CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 020478/S-011

Trade Name: Ultane

Generic Name: Sevoflurane

Sponsor: Abbott Laboratories

Approval Date: 05/24/2002

Indication: Sevoflurane is indicated for induction and maintenance of general anesthesia in adult and pediatric patients for inpatient and outpatient surgery.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 020478/S-011

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 020478/S-011

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-478/S-011

Abbott Laboratories
D-289, Bldg. AP30
200 Abbott Park Road
Abbott Park, Illinois 60064-6157

Attention: Surendera Tyagi, PhD
Manager Regulatory Affairs

Dear Dr. Tyagi:

Please refer to your supplemental new drug application dated August 31, 2001, received September 4, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ultane® (sevoflurane).

We also acknowledge receipt of your January 24, 2002, submission, which constituted a complete response to our January 4, 2002, action letter.

This supplemental new drug application provides for a new manufacturing plant in Ube City, Japan for manufacturing the bulk drug substance.

We have completed the review of this supplemental application, and it is approved, effective on the date of this letter.

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

If you have any questions, call Lisa Basham-Cruz, Regulatory Project Manager, at (301) 872-7441.

Sincerely,

{See appended electronic signature page}

Dale Koble, Ph.D.
Chemistry Team Leader for the
Division of Anesthetic, Critical Care, and
Addiction Drug Products, (HFD-170)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Ravi Harapanhalli
5/24/02 01:06:15 PM
"For Dale Koble"

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 020478/S-011

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-478/S-011

Abbott Laboratories
D-389, Bldg. AP30
200 Abbott Park, Illinois 60064-6157

Attention: Surendera K. Tyagi
Manager, Regulatory Affairs

Please refer to your supplemental new drug application dated August 31, 2001, received September 4, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ultane (sevoflurane).

This supplement proposes to add a new manufacturing plant in Ube City, Japan for manufacturing the sevoflurane bulk dug substance.

We have completed the review of this application, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

1. Submit revised drug substance acceptance specifications to be consistent with the revisions in the release specifications submitted July 10, 1999, to DMF (b) (4).

2. Provide comparative stability data of the drug product made from the drug substance from (b) (4)

3. We withhold comments on the proposed expiration dating period of Ultane at this time. Submit updated stability data, including statistical analysis.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of this supplemental application.

If you have any questions, call Sara E. Shepherd, Regulatory Project Manager, at (301) 827-7430.

Sincerely,

{See appended electronic signature page}

Dale Koble, Ph.D.
Chemistry Team Leader for the
Division of Anesthetic, Critical Care,
and Addiction Drug Products
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Dale Koble

1/4/02 03:05:33 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 020478/S-011

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW	1.ORGANIZATION DACCADP, HFD-170	2. NDA Number(s) 20-478
3. Name and Address of Applicant (City & State): Abbott Laboratories D-389, Bldg. AP30 200 Abbott Park Road Abbott park, Illinois 60064-6157		4. AF No. 5. Supplement(s) Number(s) Date(s) SCM-011 31/08/01
6. Drug Name: Ultane®	7. Nonproprietary Name: Sevoflurane	8. Amendments & Other (reports, etc) – Dates Amendment 01/24/02
9. Supplement Provides For: Addition of a new manufacturing plant in Ube City, Japan for manufacturing the sevoflurane bulk drug substance.		
10. Pharmacological Category: Anesthetic	11. How Dispensed: ☒ Rx ☐ OTC	12. Related IND(s)/ NDA(s)/DMF(s) DMF (b) (4)
13. Dosage Form(s): Volatile Liquid	14. Potency(ies): 250 ml bottle	
15. Chemical Name and Structure: 1,1,1,3,3,3-Hexafluoro-2- (fluoromethoxy) propane; Fluoromethyl 2,2,2-trifluoro-1-(trifluoromethyl) ethyl ether. $C_4H_3F_7O$		16. Records/Reports Current: ☒ Yes ☐ No Reviewed: ☒ Yes ☐ No

17. Comments: In this amendment to the prior-approval supplement, the applicant responded to the CMC deficiencies and comments listed in Agency letter dated January 04, 2002.

18. Conclusions and Recommendations: Referenced DMF (b) (4) was found adequate to support this supplement. The Abbott and (b) (4) were deemed Acceptable from the standpoint of cGMPs by the Office of Compliance in their recommendation dated 12/31/01. The applicant has provide updated Drug substance acceptance specifications in light of the revisions made in the DMF dated July 10, 1999. Applicant has also provide updated stability data of the drug product packaged in glass and (b) (4) bottles and a comparison of the stability data of the product made from the drug substance from (b) (4), and statistical analysis, which shows the equivalency of product quality. Reviewer analysis of the stability data from (b) (4) shows that the product would meet the expiration dating of 24-months. All CMC deficiencies have been addressed adequately and therefore the supplement is recommended for "approval" with the same expiration dating of 24-months as approved earlier.

CC: Original NDA# 20-478
HFD-170/Division File
HFD-170/Chemist/Harapanhalli
HFD-170/CSO/Basham
R/D initialed by : Dkoble

19. REVIEWER

Name	Signature	Date Completed
Ravi S. Harapanhalli, Ph.D.		May 22, 2002

Introduction:
Ultane® is an inhalation anesthetic that contains Sevoflurane (Fluoromethyl 2,2,2-trifluoro-1- (trifluoromethyl) ethyl ether). [redacted] Accordingly, the firm has amended their DMF [redacted]. Since the change in manufacturing facility affected this NDA, the applicant Abbott submitted a prior-approval supplement providing for the same change. The applicant stated that the new plant is the duplicate copy of the current plant and that the current approved manufacturing process is incorporated at the new facility. They also stated that the manufacturing process and specifications and other controls remained the same as approved.
The responses from the applicant to the letter of deficiencies dated January 04, 2002 are evaluated here.

FDA Question 1:

Submit revised drug substance acceptance specifications to be consistent with the revisions in the release specifications submitted July 10, 1999 to DMF [redacted].

Response:

Assay and volatile analog specifications for bulk sevoflurane have been revised to be consistent with the current release specifications in DMF [redacted]. A copy of the revised specifications (Document 14.74341) is provided in Exhibit 1. Specifications for the drug product were also revised [redacted]. S copy of the revised specifications for the drug product and marketed product stability protocol (Document 45.4456) is provided in Exhibit II. [redacted]

Evaluation: Adequate

[redacted]

[redacted]

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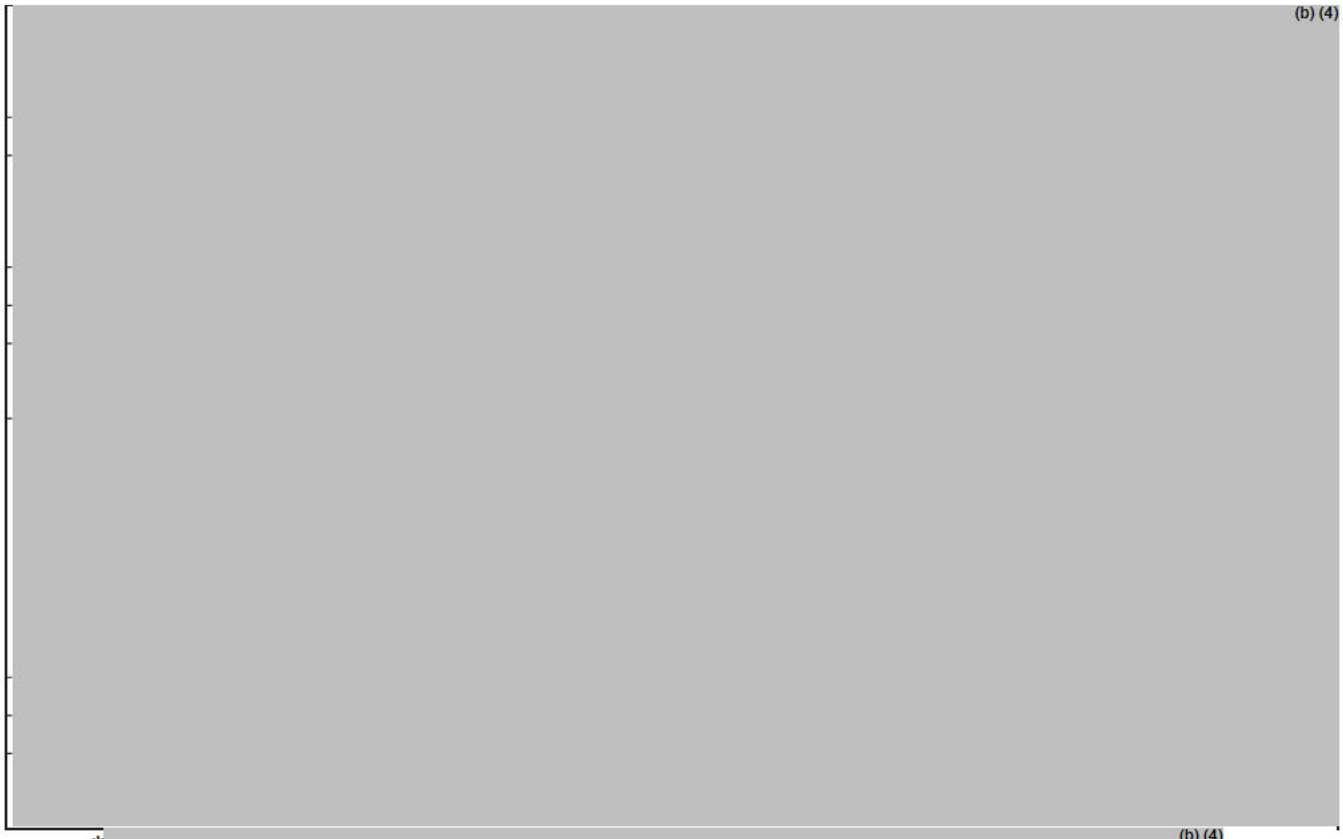

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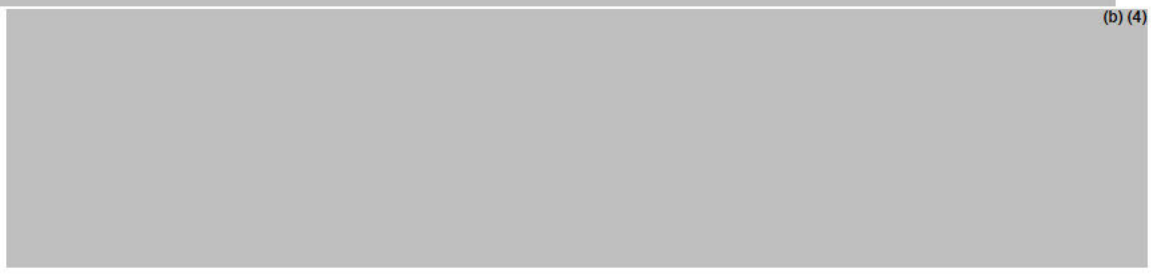

FDA Question 2:

Provide comparative stability data of the drug product (b) (4)

(b) (4).

Response:

Stability report (b) (4) has been updated to include the stability data for three lots of drug product (b) (4). A copy of the revised stability report is provided in Exhibit IV.

Evaluation: Adequate

(b) (4)

The above data is comparable to the data provided below for the drug product made from drug substance batches made at the new facility (b) (4). Since there are no stability-related trends in the data from the product made from (b) (4), statistical comparison of the data is not needed. The product made from (b) (4) and (b) (4) appears to be equivalent.

FDA Question 3:

We withhold comments on the proposed expiration-dating period of Ultane at this time. Submit updated stability data, including statistical analysis.

Response:

Updated stability data through 12 months is provided in Exhibit IV. Statistical analysis of the stability data is provided in Exhibit V. An expiration dating of 24-months is supported since there were no differences in the stability profile of the drug products (b) (4)

Container closure system for the drug product:

(b) (4)

(b) (4)

(b) (4)

Evaluation: In the original supplement, 6-months accelerated storage data was provided. (b) (4)

Long-term storage: 12-months data is provided in the amendment.

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(b) (4)

Shelf life:
NDA-approved shelf life is 24-months, and applicant requests the same shelf life for the product made at (b) (4). Applicant has provided 24-months real time data at long term and intermediate storage for three batches of the product made at the old facility (b) (4) They have also provided 12-months long-term and intermediate storage data and 6-months of accelerated data for three batches of the product made at (b) (4). Each batch was stored upright and inverted for the stability studies. For the (b) (4) batches, data was collected at 0, 3, 6, 9, 12, 18, and 24 months in upright position and at 0, 3, 6, 12, and 24 months at inverted position. For the (b) (4) batches data was collected at 0, 3, 9, and 12 months in inverted position and at 0, 6, and 12 months in upright position. The data from (b) (4) are comparable and there are no stability-related trends except for the increase in water content in (b) (4) bottles, which is not considered significant.

(b) (4)

(b) (4)

(b) (4)

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(b) (4)

Evaluation:
The specification is (b) (4) and the data is well within this limit. However, exclusion of some data as being out-of-trend is of some concern, although applicant reasons that this was done because the cause was instrument-related. The above data indicates clear significant difference between the pooled slopes for (b) (4) and (b) (4). However, the slopes appear to be nearly parallel and the data for (b) (4) appears to be consistently higher than for (b) (4). The following regression analysis was performed by the statistician Dr. Cynthia Liu (b) (4) (b) (4). As can be seen from the analysis, even with 12 months data, the 95% CI intercept the specifications well beyond the 24-months expiration dating period. Therefore, in the opinion of this reviewer, the product made at (b) (4) is chemically equivalent to the one made at (b) (4) and would meet the 24-months expiration dating.

(b) (4)

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/s/

Ravi Harapanhalli
5/22/02 06:16:13 PM
CHEMIST
Recommended for "Approval"

Dale Koble
5/23/02 02:25:03 PM
CHEMIST

CHEMIST'S REVIEW	1.ORGANIZATION DACCADP, HFD-170	2. NDA Number(s) 20-478
3. Name and Address of Applicant (City & State): Abbott Laboratories D-389, Bldg. AP30 200 Abbott Park Road Abbott park, Illinois 60064-6157		4. AF No. 5. Supplement(s) Number(s) Date(s) SCM-011 31/08/01
6. Drug Name: Ultane®	7. Nonproprietary Name: Sevoflurane	8. Amendments & Other (reports, etc) - Dates
9. Supplement Provides For:		
10. Pharmacological Category: Anesthetic	11. How Dispensed: ☒ Rx ☐ OTC	12. Related IND(s)/ NDA(s)/DMF(s)
13. Dosage Form(s): Volatile Liquid	14. Potency(ies): 250 ml bottle	
15. Chemical Name and Structure: 1,1,1,3,3,3-Hexafluoro-2- (fluoromethoxy) propane; Fluoromethyl 2,2,2-trifluoro-1-(trifluoromethyl) ethyl ether. $C_4H_3F_7O$		16. Records/Reports Current: ☒ Yes ☐ No Reviewed: ☒ Yes ☐ No

17. Comments: This is a prior-approval supplement. Applicant has provided data comparing the quality of the DS produced at the old and the new manufacturing plant located within the existing facility. For the DP, they have also provided blank and executed work order, COA for the exhibit batches, and six-months stability data.

18. Conclusions and Recommendations: Referenced DMF (b) (4) was found adequate to support this supplement. The Abbott and (b) (4) were deemed Acceptable from the standpoint of cGMPs by the Office of Compliance in their recommendation dated 12/31/01. The applicant should provide updated Drug substance acceptance specifications in light of the revisions made in the DMF dated July 10, 1999. Applicant should also provide updated stability data of the drug product packaged in glass and (b) (4) bottles and a comparison of the stability data of the product made from the drug substance from (b) (4). The supplement is "Approvable" pending satisfactory responses to the comments listed at the end of the review.

CC: Original NDA# 20-478
HFD-170/Division File
HFD-170/Chemist/Harapanhalli
HFD-170/CSO/Basham
R/D initialed by : Dkoble

19. REVIEWER		
Name Ravi S. Harapanhalli, Ph.D.	Signature	Date Completed December 31, 2001 Revised 01/03/02

1. Introduction:

Ultane® is an inhalation anesthetic that contains Sevoflurane (Fluoromethyl 2,2,2-trifluoro-1- (trifluoromethyl) ethyl ether). [redacted] ccordingly, the firm has amended their DMF [redacted]. Since the change in manufacturing facility affected this NDA, the applicant Abbott submitted this prior-approval supplement providing for the same change. The applicant states that the new plant is the duplicate copy of the current plant and that the current approved manufacturing process is incorporated at the new facility. They also state that the manufacturing process and specifications and other controls remained the same as approved.

2. Background:

[redacted]

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CMC Deficiencies and comments to NDA 20478/SCM-011

1. Submit revised drug substance acceptance specifications to be consistent with the revisions in the release specifications submitted July 10, 1999 to DMF (b) (4).

2. Provide comparative stability data of the drug product (b) (4) (b) (4).

3. We withhold comments on the expiration dating period of Ultane at this time. Please submit updated stability data, including statistical analysis.

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/s/

Ravi Harapanhalli
1/4/02 11:25:06 AM
CHEMIST
Please sign off. The supplement is "Approvable".

Dale Koble
1/4/02 11:28:23 AM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 020478/S-011

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-478/S-011

PRIOR APPROVAL SUPPLEMENT

Abbott Laboratories
200 Abbott Park., Rd D-37K, AP30
Abbott Park, IL 60054-6157

Attention: Surendera K. Tyagi,
Manager HPD Regulatory Affairs

Dear Ms. Tyagi:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Ultane (sevoflurane, USP)

NDA Number: 20-478

Supplement number: S-011

Date of supplement: August 31, 2001

Date of receipt: September 4, 2001

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on November 3, 2001, in accordance with 21 CFR 314.101(a).

All communications concerning this supplement should be addressed as follows:

Center for Drug Evaluation and Research
Division of Anesthetic Critical Care And
Addiction Drug Products, HFD-170
Attention: Division Document Room, 9B23
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-7420.

Sincerely yours,

{see appended electronic signature page}

Lisa E. Basham
Regulatory Project Manager
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Lisa Basham

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