CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-044 / S-009

Trade Name: Indium In-111 Oxyquinoline

Generic Name:

Sponsor: GE Healthcare

Approval Date: August 27, 1990

Indications: For changes in the production schedule timetable

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-044 / S-009

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-044 / S-009

APPROVAL LETTER

NDA 19-044/S-009

AUG-~~23~~ 27 1990

Amersham Corporation
2636 South Clearbrook Drive
Arlington Heights, Illinois 60005-4692

Attention: John H. Waterman
Manager, Scientific and Regulatory Affairs

Dear Mr. Waterman:

Reference is made to your supplemental new drug application dated ~~September 15~~, 1989 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for indium In 111 oxyquinoline.

OCTOBER 24,

The supplemental new drug application provides for changes in the production schedule timetable which include the times between the [redacted] (b) (4) and the addition of a specification for [redacted].

We have completed our review of this supplemental new drug application and it is approved effective on the date of this letter. However, we do have the following comments/questions.

1. [redacted] (b) (4)

2. The level of [redacted] (b) (4) impurity should be mentioned in the Description section of the package insert and the dosimetry calculations should be revised to include the contribution from the [redacted] (b) (4). These revisions may be made at the time of the next package insert printing.

We remind you that you must comply with the requirements set forth under 21 CFR 314.80 and 314.81 for an approved NDA.

Sincerely yours,

J Palmer 8-22-90

John F. Palmer, M.D.
Director
Division of Medical Imaging,
Surgical and Dental Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
NDA 19-044/S-008
HFD-160/Div File
HFD-160/CSO/Lange
HFD-160/Chacalos
HFD-160/Ruby/Sheinin
HFD-160/Stone
R/D Endorsed by:
S. Lange 8.08.90
E. Ruby 8.10.90
E. Sheinin, Ph.D. 8.13.90
E. Chacalos, M.D. 8.14.90
A.E. Jones, M.D. 8.17.90
W. Rumble 8.17.90
F/T by: RCannon 8.17.90
Wang 0476B

APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-044 / S-009

MEDICAL REVIEW(S)

AUG 22 1990

Medical Officer Review
NDA 19-044

Submission dated 10-26-89
Supplement SCS 009 Controls

Indium In-111 Oxyquinoline

Chemistry review dated 4-16-90 (E. Ruby) requests evaluations of firm's claims regarding a newly detected radionuclidic impurity (b) (4) ((b) (4)) which was discovered as a result of a (b) (4)

(b) (4)

"We believe that for a short half-life impurity like (b) (4) it would be more logical to base a specification on the time of measurement since this represents a worst case relative to earliest time of use of the product. By analogy, for a long half-life impurity such as ^{114m}In, the worst case is represented by the specified value at expiration of the product (DOE)."

"Consequently, to allow flexibility to cover emergency manufacturing sequences we propose revising the production schedule to:

(b) (4)

"This would cover all eventualities that we have already experienced or could envisage in the future. It does not alter the critical ^{114m}In specification since the worst case interval of [redacted](b)(4), addressed in our product stability studies, would be unchanged."

"We also [redacted](b)(4) not more [redacted]. This would give an additional radiation dose to the patient of not more than [redacted](b)(4) of the dose from the ^{111}In at time of earliest use, and in relation to our current specification of [redacted](b)(4). No batch of Indium ^{111}In Oxyquinoline would be released for shipment to customers until the [redacted](b)(4) impurity level has been measured and shown to meet specification."

To put this matter in perspective we note below some pertinent facts.

[redacted](b)(4)

[redacted](b)(4)

How has the firm established that it has only the [redacted](b)(4) and not the [redacted](b)(4)?

2. In addition to In-114m impurity ([redacted](b)(4) of In-111 at expiry) acknowledged in the package insert and dosimetry there are many other radionuclidic impurities, most of them neglegible.

[redacted](b)(4)

3. The absorbed radiation dosages from In-111 and In-114m are by no means small e.g. in Rads/500 uCi-In-111 plus 1.25 microcuries In-114m 20 to spleen, 2.7 to liver, 2.0 bone marrow; 0.9 x 10^4 rads to the 10^{+8} incubated leukocytes. At lower levels 150 uCi/10^8 leukocytes at least 93% of the cells were abnormal (chromosome gaps, breaks, exchanges). Moreover, during approval there were controversies and uncertainties concerning the radiation burden.

   The low level ionizing radiations from Cd-(b) (4) (t 1/2 = (b) (4) days) ((b) (4) (b) (4)) are disregarded in dosimetries.

Evaluation:

As far as image quality and efficacy is concerned (b) (4) will not have the slightest effect for before imaging is begun (b) (4) will have gone through about (b) (4) half-lives and there would be nothing left (b) (4) hours for preparation of In-111 WBC plus imaging at 24 hours following administration)

Applicant proposes to revise specifications of (b) (4) to not more than (b) (4) at time of measurement which would increase radiation dose to patient by about (b) (4). This would be insignificant if the absorbed radiation doses as presented in package insert were lower and not possibly underestimates as we suspect. However, if firm agrees to revise their dosimetry table to include contributions from (b) (4) on a worst case scenario and to mention the levels of (b) (4) in their description section we would have not objection to these release criteria.

Action Recommended:

Release specifications for (b) (4) (b) (4) radionuclidic impurity are acceptable with regard to efficacy and safety, provided firm mentions level of In-(b) (4) impurity in the Description section of their insert and revise their dosimetry calculations to include contributions from (b) (4). This can be done at next printing of insert.

Firm should also be asked how they have established that they have only (b) (4) with a (b) (4) hour and none of the (b) (4) with (b) (4) min. and different emissions.

E. H. Chacalos

E. H. Chacalos, M.D

cc:Orig. NDA 19-044
HFD-160/Division File
HFD-160/EHChacalos
HFD-161/MAnderson /F.Stone
HFD-340
R/D Init. by: AEJones/
F/T by: SDavis/5-7-90
Wang 2879M

GROUP LEADER'S COMMENTS
NDA 19-044
Supplement 009

Agent: Indium In-111 oxyquinoline
Applicant: Amersham Corporation

At issue is the [redacted] (b) (4) radionuclidic impurity, [redacted] (b) (4). Dr. Chacalos concluded that "release specifications for [redacted] (b) (4)% [redacted] (b) (4) radionuclidic impurity are acceptable with regard to efficacy and safety - "

Dr. Chacalos's concern, lastly stated in his review, is not appropriate since the chemist's review noted that [redacted] (b) (4) decays by [redacted] (b) (4) pathways i.e. [redacted] (b) (4). Dr. Ruby wishes to know the proportion of decay between the [redacted] (b) (4) pathways.

Finally, I agree with Dr. Chacalos that safety and efficacy are acceptable, neither are compromised by the presence of the trace amount of [redacted] (b) (4).

Alfred E. Jones MD

Alfred E. Jones, M.D.

cc:Orig. NDA 19-044
HFD-160/Division File
HFD-160/EChacalos
HFD-161/MAnderson /F.Stone
HFD-340
R/D Init. by: /
F/T by: SDavis/5-7-90
Wang 2878M

JPalmer 5-22-90

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-044 / S-009

CHEMISTRY REVIEW(S)

APR 26 1990

APR 26 1990

CHEMIST'S REVIEW | **Organization** HFD-160 | **NDA Number** 19-044

Name and Address of Applicant
Amersham Corporation
2636 South Clearbrook Dr.
Arlington Heights, IL 60005-4692
(312) 593-6300

AF Number

Supplements

Number	Date
S-009	26Oct89

Name of Drug | **Non-Proprietary Name**
Indium In-111 Oxyquinoline

Supplement Provides For:
a.) Changes in the production schedule timetable, that is, the times between [redacted] (b) (4), and b.) addition of a specification for [redacted] (b) (4) as a radionuclidic impurity.

Pharmacological Category	How Dispensed	Related NDA/DMF
diagnostic radiopharmaceutical	Rx	

Dosage Form	Potency
injectable solution	about 1 mCi In-111; and 50 ug 8-hydroxyquinoline

Chemical Name and Structure
complex of 8-hydroxyquinoline and In-111 [redacted] (b) (4)

Comments
1. In-111 has a physical half-life of 2.81 days. It decays to Cd-111, a stable nuclide, by [redacted] (b) (4) and 171 KeV and 245 KeV gamma emissions.

2. [redacted] (b) (4) decays by [redacted] (b) (4), [redacted] (b) (4) involves [redacted] (b) (4) only, with a half-life of [redacted] (b) (4) hours, [redacted] (b) (4) involves [redacted] (b) (4). [redacted] (b) (4) decay to Cd-[redacted] (b) (4), a stable nuclide.

Conclusions and Recommendations
From the chemistry standpoint, supplement S-009 is approvable. The deficiency/comment at the end of this review should be communicated to the firm. However, a medical officer and/or pharmacologist/toxicologist should review the firm's claims with regard to the effect of small levels of [redacted] (b) (4) on the quality of the image and the radiation dose to the patient. CSO Lange was informed on 10April90 that a medical review would be needed.

Please note - sl rec'd review 4-26-90.

Reviewer E. Ruby 24 Apr 90
Eric Ruby, Chemist, HFD-160

Date Completed 16April90
revised 24 Apr 90

Orig. NDA 19-044/S-009
HFD-160/Div. File
HFD-160/ERuby
HFD-160/FStone
HFD-161/SLange
R/D Init. by: ESheinin/
F/T by: ERuby
C:\RUBYSUPP\19044S09.CR1

E B Sheinin
4-26-90

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-044 / S-009

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Food and Drug Administration
Rockville MD 20857

NDA 19-044/S-009

Amersham Corporation
2636 S. Clearbrook Drive
Arlington Heights, IL 60005

NOV - 2 1989

Attention: Frank J. Lyman
Manager, Medical Regulatory Affairs

Gentlemen:

We acknowledge receipt of your supplemental application(s) for the following:

Name of Drug: Indium (In-111) Oxyquinoline

NDA Number: 19-044

Supplement Number: S-009 Controls

Date of Supplement: October 26, 1989

Date of Receipt: October 30, 1989

File Date: January 2, 1990

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research, HFD-160
Attention: Document Control Room 18B-03
5600 Fishers Lane
Rockville, MD 20857

Sincerely Yours,

Regina D. Joyce

Regina D. Joyce
Acting Supervisory Consumer Safety Officer
Division of Medical Imaging,
Surgical and Dental Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001
Expiration Date; August 31,1989.

FOR FDA USE ONLY

DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	**NDA/ANDA NO. ASS.**

NOTE: No application may be filed unless a completed application form has been received *(21 C.F.R. Part 314).*

NAME OF APPLICANT
Amersham Corporation

DATE OF SUBMISSION
10/26/89

TELEPHONE NO. *(Include Area Code)*
(312) 593-6300

ADDRESS *(Number, Street, City, State and Zip Code)*
2636 S. Clearbrook Drive
Arlington Heights, IL 60005

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (If previously issued)
NDA 19-044

DRUG PRODUCT

ESTABLISHED NAME *(e.g., USP/USAN)*
Indium (^{111}IN) Oxyquinoline Solution

PROPRIETARY NAME *(If any)*

CODE NAME *(If any)*

CHEMICAL NAME

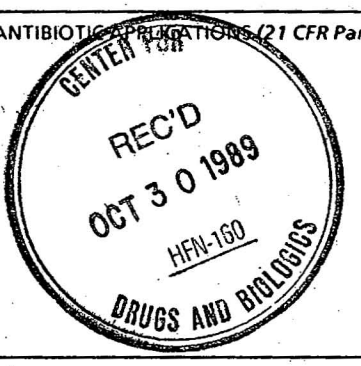
DOSAGE FORM	ROUTE OF ADMINISTRATION	STRENGTH(S)
1.0 ml (1.0mCi) single use vial	Intravenous Injection	1.0mCi

PROPOSED INDICATIONS FOR USE

Diagnostic - For intravenous use in radiolabeling autologous leukocytes

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, AND DRUG MASTER FILES *(21CFR 314.420)* REFERRED TO IN THIS APPLICATION:

NDA 19-044



INFORMATION ON APPLICATION

TYPE OF APPLICATION *(Check one)*

☒ THIS SUBMISSION IS A FULL APPLICATION *(21 CFR 314.50)* ☐ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21 CFR 314.55)

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION

STATUS OF APPLICATION *(Check one)*

☐ PRESUBMISSION
☐ ORIGINAL APPLICATION
☐ AN AMENDMENT TO A PENDING APPLICATION
☐ RESUBMISSION
☒ SUPPLEMENTAL APPLICATION

PROPOSED MARKETING STATUS *(Check one)*

☒ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT *(Rx)*
☐ APPLICATION FOR AN OVER - THE - COUNTER PRODUCT *(OTC)*

FORM FDA 356h (3/87)

CONTENTS OF APPLICATION	
This application contains the following items: *(Check all that apply)*	
1. Index	X
2. Summary (21 CFR 314.50 (c))	X
3. Chemistry, manufacturing, and control section (21 CFR 314.50 (d) (1))	X
4. a. Samples (21 CFR 314.50 (e) (1)) (Submit only upon FDA's request)	
b. Methods Validation Package (21 CFR 314.50 (e) (2) (i))	
c. Labeling (21 CFR 314.50 (e) (2) (ii))	
i. draft labeling *(4 copies)*	
ii. final printed labeling (12 copies)	
5. Nonclinical pharmacology and toxicology section (21 CFR 314.50 (d) (2))	
6. Human pharmacokinetics and bioavailability section (21 CFR 314.50 (d) (3))	
7. Microbiology section (21 CFR 314.50 (d) (4))	
8. Clinical data section (21 CFR 314.50 (d) (5))	
9. Safety update report (21 CFR 314.50 (d) (5) (vi) (b))	
10. Statistical section (21 CFR 314.50 (d) (6))	
11. Case report tabulations (21 CFR 314.50 (f) (1))	
12. Case reports forms (21 CFR 314.50 (f) (1))	
13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))	
14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))	
15. OTHER *(Specify)*	

I agree to update this application with new safety information about the drug that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit these safety update reports as follows: (1) 4 months after the initial submission, (2) following receipt of an approvable letter and (3) at other times as requested by FDA. If this application is approved, I agree to comply with all laws and regulations that apply to approved applications, including the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211.
2. Labeling regulations in 21 CFR 201.
3. In the case of a prescription drug product, prescription drug advertising regulations in 21 CFR 202.
4. Regulations on making changes in application in 21 CFR 314.70, 314.71, and 314.72.
5. Regulations on reports in 21 CFR 314.80 and 314.81.
6. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the controlled substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

NAME OF RESPONSIBLE OFFICIAL OR AGENT	SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	DATE
Frank J. Lyman	Frank J. Lyman	10/26/89

ADDRESS *(Street, City, State, Zip Code)*	TELEPHONE NO. *(Include Area Code)*
2636 S. Clearbrook Drive Arlington Heights, IL 60005	(312) 593-6300

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

☆ U.S GOVERNMENT PRINTING OFFICE:1987-181-338/55255

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-044/S-009

AUG 27 DISTRIBUTION
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Amersham Corporation
2636 South Clearbrook Drive
Arlington Heights, Illinois 60005-4692

Attention: John H. Waterman
Manager, Scientific and Regulatory Affairs

Dear Mr. Waterman:

Reference is made to your supplemental new drug application dated October 26, 1989 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for indium In 111 oxyquinoline.

The supplemental new drug application provides for changes in the production schedule timetable which include the times between the [redacted] (b) (4) and the addition of a specification for [redacted] (b) (4) as a radionuclidic impurity.

We have completed our review of this supplemental new drug application and it is approved effective on the date of this letter. However, we do have the following comments/questions.

[redacted] (b) (4)

We remind you that you must comply with the requirements set forth under 21 CFR 314.80 and 314.81 for an approved NDA.

Sincerely yours,

John F. Palmer

John F. Palmer, M.D.
Director
Division of Medical Imaging,
Surgical and Dental Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

11 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

Not For Publication

February 1987 PTN 87/2

AMERSHAM INTERNATIONAL plc

CORPORATE SAFETY TECHNICAL NOTE 87/2

The Dosimetric Effect of [redacted] (b) (4) When Present as an Impurity in Indium-111

R G Soundy

SUMMARY

The decay schemes of [redacted] (b) (4) and indium-111 are compared and applied to simple calculations to deduce the dosimetric effect of [redacted] (b) (4) when present as an impurity in indium-111.

CONTENTS

5 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

RECORD OF TELEPHONE CONVERSATION/MEETING

Date: 13April90 **NDA #:** 19-044/S-009

Initiated by: Eric Ruby **Product:** In-111 Oxyquinoline

With: Frank Lyman, Amersham Corp. **Firm:** Amersham Corp.,
Manager, Medical Regulatory Affairs Arlington Heights, IL
Telephone #: (708) 593-6300 ext. 378

I called Mr. Lyman to clarify something that Barry Laidler of Amersham U.K. had said in our 11April90 telecon. Mr. Laidler said that at (b) (4)

(b) (4)

My question was whether it would be possible for a local customer to receive a vial of the product on the same day that it arrives from the U.K. (b) (4)

.

In answer to this question Mr. Lyman gave the following description (b) (4)

. See memo of 11April telecon with Barry Laidler for additional information and comments.

E. Ruby 13April90
Eric Ruby Chemist HFD-160

C:\RUBY.02\19044S09.TC3

CC
~~HFD~~ orig 19-044/S-009
HFD-160/D.V. File

G.B. Sheiman
4-23-90

RECORD OF TELEPHONE CONVERSATION/MEETING

Date: 11April90

NDA #: 19-044/S-009

With: J. Barry Laidler
Regulatory Affairs Executive

Product: In-111 Oxyquinoline

Initiated by: Dr. Laidler

Firm: Amersham
(United Kingdom)

Telephone #: 011-44-494-543611

I had called Frank Lyman of Amersham Corporation in Arlington Heights, IL on 06April90 to discuss NDA 19-044/S-009 (see telecon memo). The point of the call was to find out how the term "time of measurement" is related to "(b) (4) and/or "(b) (4) as these terms are used in the supplement.

Mr. Laidler of Amersham U.K. called to discuss the issue. He said that the "time of measurement" of radionuclidic purity is approximately (b) (4)

(b) (4)

Mr. Laidler also stated that (b) (4)

I checked the latter point with Frank Lyman of Amersham Arlington Heights (Amersham A.H.) and he said that, in fact, (b) (4)

(b) (4)

This is an important point when (b) (4)

In any case Mr. Laidler felt that even levels of (b) (4) were medically insignificant in terms of additional radiation dose to the patient ((b) (4) more radiation dose than the patient would be getting due to the In-111) or affects on image quality. However, it is up to the medical officer to judge those issues.

E. Ruby 13 April 90
Eric Ruby Chemist HFD-160

C:RUBY.02\19044S09.TC2

CBS Review 4-23-90

CC
Orig 19-044/S-009
HFD-160 / Div. File
HFD-160/Ruby