CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

020118Orig1s008

Trade Name: **SUPRANE**

Generic Name: Desflurane

Sponsor: Baxter Pharmaceutical Products, Inc.

Approval Date: 8/8/02

Indications: SUPRANE (desflurane, USP) is indicated as an inhalation agent for induction and/or maintenance of anesthesia for inpatient and out patient surgery in adults

SUPRANE (desflurane, USP) is not recommended for induction of anesthesia in pediatric patients because of a high incidence of moderate to severe upper airway adverse events (see WARNINGS). After induction of anesthesia with agents other than SUPRANE, and tracheal intubation, SUPRANE is indicated for maintenance of anesthesia in infants and children.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-118/S-008

Baxter Pharmaceutical Products, Inc.
95 Spring Street
Providence, NJ 07974

Attention: Priya Jambhekar
Director, Regulatory Affairs

Dear Ms. Jambhekar:

Please refer to your supplemental new drug application dated April 5, 2002, received April 8, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Suprane (desflurane).

This supplemental new drug application provides for a change in the O-ring of the closure system from [redacted] (b) (4)

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

The referenced DMF [redacted] (b) (4) was not updated with the information on the new O-rings. A letter was sent to the DMF holder on August 7, 2002, asking them to update the DMF.

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) 827-7420.

Sincerely,

{See appended electronic signature page}

Dale Koble, Ph.D.
Acting 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/

Ravi Harapanhalli
8/8/02 12:52:08 PM
Supplement is approved. However, DMF holder was asked to update their DMF appropriately. Signing off this letter on behalf of Dale KOble, Ph.D.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020118Orig1s008

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW	1.ORGANIZATION **HFD-160**	2. NDA Number(s) 20-118
3. Name and Address of Applicant (City & State): Baxter Healthcare Corporation, Anesthesia & Critical Care 95 Spring Street Providence, NJ 07974		4. AF No. 5. Supplement(s) Number(s) Date(s) SCP-008 04/05/02
6. Drug Name: Suprane®	7. Nonproprietary Name: Desflurane, USP	8. Amendments & Other (reports, etc) - Dates
9. Supplement Provides For: A change in one of the components of the closure system, the O-ring from (b) (4) material to (b) (4)		
10. Pharmacological Category: General inhalation anesthetic	11. How Dispensed: ☒ Rx ☐ OTC	12. Related IND(s)/ NDA(s)/DMF(s) DMF (b) (4)
13. Dosage Form(s): 240-ml Bottle	14. Potency(ies):	
15. Chemical Name and Structure: 1, 2,2,2-tetrafluoroethyl difluromethyl ether		16. Records/Reports Current: ☒ Yes ☐ No Reviewed: ☒ Yes ☐ No

17. Comments: Prompted by the infrequent reports of product leakage from the vaporizer during filling, the firm found that the silicon O-rings were not adequately protecting the bottle during product transfer to the vaporizer. The wider diameter of the O-rings and the (b) (4) material of construction were changed to somewhat narrower diameter and (b) (4) system.

18. Conclusions and Recommendations: The new EP O-rings were shown to be superior to the (b) (4) rings and were also shown to be compatible with desflurane. The compatibility studies indicated that the assay remained at 99.999% and no identified or unidentified impurities were seen, demonstrating excellent compatibility of new O-rings with desflurane. Firm commits to place the first commercial batch of the drug product on long term stability. However, the referenced DMF (b) (4) from (b) (4) is inadequate as it was not updated since 1999 and since it does not include information on the new O-ring. In view of the product improvements and in view of the available information within the supplement, the supplement is recommended for approval. A letter will be sent to the DMF holder requesting adequate update of the DMF. The comment listed at the end of the review should be included in the approval letter.

CC: Original NDA#20-118
HFD-170/Division File
HFD-170/Chemist/Harapanhalli
HFD-170/CSO/basham-Cruz
R/D initialed by : DKoble

19. REVIEWER

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

CMC Review Notes:

Introduction:

Suprane® (desflurane USP) is a volatile liquid anesthetic, packaged in a 240-ml glass bottle, which is capped using a crimped closure fitted with a one-way valve. The outside of the valve neck is fitted with an O-ring that is not in contact with the product while the bottle is on the shelf. This valve releases desflurane one-way only, when the bottle is inserted into the port of the vaporizer. The O-ring provides a tight seal between the vaporizer filling port and the outside surface of the one-way valve to prevent leakage or spilling. The valve releases desflurane only when the inverted bottle is inserted into the entry port of the vaporizer.

Reason for proposed change:

According to the applicant, since the launch of desflurane, there have been infrequent reports of product leakage from the vaporizer during filling, due to improper insertion of the bottles into the vaporizer filling port, resulting in either a misaligned or a twisted valve. This results in friction between the O-rings and the walls of the vaporizer and leads to bulging and/or twisting of the O-rings. According to the applicant, the currently approved O-rings, made of (b) (4) and therefore, when caught between the walls of the vaporizer, they can twist and crack or break, resulting in product leakage.

Proposed changes:

Firstly, Baxter Healthcare instituted an ongoing training program for users of desflurane in proper handling and insertion techniques. Applicant states that this measure has significantly reduced complaints of product leakage.

Secondly, Baxter has modified the O-ring (both material and diameter) to better fit the valve and the vaporizer.

- Construction material was changed to a more pliable and breakage-resistant material, (b) (4) .
- The diameter was reduced for a tighter fit around the valve neck, from (b) (4)

Data and evaluation:

The following data is provided in support of the proposed change in the O-ring.

Data	Evaluation
Comparative table of approved and proposed container/closure systems	Adequate: The table indicates that there are no changes to the components of the system except for the O-ring. The following components have remained unchanged: (b) (4)
Drawings and specifications of the valve closure system, revised to include (b) (4) issued 9/26/01	Adequate: The following are the revised specifications: (b) (4)

	[redacted]
DMF [redacted] LOA from [redacted] the supplier of the closure system.	Inadequate. LOA from [redacted] to reference Type III DMF [redacted] pertaining to the manufacture of [redacted] for the dispensing of Suprane is provided. However, the DMF was not updated since 1999 and it does not include updated information in the new O-ring described in the supplement.
Components of the [redacted] O-ring, supplied by [redacted] manufacturer of the O-rings.	The components of [redacted] and CFR compliance to 21CFR177.2600 are provided in the supplement are copied here. [redacted]
Performance study report on the new O-ring:	The objective was to determine if an O-ring made of [redacted] from [redacted] is more resistant to breakage during the vaporizer filling process than O-rings made of [redacted] material. [redacted] Evaluation: Adequate. The new O-rings were shown to be superior to [redacted] rings in these experiments.
Compatibility study report on the evaluation of desflurane compatibility with [redacted] O-rings.	The compatibility of desflurane with the [redacted] O-ring was evaluated by examining desflurane for purity, impurities and non-volatile residue by approved [redacted]
Stability commitment to place first commercial lot of desflurane packaged using new O-ring on	Adequate. The drug product is the same as the drug substance, which is desflurane in 240-ml bottles. The extensive data

long-term stability using currently approved stability protocol.	presented in the supplement indicates that the new (b) (4) O-rings are compatible with desflurane. The commitment to place one commercial batch on stability is acceptable.

Evaluation: Inadequate

DMF (b) (4) was not updated since 1999 and it does not include updated information on the new O-ring. Initially, the reviewer thought that the supplement can not be approved until the DMF is updated adequately. However, after discussion with Dr. Duffy, it was realized that the supplement contains all the information and it is the matter of updating the DMF to include the required information. Moreover, the supplement has demonstrate excellent product quality improvement and may not be delayed until the DMF update. Therefore, the supplement should be approved. A letter will be sent to the DMF holder asking them to update the DMF.

Comment:
The referenced DMF (b) (4) was not updated with the information on new EO O-rings. A letter was sent to the DMF holder on August 6, 2002 asking them to update the DMF.

The referenced DMF (b) (4) was not updated with the information on new EO O-rings. A letter was sent to the DMF holder on August 6, 2002 asking them to update the DMF.

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/s/

Ravi Harapanhalli
8/6/02 05:34:03 PM
CHEMIST
Supplement is recommended for approval since adequate information is provided in it. As discussed, a letter will
be sent to the DMF holder asking them
to update the DMF.

Eric Duffy
8/8/02 09:57:03 AM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020118Orig1s008

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-118/S-008

PRIOR APPROVAL SUPPLEMENT

Baxter Healthcare Corporation
Anesthesia & Critical Care
95 Spring Street
New Providence, NJ 07974

Attention: Priya Jambhekar
Director, Regulatory Affairs

Dear Ms. Jambhekar:

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:	Suprane® (desflurane, USP) Liquid for Inhalation
NDA Number:	20-118
Supplement number	S-008
Date of supplement:	April 5, 2002
Date of receipt:	April 9, 2002

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 June 8, 2002, 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 question, call Lisa Basham-Cruz, Regulatory Project Manager, at (301) 827-7420.

Sincerely yours,

{see appended electronic signature page}

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

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/s/

Lisa Basham-Cruz

4/25/02 04:46:06 PM