

Milagros Salazar, Ph.D.
Division of Medical Imaging and Radiopharmaceutical DPs
HFD-160

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2. MANUFACTURER: Adequate, Review#2 , ... 10.
3. SYNTHESIS: Adequate , Review#2, ... 10.
4. SPECIFICATIONS/TEST METHODS/REF.STD.: Adequate, Review #2 10
5. CONTAINER/CLOSURE SYSTEM: Adequate, Review#2, ... 10
6. STABILITY: Adequate, Review#2, ... 10

B. DRUG PRODUCT

1. COMPONENTS/COMPOSITION: Adequate, Review#1, p 6..... 18
2. SPECIFICATIONS & METHODS FOR INGREDIENTS: Adequate, Review#1, pp 6-7 and Review #2 ..... 24.

3. MANUFACTURER: Adequate, Review#1, p 7.....24
4. MANUFACTURING AND PACKAGING: Adequate, Review#2, ...25.
5. SPECIFICATIONS AND TEST METHODS: Adequate, Review #2, p13-14..... 16
6. CONTAINER/CLOSURE SYSTEM: Adequate, Review#1, p 14-15.....28
7. STABILITY: Adequate (supporting 28 days after manufature/ 7days after capsule preparation, Review#2,p 14 , pp18-20..... 30

II. Review of NDA

A. Labeling & Package Insert

B. Environmental Assessment Or Claim Of Categorical Exclusion

C. MV & Others

C. INVESTIGATIONAL FORMULATIONS: Adequate, Review#1, p 16 31

D. ENVIRONMENTAL ASSESSMENT: Adequate, Review#1-Categorical Exclusion, p 17...32

E. METHODS VALIDATION: Adequate, Review#2, p 12, 15 32

F. LABELING: Adequate/with revisions, Review#2, ... 34

G. ESTABLISHMENT INSPECTION: Overall Recommendations: ACCEPTABLE, 29-Jun-2001 Review#2, Attachment 6 39

III. List Of Deficiencies To Be Communicated.....(Only Labeling issues)

H. REFERENCES : Adequete Review# 1 39

I. DEFICIENCY LETTER TO APPLICANT: No 40

ATTACHMENT 1 CoA of NaI-131 alkaline solution (raw material) from [redacted]
ATTACHMENT 2 Specifications and CoA for NaI-131 solution USP, 1000mCi/mL
ATTACHMENT 3 Representative Stability Data.
ATTACHMENT 4 Instructions for Capsule preparation and validation data for their performance after preparation
ATTACHMENT 5 Labeling proposed primary labels for all kit components and package insert.
ATTACHMENT 6 EES report

MEDICAL IMAGING AND RADIOPHARMACEUTICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls
DIVISION OF NEW DRUG CHEMISTRY 2

1. NDA #: 21-305

2. DATE REVIEWED: 20-NOV-02

3. REVIEW #: 2

4. REVIEWER: Milagros Salazar, Ph.D.

5. Previous Documents:

Previous Documents	Document Date
Original	24-Aug-2000
Fax amendment	18-Dec-2000

6. SUBMISSION (S) BEING REVIEWED:

Submision(s) Reviewed	Document Date
Amendment N-000 AZ	25-JUL-2002
T-con (with Mr. Vachon)	19-Nov-2002

7. NAME & ADDRESS OF APPLICANT: DRAXIMAGE INC.
16751 Trans-Canada Highway
Kirkland, Quebec
H9H 4J4, CANADA

8. DRUG PRODUCT NAME

Proprietary:	Sodium Iodide I 131 Solution USP, Therapeutic Oral
Established:	Sodium Iodide I 131 Solution USP
Code Name/#:	CAS 7681-72-5
Chem.Type/Ther.Class:	3,5 S

9. LEGAL BASIS FOR SUBMISSION: NA

10. PHARMACOL.CATEGORY/INDICATION: Therapeutic radiopharmaceutical/
/Hypertyroidism and Thyroid cancer

11. DOSAGE FORM: SOLUTION and CAPSULES

12. STRENGTHS: 1000 mCi/mL; and
presentations in 250 mCi and 500 mCi per vial

13. ROUTE OF ADMINISTRATION: ORAL

14. Rx/OTC: _X_ Rx __ OTC

15. SPECIAL PRODUCTS: __ Yes _X_ No

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: Sodium Iodide I-131, $Na\ ^{131}I$
Half life = 8.04 days Decay Mode : β- max (0.806 MeV) and various γs (0.364 MeV – 82 %)
M.W. 153.99
Expiry date : 28 days post- manufacture

17. RELATED/SUPORTING DOCUMENTS :

A. DMFs:

DMF # / Type	ITEM	HOLDER	STATUS	REVIEW DATE	COMMENTS
[redacted] (Version 13-Mar-02) /Type II	Sodium iodide I 131	[redacted]	Adequate	18-Oct-02 Review #2	Active ingredient, DS LoA: 22-Mar-00 Vol. 2 p 316
[redacted] Type III	[redacted]	[redacted]	Adequate	24-Mar-98	Container /closure component LoA 22-Mar-00 Vol. 2 p 318

B. Other Documents (related):

DOCUMENT	APPLICATION no. / Supplier's name	DESCRIPTION
NDA		
NDA	10-929 / Bracco	NaI-131 Caps & Solution
NDA	16-517 / Mallinckrodt	NaI-131 Caps
NDA		
NDA		
NDA	17-315 / CIS-US	NaI-131 Solution

18. CONSULTS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Overall: Acceptable 29-Jun-2001	Requested 26-Nov-99	P. Lefler, HFD-324
Biostatistics	NA		
LNC	NA – USP product		
Methods Validation	NA –USP product		
DDS	Question to PM 19-Nov-02		
Pharm/Tox	NA		

EA	Categorical Exclusion granted	30-Mar-2001	Milagros Salazar, Ph.D.
Microbiology	NA - Oral		
Biopharm	NA		
Other	NA		

Patent/Trademark: NA – this not a new product , and the applicant did not provide any claim.

Exclusivity: NA –This is not a new chemical entity, the company did not make any exclusivity claim.

19. ORDER OF REVIEW: NA

CHEMISTRY EXECUTIVE SUMMARY

I. Recommendations

A. Recommendations and Conclusions on Approvability

The chemistry section is recommending the APPROVAL of the Kit for the Preparation of Sodium Iodide I -131 (NaI-131) Capsules and Solution USP, 1000 mCi/mL as a therapeutic agent and for Oral administration based on the adequate chemistry, manufacturing and controls presented in support of this product and the acceptable cGMP status of the manufacturing facilities for the DS and DP.

B. Recommendations on Phase 4 (post-marketing) Commitments: None

II. Summary of Chemistry Assessments

A. Description of the Drug Product and Drug Substance

The Sodium Iodide I-131 is the active ingredient in the Sodium Iodide I-131 Solution, USP products and it contains radioactive iodine (I-131) processed in the form of sodium iodide from the neutron bombardment of tellurium to yield a non carrier-added product. The half life of I-131 is 8.04 days. The nuclear reactions, chemical preparation , manufacturing controls, specifications and stability of the NaI-131 raw material are described in DMF # The DMF holder and manufacturer supplier of NaI-131 drug substance is Two reviews of the DMF were done during the review time of this NDA; the second review resulted in an acceptable status in support of the NaI-131 alkaline solution as the drug substance. In addition, facilities in Ottawa-Ontario, Canada were inspected in May 2001 and had an acceptable cGMP inspection as of 29-Jun-2001.

The kit for the Preparation of NaI-131 Capsules and Solution, USP represents a product with new strength (1000 mCi/mL), formulation (buffer, stabilizer and reducing agent) and presentation (kit) in the market. The kit includes a 1 mL glass V-vial with concentrated, NaI-131 solution 37GBq/mL (1000 mCi/mL); one blister package of five to ten small (No. 2) hard gelatin capsules containing 300 mg of dibasic sodium phosphate ; and one blister package with 5 to 10 empty large (No. 1) hard gelatin capsules. Each mL of the concentrated NaI-131 solution contains 37 GBq (1000 mCi) of I-131, < 2.0 mg of disodium edetate dihydrate, USP as a stabilizer, < 4.4 mg of sodium thiosulfate pentahydrate, USP as a reducing agent, and < 40 mg of disodium phosphate anhydrous, USP. The pH of the solution is 7.5 to 9.0.

The kit for the Preparation of NaI-131 Capsules and Solution, USP is available in 2 fill sizes for the vial of the concentrated NaI-131 solution, USP: one of 0.25 mL containing 9.25 GBq (250 mCi) and another of 0.50 mL with 18.5 GBq (500 mCi).

The original application, 24- Aug-2000, was to support the approval of Sodium Iodide I-131 Solution USP, 1000 mCi/mL. The Agency recommendation was to redesign the product to resolve the concern about the need of a more uniform, reliable and safe to handle this radiotherapeutic dosage form. The applicant responded with amendment of 29-Jul-2002 in which a kit presentation provides for all the components and directions for the use of the concentrated NaI-131 Solution, USP, 1000mCi/mL, in the preparation of NaI-131 capsules and solutions of varying strengths at the radiopharmacy/clinical sites. Draximage, Inc., the applicant, manufacturer and distributor of the drug

product, has also responded to the deficiencies found in the CMC review #1 . Specifically, adequate information has been provided to satisfy the CMC safety concerns in the following areas: Manufacturing information related to composition and batch sizes and control; Specifications for the control of all ingredients in the preparation,; Stability related to both the concentrated NaI-131 solution and the capsules manufactured at the radiopharmacy sites; the information provided to support the validation of analytical methods (i.e., use of USP methods and a comparison study of the USP-NDA methods for Radiochemical Purity testing). In addition, Draximage Inc. Kirkland-Quebec, Canada facilities were inspected in May of 2001 and had an acceptable cGMP status as of 29-Jun-2001.

B. Descriptions of How the Drug Product is intended to be Used
The kit for the preparation of NaI-131 Capsules and Solution, USP, 1000mCi/mL is intended for therapeutic agent in the treatment of hyperthyroidism and selected cases if carcinoma of the thyroid and is supplied for oral administration. The kit provides the concentrated 1000mCi/mL solution, USP, capsule components and directions for the preparation, at radiopharmacy sites, of NaI-131 capsules and solutions of varying strengths, depending on individual patient dose requirements. The expiry of the concentrated NaI-131 Solution, USP is 28 days after manufacture. The shelf life for the capsules is 7 days after preparation or before the expiration date of the concentrated NaI-131 solution. The storage conditions for the kit and components is between 2 to 30 °C (36 to 86 °F)

C. Basis for Approvability or Not-Approvability Recommendations
This NDA for the Kit for the Preparation of NaI-131 Capsules and Solution, USP- Therapeutic for Oral administration has been filed under 502(b)(2) of the FD&C Act. The applicant did not perform investigational clinical trials on their own but used published literature data in support of the intended use. Indications: Treatment of hyperthyroidism and selected cases of carcinoma of the thyroid.
The Chemistry Assessments of CMC Review #2 (see also II. A. Summary section above) found acceptable CMC to support the identity, purity, strength and quality of this product .
A recommendation for the APPROVAL of the Kit for the Preparation of Sodium Iodide I –131 (NaI-131) Capsules and Solution USP, 1000 mCi/mL as a therapeutic agent and for Oral administration is made under section 505(b)(1) based on the chemistry, manufacturing and controls presented in the original application of 24-Aug-2000, amendment of 25-Jul-2001 and DMF # [redacted] (version 13-Mar-2002).

III. Administrative

/S/

Milagros Salazar, Ph.D.
Review Chemist, HFD-160/-820

/S/ 11/26/2002

Eldon Leutzinger, Ph.D.
Chemistry Team Leader, HFD-820/160

cc:
Org. NDA 21-305
HFD-160/Division File
HFD-160/M Salazar
HFD-160/E Leutzinger
HFD-160/ R Tyson
R/D Init by: E Leutzinger

filename: **N 21-305NaI#2.doc** (under **c:\\ ...\nda** and **N:\\....\salazar**)

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FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **NDA 21305/000**
Priority: **35S** Org Code: **160**
Stamp: **31-AUG-2000** Regulatory Due: **26-JAN-2003**
Action Goal: District Goal: **01-MAY-2001**
Applicant: **DRAXIMAGE**
H9H 4J4
KIRKLAND, QUEBEC, CA
Brand Name: **SODIUM IODIDE I 131 SOL 1-30 50-200 MCI**
Established Name:
Generic Name: **SODIUM IODIDE I 131 SOL 1-30 50-200 MCI**
Dosage Form: **SOL (SOLUTION)**
Strength: **1000 MCI/ML**

FDA Contacts: **A. REDDY (HFD-580) 301-827-5424 , Project Manager**
M. SALAZAR DRIVER (HFD-160) 301-827-7510 , Review Chemist
E. LEUTZINGER (HFD-160) 301-827-7510 , Team Leader

Overall Recommendation:

ACCEPTABLE on 29-JUN-2001 by P. LEFLER (HFD-324) 301-827-0062

Establishment: [redacted]
DMF No: [redacted]
AADA No:

Profile: **CRU** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **29-JUN-2001**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
Responsibilities:

Establishment: **9617567**
DRAXIMAGE INC
16751 TRANS CANADA HIGHWAY
KIRKLAND, QUEBEC, CA
DMF No:
AADA No:

Profile: **LIQ** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **29-JUN-2001**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
Responsibilities: **FINISHED DOSAGE MANUFACTURER**

Establishment: [redacted]
DMF No: [redacted]
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Responsibilities:

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Milestone Date: **29-JUN-2001**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

DMF Number: [redacted] DMF Type: II

Sodium Iodide I-131 (Tellurium-derived)

[redacted]

1. CHEM REVIEW No. 2 2. REVIEW DATE: 18-OCT-2002

3. ITEM REVIEWED

A. IDENTIFICATION

USAN	Sodium iodide I-131
Manufacturer's ID codes	IPG-I-131, IPG-I-131-A
Chemical name	Sodium iodide I 131
CAS number, if available	CAS-7790-26-3
Other names	Iodine-131, I-131 radiochemical, I-131, I-131 Bulk

B. LOCATION IN DMF

Type of Submission	Date of Submission	Location of Information
Amendment	13-MAR-2002 (revision#4)	Vol. 2.1

4. PREVIOUS DOCUMENTS

Type of Document	Date of Document	Location	Description

No other documents have been submitted to this DMF other than the listed above and a list of firms authorized to reference the DMF.

5. NAME & ADDRESS OF DMF HOLDER AND REPRESENTATIVE(S):

NAME:

ADDRESS:

CONTACT PERSON'S NAME, TITLE, DEPARTMENT:

6. DMF REFERENCED FOR:

NDA 21-305: Re-submission dated 25-Jul-2002
PRIMARY DMF : YES
APPLICANT NAME: Draximage Inc.
LOA DATE: 22- Mar-2000
DRUG PRODUCT NAME: Sodium Chloride I 131 solution /Capsules, USP
DOSAGE FORM: Solution CODE: 138
STRENGTH: 1000 mCi/mL
ROUTE OF ADMINISTRATION: ORAL CODE: 001

7. **SUPPORTING DOCUMENTS:** DMF [redacted] Type I - [redacted] Facilities description and process flow charts.

8. **CURRENT STATUS OF DMF:**
DATE OF LAST UPDATE OF DMF: 13-Mar-2002
DATE OF MOST RECENT LIST OF COMPANIES FOR WHICH LOA's HAVE BEEN PROVIDED: 13-Mar-2002.
LAST INDIVIDUAL LOA PROVIDED: 2-Jun-2000

9. **CONSULTS:** None

10. **COMMENTS:** The review of this DMF is for the Drug substance, Sodium Iodide I-131 solution, is made in support for its use as the active ingredient in the Sodium iodide I-131 oral capsules and their use in therapy. This revision responded to the request made in the Chemistry review # 1 of this DMF and during the Y-2000 [redacted] site Inspection. This revision consolidates the manufacturing information which had been fragmented since 1986 to 2000. The information and data provided is Adequate for control of the starting target material [redacted] the manufacturing /process description and controls, stability, Container/Closure, and labeling of the NaI 131 solution as manufactured in the [redacted] CANADA facility. See ATTACHMENTS for the CMC deficiencies listed in Review #1.

11. **CONCLUSION: ADEQUATE** in support of Sodium Iodide I-131 solution, made in the [redacted] site as the active ingredient in the Sodium iodide I-131 oral capsules drug product used for therapy. **A letter to the DMF holder should be issued to request revisions in their routine stability protocol. See Section X. Overall Comments and List of Deficiencies on page 19 of this review.**

/S/

Milagros Salazar, Ph.D.
Review Chemist, HFD-160/-820

/S/ 11/6/2002

Eldon Leutzinger, Ph.D.
Chemistry Team Leader, HFD-160/-820

cc:
Original DMF# [redacted] (2 copies)
HFD-160 /Division File NDA 21-305
HFD-160 /MSalazar
HFD-160 /ELeutzinger
HFD-160/ RTyson
R.D. Init by: ELeutzinger 6-Nov-2002
Document name: DMF [redacted] NaI-#2.doc

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/s/

Milagros Salazar
12/13/02 04:09:43 PM
CHEMIST
Approval Recommended with Labeling Revisions for CMC.
See Signature Comments.

Eldon Leutzinger
12/16/02 12:59:48 PM
CHEMIST
I concur with all conclusions made in the review,
and the recommendation based on chemistry, manufacturing and controls.

NDA 21-305

Kit for the Preparation of
Sodium Iodide I-131 Capsules and Solution, USP

1000 mCi/mL
(Concentrated NaI –131 Solution USP)

250 mCi/vial and 500 mCi/vial

Therapeutic – for Oral Administration

DRAXIMAGE , Inc.

Milagros Salazar, Ph.D.
Division of Medical Imaging and Radiopharmaceutical DPs
HFD-160

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C. Basis for Approvability or Not-Approval Recommendation 8

III. Administrative 8

A. Reviewer's Signature 8

B. Endorsement Block 9

C. CC Block 9

Chemistry Assessment 10

I. Review Of NDA Body Of Data 10

A. DRUG SUBSTANCE (NaI-131 alkaline solution) -DMF [redacted] Review #2 Adequate 10

1. DESCRIPTION & CHARACTERIZATION: Adequate, Review#2, ... 10
2. MANUFACTURER: Adequate, Review#2 , ... 10.
3. SYNTHESIS: Adequate , Review#2, ... 10.
4. SPECIFICATIONS/TEST METHODS/REF.STD.: Adequate, Review #2 10
5. CONTAINER/CLOSURE SYSTEM: Adequate, Review#2, ... 10
6. STABILITY: Adequate, Review#2,..... 10

B. DRUG PRODUCT

1. COMPONENTS/COMPOSITION: Adequate, Review#1, p 6..... 18
2. SPECIFICATIONS & METHODS FOR INGREDIENTS: Adequate, Review#1, pp 6-7 and Review #2 ..... 24.

3. MANUFACTURER: Adequate, Review#1, p 7.....24
4. MANUFACTURING AND PACKAGING: Adequate, Review#2, ...25.
5. SPECIFICATIONS AND TEST METHODS: Adequate, Review #2, p13-14..... 16
6. CONTAINER/CLOSURE SYSTEM: Adequate, Review#1, p 14-15.....28
7. STABILITY: Adequate (supporting 28 days after manufacture/ 7days after capsule preparation, Review#2,p 14 , pp18-20..... 30

II. Review of NDA

A. Labeling & Package Insert

B. Environmental Assessment Or Claim Of Categorical Exclusion
C. MV & Others

C. INVESTIGATIONAL FORMULATIONS: Adequate, Review#1, p 16 31

D. ENVIRONMENTAL ASSESSMENT: Adequate, Review#1-Categorical Exclusion, p 17...32

E. METHODS VALIDATION: Adequate, Review#2, p 12, 15 32

F. LABELING: Adequate/with revisions, Review#2, ... 34

G. ESTABLISHMENT INSPECTION: Overall Recommendations: ACCEPTABLE, 29-Jun-2001 Review#2, Attachment 6 39

III. List Of Deficiencies To Be Communicated.....(Only Labeling issues)

H. REFERENCES : Adequete Review# 1 39

I. DEFICIENCY LETTER TO APPLICANT: No 40

ATTACHMENT 1 CoA of NaI-131 alkaline solution (raw material) from [redacted]
ATTACHMENT 2 Specifications and CoA for NaI-131 solution USP, 1000mCi/mL
ATTACHMENT 3 Representative Stability Data.
ATTACHMENT 4 Instructions for Capsule preparation and validation data for their performance after preparation
ATTACHMENT 5 Labeling proposed primary labels for all kit components and package insert.
ATTACHMENT 6 EES report

MEDICAL IMAGING AND RADIOPHARMACEUTICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls
DIVISION OF NEW DRUG CHEMISTRY 2

1. NDA #: 21-305

2. DATE REVIEWED: 20-NOV-2002 and 13-DEC-02 revision

3. REVIEW #: 2

4. REVIEWER: Milagros Salazar, Ph.D.

5. Previous Documents:

Previous Documents	Document Date
Original	24-Aug-2000
Fax amendment	18-Dec-2000

6. SUBMISSION (S) BEING REVIEWED:

Submision(s) Reviewed	Document Date
Amendment N-000 AZ	25-JUL-2002
T-con (with Mr. Vachon)	19-Nov-2002
Amendment N-000 BC	21-Nov-2002

7. NAME & ADDRESS OF APPLICANT: DRAXIMAGE INC.
16751 Trans-Canada Highway
Kirkland, Quebec
H9H 4J4, CANADA

8. DRUG PRODUCT NAME

Proprietary:	Sodium Iodide I 131 Solution USP, Therapeutic Oral
Established:	Sodium Iodide I 131 Solution USP
Code Name/#:	CAS 7681-72-5
Chem.Type/Ther.Class:	3,5 S

9. LEGAL BASIS FOR SUBMISSION: NA

10. PHARMACOL.CATEGORY/INDICATION: Therapeutic radiopharmaceutical/
/Hypertyroidism and Thyroid cancer

11. DOSAGE FORM: SOLUTION and CAPSULES

12. STRENGTHS: 1000 mCi/mL; and
presentations in 250 mCi and 500 mCi per vial

13. ROUTE OF ADMINISTRATION: ORAL

14. Rx/OTC: _X_ Rx __ OTC

15. SPECIAL PRODUCTS: __ Yes _X_ No

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: Sodium Iodide I-131, $Na\ ^{131}I$

Half life = 8.04 days Decay Mode : β- max (0.806 MeV) and various γs (0.364 MeV – 82 %)
M.W. 153.99
Expiry date: 28 days post- manufacture of concentrated solution, and 7-days storage time after capsule preparation.

17. RELATED/SUPORTING DOCUMENTS :

A. DMFs:

DMF # / Type	ITEM	HOLDER	STATUS	REVIEW DATE	COMMENTS
[redacted] (Version 13-Mar-02) /Type II	Sodium iodide I 131	[redacted]	Adequate	18-Oct-02 Review #2	Active ingredient, DS LoA: 22-Mar-00 Vol. 2 p 316
[redacted] Type III	[redacted]	[redacted]	Adequate	24-Mar-98	Container /closure component LoA 22-Mar-00 Vol. 2 p 318

B. Other Documents (related):

DOCUMENT	APPLICATION no. / Supplier's name	DESCRIPTION
NDA		
NDA	10-929 / Bracco	NaI-131 Caps & Solution
NDA	16-517 / Mallinckrodt	NaI-131 Caps
NDA		
NDA		
NDA	17-315 / CIS-US	NaI-131 Solution

18. CONSULTS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Overall: Acceptable 29-Jun-2001	Requested 26-Nov-99	P. Lefler, HFD-324
Biostatistics	NA		
LNC	NA – USP product		
Methods Validation	NA –USP product		
DDS	Question to PM 19-Nov-02		
Pharm/Tox	NA		

EA	Categorical Exclusion granted	30-Mar-2001	Milagros Salazar, Ph.D.
Microbiology	NA - Oral		
Biopharm	NA		
Other	NA		

Patent/Trademark: NA – this not a new product , and the applicant did not provide any claim.

Exclusivity: NA –This is not a new chemical entity, the company did not make any exclusivity claim.

19. ORDER OF REVIEW: NA

CHEMISTRY EXECUTIVE SUMMARY

I. Recommendations

A. Recommendations and Conclusions on Approvability

The chemistry section is recommending the APPROVAL of the Kit for the Preparation of Sodium Iodide I-131 (NaI-131) Capsules and Solution USP, 1000 mCi/mL as a therapeutic agent and for Oral administration based on the adequate chemistry, manufacturing and controls presented in support of this product and the acceptable cGMP status of the manufacturing facilities for the DS and DP. **NOTE: CONFIDENTIAL INFORMATION AND MATERIAL IS PRESENTED IN THE ATTACHMENTS OF THIS REVIEW AND MUST NOT BE RELEASED TO THE PUBLIC.**

B. Recommendations on Phase 4 (post-marketing) Commitments: None

II. Summary of Chemistry Assessments

A. Description of the Drug Product and Drug Substance

The Sodium Iodide I-131 is the active ingredient in the Sodium Iodide I-131 Solution, USP products and it contains radioactive iodine (I-131) processed in the form of sodium iodide from the neutron bombardment of tellurium to yield a non carrier-added product. The half life of I-131 is 8.04 days. The nuclear reactions, chemical preparation , manufacturing controls, specifications and stability of the NaI-131 raw material are described in DMF # [redacted] The DMF holder and manufacturer supplier of NaI-131 drug substance is [redacted] Two reviews of the DMF were done during the review time of this NDA; the second review resulted in an acceptable status in support of the NaI-131 alkaline solution as the drug substance. In addition, [redacted] facilities in Ottawa-Ontario, Canada were inspected in May 2001 and had an acceptable cGMP inspection as of 29-Jun-2001.

The kit for the Preparation of NaI-131 Capsules and Solution, USP represents a product with new strength (1000 mCi/mL), formulation (buffer, stabilizer and reducing agent) and presentation (kit) in the market. The kit includes a 1 mL glass V-vial with concentrated, NaI-131 solution 37GBq/mL (1000 mCi/mL); one blister package of five to ten small (No. 2) hard gelatin capsules containing 300 mg of dibasic sodium phosphate ; and one blister package with 5 to 10 empty large (No. 1) hard gelatin capsules. Each mL of the concentrated NaI-131 solution contains 37 GBq (1000 mCi) of I-131, < 2.0 mg of disodium edetate dihydrate, USP as a stabilizer, < 4.4 mg of sodium thiosulfate pentahydrate, USP as a reducing agent, and < 40 mg of disodium phosphate anhydrous, USP. The pH of the solution is 7.5 to 9.0.

The kit for the Preparation of NaI-131 Capsules and Solution, USP is available in 2 fill sizes for the vial of the concentrated NaI-131 solution, USP: one of 0.25 mL containing 9.25 GBq (250 mCi) and another of 0.50 mL with 18.5 GBq (500 mCi).

The original application, 24- Aug-2000, was to support the approval of Sodium Iodide I-131 Solution USP, 1000 mCi/mL. The Agency recommendation was to redesign the product to resolve the concern about the need of a more uniform, reliable and safe to handle this radiotherapeutic dosage form. The applicant responded with amendment of 29-Jul-2002 in which a kit presentation provides for all the components and directions for the use of the concentrated NaI-131 Solution,

USP, 1000mCi/mL, in the preparation of NaI-131 capsules and solutions of varying strengths at the radiopharmacy/clinical sites. Draximage, Inc., the applicant, manufacturer and distributor of the drug product, has also responded to the deficiencies found in the CMC review #1 . Specifically, adequate information has been provided to satisfy the CMC safety concerns in the following areas: Manufacturing information related to composition and batch sizes and control; Specifications for the control of all ingredients in the preparation,; Stability related to both the concentrated NaI-131 solution and the capsules manufactured at the radiopharmacy sites; the information provided to support the validation of analytical methods (i.e., use of USP methods and a comparison study of the USP-NDA methods for Radiochemical Purity testing). In addition, Draximage Inc. Kirkland-Quebec, Canada facilities were inspected in May of 2001 and had an acceptable cGMP status as of 29-Jun-2001.

B. Descriptions of How the Drug Product is intended to be Used
The kit for the preparation of NaI-131 Capsules and Solution, USP, 1000mCi/mL is intended for therapeutic agent in the treatment of hyperthyroidism and selected cases if carcinoma of the thyroid and is supplied for oral administration. The kit provides the concentrated 1000mCi/mL solution, USP, capsule components and directions for the preparation, at radiopharmacy sites, of NaI-131 capsules and solutions of varying strengths, depending on individual patient dose requirements. The expiry of the concentrated NaI-131 Solution, USP is 28 days after manufacture. The shelf life for the capsules is 7 days after preparation or before the expiration date of the concentrated NaI-131 solution. The storage conditions for the kit and components is between 2 to 30 °C (36 to 86 °F)

C. Basis for Approvability or Not-Approvability Recommendations
This NDA for the Kit for the Preparation of NaI-131 Capsules and Solution, USP- Therapeutic for Oral administration has been filed under 502(b)(2) of the FD&C Act. The applicant did not perform investigational clinical trials on their own but used published literature data in support of the intended use. Indications: Treatment of hyperthyroidism and selected cases of carcinoma of the thyroid.
The Chemistry Assessments of CMC Review #2 (see also II. A. Summary section above) found acceptable CMC to support the identity, purity, strength and quality of this product .
A recommendation for the APPROVAL of the Kit for the Preparation of Sodium Iodide I –131 (NaI-131) Capsules and Solution USP, 1000 mCi/mL as a therapeutic agent and for Oral administration is made under section 505(b)(1) based on the chemistry, manufacturing and controls presented in the original application of 24-Aug-2000, amendment of 25-Jul-2001 and DMF # [redacted] (version 13-Mar-2002).

III. Administrative

/S/

Milagros Salazar, Ph.D.
Review Chemist, HFD-160/-820

/S/

Eldon Leutzinger, Ph.D.
Chemistry Team Leader, HFD-820/160

cc:
Org. NDA 21-305
HFD-160/Division File
HFD-160/M Salazar
HFD-160/E Leutzinger
HFD-160/ R Tyson
R/D Init by: E Leutzinger

filename: **N 21-305NaI#2.doc** (under c:\\ ...\nda\ and N:\\....\salazar\ )

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secret and/or

confidential

commercial

information

5 pages redacted from this section of the approval package consisted of draft labeling

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secret and/or

confidential

commercial

information

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Milagros Salazar
12/13/02 04:09:43 PM
CHEMIST
Approval Recommended with Labeling Revisions for CMC.
See Signature Comments.

Eldon Leutzinger
12/16/02 12:59:48 PM
CHEMIST
I concur with all conclusions made in the review,
and the recommendation based on chemistry, manufacturing and controls.

Commitments to Sponsor
Sodium Iodide I-131 Capsules and Solution USP
NDA 21-305

The following Phase 4 Commitments need to be agreed prior to the issuance of the action letter:

Submit a labeling supplement within 2 weeks of receiving the action letter for the following changes:

1. On the vials, move the radioactivity symbol from the center to accommodate the addition of radioactivity concentration, and expiration date.

2. On the carton, add the "Rx only" statement.

3. On the package insert, provide pictorial illustrations for preparation instructions for the capsules only.