CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 020478/S-029

Trade Name: Ultane

Generic Name: Sevoflurane

Sponsor: AbbVie Inc.

Approval Date: 10/26/2015

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

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APPLICATION NUMBER:

NDA 020478/S-029

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APPLICATION NUMBER:

NDA 020478/S-029

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 020478/S-029

APPROVAL LETTER

AbbVie Inc.
Attention: Robert Baker
Senior Manager, Regulatory Affairs
1 N. Waukegan Road
Dept. PA77/Bldg. AP30
North Chicago, IL 60064

Dear Mr. Baker:

Please refer to your Supplemental New Drug Application (sNDA) dated and received June 25, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Ultane® (sevoflurane) Liquid.

We acknowledge receipt of your amendments dated October 7 and October 14, 2015.

This "Prior Approval" supplemental new drug application provides for the addition of AbbVie's facility located in Campoverde, Italy as an alternate filling and packaging site for the (b) (4)

We have completed our review of this supplemental new drug application, as amended. This supplement is approved.

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, please call Hongly La, Regulatory Business Process Manager, at 240-402-8681.

Sincerely,

Ramesh Raghavachari, Ph.D.
Chief, Branch I
Division of Post Marketing Activities I
Office of Lifecycle Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 020478/S-029

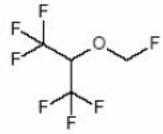
CHEMISTRY REVIEW(S)

CHEMIST REVIEW
OF **SUPPLEMENT**

1. ORGANIZATION:	OPQ-Office of Lifecycle Drug Product (OLDP)
2. NDA Number:	**20478**
3. SUPPLEMENT NUMBERS/DATES:	**S029 (PAS)**
Letter date:	**June 25, 2015**
Stamp date:	**June 25, 2015**
4. AMENDMENTS/REPORTS/DATES:	**Amendment (SDN540)**
Letter date:	**October 7, 2015**
Stamp date:	**October 7, 2015**
5. RECEIVED BY CHEMIST:	**July 30, 2015**

6. APPLICANT NAME & ADDRESS: AbbVie Inc.
1 N. Waukegan Road
Dept. PA77/Bldg. AP30
North Chicago, IL 60064

7. NAME OF DRUG: Ultane®
8. NONPROPRIETARY NAME: sevoflurane
9. CHEMICAL NAME/STRUCTURE: Fluromethyl 2,2,2-trifluoro-1(trifluoromethyl)ethyl ether
$C_4H_3F_7O$; Mol. Wt.: 200.05; [*28523-86-6*]



10. DOSAGE FORM(S): Volatile liquid for inhalation (containing no additives)
11. POTENCY: 250mL (contains 100% of the active substance sevoflurane)
12. PHARMACOLOGICAL CATEGORY: Sevoflurane is an inhalational anesthetic agent for use in induction of general anesthesia in adult and pediatric patients for inpatient and outpatient surgery.

13. HOW DISPENSED:	X	(R_X)		(OTC)
14. RECORDS & REPORTS CURRENT:	X	Yes		No
REVIEW RECORDS & REPORTS CURRENT	X	Yes		No

15. RELATED IND/NDA/DMF: **none**

16. SUPPLEMENT PROVIDES FOR: Addition of AbbVie's facility in Campoverde, Italy as an alternate filling and packaging site for the Ultane (Sevoflurane) Liquid with [redacted] (b) (4) drug product presentation.

17. COMMENTS: AbbVie Inc. (AbbVie) NDA 20478 for Ultane (Sevoflurane) Liquid (Ultane) was approved September 19, 1996. AbbVie has submitted a Prior Approval Supplement (PAS) in order to add an alternate Ultane filling and packaging site. The alternate site will be responsible for filling and packaging of Ultane (Sevoflurane) Liquid with [redacted] (b) (4) The FDA will review AbbVie's proposed change as PAS 20478/S029. The Initial Quality Assessment (IQA) is provided in Panorama.

Background and Introduction:
Ultane with [redacted] (b) (4) was submitted previously as [redacted] (b) (4)
However, the [redacted] (b) (4) presentation was not commercially launched. AbbVie now plans to introduce Ultane with [redacted] (b) (4) into the US market. AbbVie will manufacture this product at their facility in Campoverde, Italy (FEI: 3002806277).

The Campoverde site will be responsible for filling, packaging and release testing of the drug product. [redacted] (b) (4) As is the case with

the current packaging site (AbbVie Inc. North Chicago, IL (FEI: 1411365)) no drug product processing or formulating will be carried out at Campoverde.

AbbVie states in the cover letter that the Campoverde manufacturing process (i.e., solution fill) will use equipment of the same operating principles as currently approved, with no drug product processing or formulation, i.e., no excipients are used to manufacture Ultane. In addition, AbbVie states that the Campoverde manufacturing process, the drug product specifications, and the drug product analytical test methods at the new site are the same as currently approved in the NDA.

3.2.P.1 Description and Composition of Sevoflurane, 250mL

Ultane is packaged in (b) (4)) plastic bottles containing 250mL sevoflurane (NDC # 0074-4456-04). Ultane with (b) (4) will use the same 250mL plastic bottle. Section **3.2.P.1** has been updated to include the (b) (4) along with Ultane composition and currently approved Ultane container closure systems.

Evaluation: **Adequate**

The only difference between the approved Ultane drug product and Ultane with (b) (4) is the use of the (b) (4). The (b) (4) is described below in Section **3.2.P.7 Container Closure System for Sevoflurane, 250mL**.

3.2.P.3.1 Manufacturer(s) of Sevoflurane, 250mL

The facilities involved in the manufacture of Ultane are listed below:

Ultane Manufacturing, Packaging & Testing Sites

Site	Establishment Registration Number	Function(s)
AbbVie Inc. 1 N Waukegan Rd North Chicago, IL 60064 USA	3009751352	Manufacturing Packaging
AbbVie Inc. 1401 Sheridan Road North Chicago, IL 60064 USA	1411365	Analytical testing for Release Analytical testing for Stability
(b) (4)		Manufacturing Packaging Analytical testing for Release Analytical testing for Stability
AbbVie S.r.l. SR. 148 Pontina Km 52 SNC 04011 Campoverde di Aprilia (LT) Italy	3002806277	Manufacturing Packaging Analytical testing for Release
(b) (4)		

On July 4, 2015, the AbbVie Campoverde, Italy (FEI: 3002806277) site was submitted for inspection/evaluation under facility specific criteria LIQ Non-Sterile Liquid (other than Suspension & Emulsions). On October 23, 2015, Office of Process and Facilities (OPF) Division of Inspectional Assessment issued an Approve Overall Application Recommendation with respect to the Campoverde, Italy (FEI: 3002806277) facility. The Panorama Overall Manufacturing Inspection Recommendation for 20478/S029 is provided in Attachment 1 of this review.

Evaluation: **Adequate**

3.2.P.3.5 Process Validation and/or Evaluation for Sevoflurane

In order to validate the Ultane with (b) (4) Campoverde manufacturing process, three validation lots of the drug product were filled and tested per the validation scheme provided in **3.2.P.3.5** and Attachment 2 of this review. The three validation lots are listed below:

Ultane with (b) (4) Validation Lots

Drug Product Lot Number	Drug Product Mfg. Site	Date of Manufacturing
28442TF	Campoverde, Italy	February 2013
29494TF	Campoverde, Italy	February 2013
29473TF	Campoverde, Italy	February 2013

The samples for testing were taken from the filled product and tested per the Ultane specification provided in **3.2.P.5.1 Specifications for Sevoflurane, 250mL**.

The validation results are provided in **3.2.P.3.5**. These results confirm the three validation lots were within specification and results comparable to each other and showed no trends in the data during the manufacturing process. Based on the validation results the Campoverde filling process has been successfully validated.

Evaluation: **Adequate**

AbbVie has not included functionality testing of Ultane with (b) (4) manufactured at Campoverde. Since the Ultane with (b) (4) is an approved product (20478/S001), and the Campoverde site has been approved for the manufacture of Ultane with (b) (4) the validation data presented in 20478/S029 is sufficient and adequate validation of the manufacturing process.

3.2.P.3.4 Batch Analysis for Sevoflurane

Batch analysis data for commercial scale batches of the current drug product manufactured at AbbVie's North Chicago, IL facility and Ultane with (b) (4) manufactured at Campoverde are provided. The descriptions of these batches are listed below:

Ultane (North Chicago) and Ultane with (b) (4) (Campoverde)

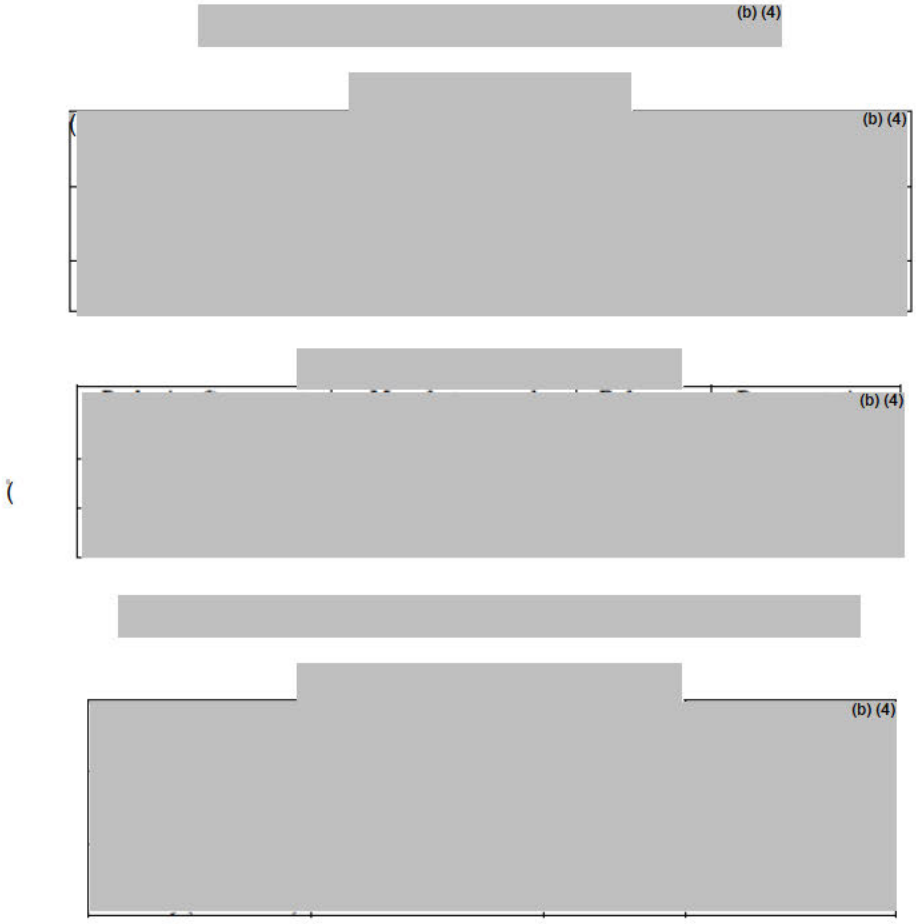
Batch Number	(b) (4)	Site of manufacture (filling)	Date of Manufacture
1010511	(b) (4)	AbbVie, US	July 11, 2013
1012354		AbbVie, US	September 25, 2013
1020782		AbbVie, US	December 6, 2013
30613TF		AbbVie S.r.l., Italy	November, 2012
30639TF		AbbVie S.r.l., Italy	November, 2012
30654TF		AbbVie S.r.l., Italy	November, 2012

The batch analysis data shows that Campoverde manufactured drug product is of comparable quality compared to the current approved drug product (see Attachment 3 of this review).

Evaluation: Adequate

3.2.P.7 Container Closure System for Sevoflurane, 250mL

The description of the primary packaging components for the current approved Ultane drug product container closure system and Ultane with (b) (4) is shown below:



The specification documents for the Ultane with (b) (4) (i.e., CMS.R.60A020.US and CMS.R.963008.US, listed above) are included in 20478/S029 and Attachment 4 of this review.

On Monday, September 28, 2015, the following Information Request was sent to AbbVie. :

> *Confirm that the information/description provided in the revised 3.2.P.7 section for Quik-Fil is the same as that for the Ultane (Sevoflurane) Liquid with (b) (4) approved in 20478/S001. If the (b) (4) you are proposing to use at Campoverde is different from that approved in S001 provide necessary updated information (i.e., shape, dimensions, material of construction, etc.) as well as safety information (CFR citations) which establishes that the new materials are safe to use in packaging Ultane (Sevoflurane) Liquid.*

On October 7, 2015, AbbVie amended (**SDN540**) 20478/S029 with their response to the September 28, 2015 Information Request. In the cover letter to the October 7, 2015 amendment, Mr. Robert Baker, Senior Manager, Regulatory Affairs-US & Canada, AbbVie stated the following:

> *AbbVie confirms that the information/description provided in the revised 3.2.P.7 section is the same as originally approved in NDA 20-478, S001.*

The FDA's Information Request and AbbVie's amendment are available in Panorama.

Evaluation: Adequate

3.2.P.8.1 Stability Summary and Conclusions for Sevoflurane

The stability lots of Ultane with [redacted] (b) (4) (Campoverde) are described below:

Stability Lots of Ultane with [redacted] (b) (4) (Campoverde)

Study Number:	GCVS20130051	GCVS20130052	GCVS20130053
Drug Product Lot #:	30613TF	30639TF	30654TF
Use of Lot	Registration	Registration	Registration
Batch Size:	500 Liter	500 Liter	500 Liter
Storage Conditions:	25°C/60% RH and 40°C/75% RH	25°C/60% RH and 40°C/75% RH	25°C/60% RH and 40°C/75% RH
Container	[redacted] (b) (4)		
Container Fill	250 mL	250 mL	250 mL
Closure	[redacted] (b) (4)		
Manufacturing Site:	AbbVie S.r.l. Campoverde, Italy	AbbVie S.r.l. Campoverde, Italy	AbbVie S.r.l. Campoverde, Italy
Filling Date:	June, 2013	June, 2013	June, 2013
Drug Substance Manufacturer /Mfg. Site:	[redacted] (b) (4)		
Length of Study:	36 months (long term) 6 months (accelerated)	36 months (long term) 6 months (accelerated)	36 months (long term) 6 months (accelerated)
Study Start Date	July, 2013	July, 2013	July, 2013

These stability lots were placed on ICH long term and accelerated storage, and stability tested according to the following stability testing protocol:

Stability Testing Protocol Ultane with [redacted] (b) (4) (Campoverde)

		Sevoflurane Assay, Physical Appearance, Refractive Index	Compound A, Compound B, Other Single Largest Impurity, Total Impurities (excluding Compound A and B)	Acidity/ Alkalinity, Water, Fluoride	Non Volatile Residue, Fill Volume*
	Initial	X	X	X	X
25°C 60% RH	3 months	X	X	X	X
	6 months	X	X	X	X
	9 months	X	X	X	X
	12 months	X	X	X	X
	18 months	X	X	X	X
	24months	X	X	X	X
	36 months	X	X	X	X
40°C 75% RH	3 months	X	X	X	X
	6 months	X	X	X	X

*Fill volume test was added starting at 12 months and only conducted at 25°C/60% RH.

The stability data for up to 18 months of long term and six months accelerated (complete) showed no significant changes or trends in the test results on stability samples packaged in the [redacted] (b) (4). These stability results supports the current approved 36 month shelf life for Ultane packaged with the [redacted] (b) (4) and stored at the approved storage condition, namely "Store at controlled room temperature, 15°-30°C (59°-86°F). See USP."

Evaluation: Adequate

1.14.1.1 Carton & Container Labeling

AbbVie has not included in 20478/S029 copies of the proposed carton and container labeling for the Ultane with [redacted] (b) (4) drug product presentation. However, the identical drug product was

previously approved (20478/S001, approved July 2, 1997), Thus the Ultane (b) (4), labeling, including the PI, has already been reviewed and found acceptable.

Evaluation: Adequate
The applicant will not be asked to provide labeling for the (b) (4) since Ultane (b) (4) drug product has already been approved.

Overall Evaluation: Adequate
The proposed Ultane with (b) (4) was previously approved in 20478/S001 (July 2, 1997). AbbVie has stated, in the October 7, 2015 20478/S029 amendment (**SDN540**), that the Ultane (b) (4) closure approved in S001 is identical to the Ultane (b) (4) described in the current supplemental application. The latter will be manufacture at AbbVie's Campoverde manufacturing facility. AbbVie has provided adequate data to support the conclusion the Campoverde facility is capable of reproducibly manufacturing Ultane with (b) (4) drug product that is of comparable quality to the current approved drug product. The Office of Process and Facilities (OPF) Division of Inspectional Assessment has issued an Approve Overall Application Recommendation with respect to the Campoverde, Italy (FEI: 3002806277) facility for the manufacture of Ultane with (b) (4) drug product.

18. CONCLUSIONS & RECOMMENDATIONS: Recommend issuing approval letter.

19. REVIEWER NAME	SIGNATURE	DATE COMPLETED
Lorenzo A. Rocca	Signed Electronically	

20. BRANCH CHIEF NAME	SIGNATURE	DATE COMPLETED
Ramesh Raghavachari	Signed Electronically	

cc:
OLDP/RRaghavachari
OLDP/LRocca
PM/OPQ/HLa

F/T by: LRocca, File: C:Data\LR\Supplement\n20478pm\S029(PAS)\20478_S-029Review1.doc

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/s/

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 020478/S-029

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 09/28/2015 11:21:49 AM
To: robert.j.baker@abbvie.com
CC: hongly.la@fda.hhs.gov
BCC:
Subject: INFORMATION REQUEST NDA 020478

NDA 020478/S-029
Prior Approval Supplement

Dear Mr. Baker,

We have the following Information Request concerning sNDA 020478/S-029 dated June 25, 2015. We request a prompt response to this IR request no later than Friday October 2, 2015.

(b) (4)

[redacted]

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Please confirm receipt of this Information Request to hongly.la@fda.hhs.gov. Also, please provide me with a courtesy copy via e-mail when you submit your official amendment. Note: Official amendment needs to be submitted by due date in order to be included in the review cycle. If you have any questions or comments, please contact me.

Best regards,
Hongly La, Pharm.D, MBA
Regulatory Business Process Manager
Office of Program and Regulatory Operations

FDA/CDER/OPQ
240-402-8681 (office)
hongly.la@fda.hhs.gov

From:	Dong, Zedong
To:	La, Hongly; Knight, Yvonne
Cc:	Rocca, Lorenzo A; Dong, Zedong
Subject:	NDA 20478/S029 IQA
Date:	Wednesday, July 29, 2015 10:58:04 PM

Hi Ly and Lorenzo,

The supplement provides for the addition of AbbVie's facility located in Campoverde, Italy as an alternate filling and packaging site for the (b) (4). A brief validation report is provided, together batch analysis (three batches) and stability data (18 months under long term and 6 months under accelerated conditions for three batches).

The facility info for the new site (Abbvie SRL, S.R. 148 Pontina Km 52 Snc, Campoverde di Aprilia, Italy 04011, FEI 3002806277) needs to be entered into Panorama.

Thanks,

Zedong