DIVISION OF ANESTHESIA, ANALGESIA, AND RHEUMATOLOGY PRODUCTS

SUMMARY OF CLINICAL REVIEW OF STUDIES SUBMITTED IN RESPONSE TO A PEDIATRIC WRITTEN REQUEST

Application:	NDA 20-118/SE8-012
Applicant:	Baxter Healthcare Corporation Anesthesia and Critical Care 95 Spring Street New Providence, NJ 07974
Drug names	
Chemical:	(±) 1,2,2,2-tetrafluoroethyl difluoromethyl ether
Established:	Desflurane
Proprietary:	Suprane
Route:	Liquid for vaporization

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Background

Desflurane is an inhaled anesthetic agent that was initially approved in 1992. The drug is currently approved in adults for the induction and maintenance of anesthesia. In children, it is approved for maintenance anesthesia in intubated children. The reason for the more limited indication in children is that desflurane has been recognized as being more pungent and irritating than similar agents (sevoflurane and isoflurane), particularly in children. Therefore, it is only labeled for use in intubated children, where the airway is protected.

Additional data to further address the tolerability of desflurane in pediatric patients was a priority for the safe use of the drug in the pediatric population. To meet the requirements of the Agency's Pediatric Written Request (PWR), the applicant has completed one adequate and well-controlled study in children aged 2-16 years to evaluate the safety of desflurane used for the maintenance of anesthesia in non-intubated children. The pediatric program, as stipulated in the PWR, initially planned to evaluate the safety of desflurane in children down to age 1 month. However, after it became apparent that the incidence of severe respiratory adverse events was highest in the youngest age stratum (2-6 years old) for desflurane, a second planned study in children aged 1 month to 2 years was cancelled at the Division's request and the PWR so modified. Therefore, the response to the Agency's Pediatric Written Request for desflurane consists of one study.

Efficacy

The study currently submitted did not assess efficacy.

Safety

Study 32,363-002 evaluated a total of 400 children aged 2-16 years. Three hundred patients received maintenance anesthesia by laryngeal mask airway (LMA) or facemask (FM) using desflurane and 100 received anesthesia by LMA or FM using isoflurane. Patients were stratified into three groups: 2-6 years old, 7-11 years old, and 12-16 years old. The study was designed to evaluate the incidence of major respiratory events between the treatment arms. Study drug was administered single-blind.

The clinical trial data revealed the following:

1. The incidence of major and minor respiratory events was higher in the desflurane cohort (particularly in the 2-6 year old stratum) which was the primary study endpoint.
2. The difference in raw respiratory adverse event rates is supported by complementary observations.
    a. All early discontinuations (for adverse events) occurred in the desflurane arm.

   b. Intraoperatively, a greater proportion of patients required treatment with dexamethasone and propofol in the desflurane cohort than those patients treated with isoflurane, predominantly to manage adverse events.
3. The incidence of adverse events in the desflurane arm may be underestimated.
   a. Patients randomized to desflurane received, on average, lower doses of study drug compared to the isoflurane cohort [on the basis of the proportion of mean alveolar concentration (MAC)]. This finding is relevant to the interpretation of the adverse event rate because the study data suggest that respiratory events are correlated with increasing inspired concentrations of desflurane. Since the patients in the desflurane cohort were exposed to lower concentrations of drug, it is not unreasonable to suggest that the adverse event rate might have been higher in the desflurane cohort if the MAC proportions were matched between treatment arms.
   b. The study was single-blind where only the patient was blinded to the identity of the study drug.
4. Other observations.
   a. Respiratory events occurred during all phases of anesthesia (post-induction, maintenance, and emergence).
   b. The serious adverse events (SAEs) did not appear to be drug-related. However all three of the SAEs occurred in the desflurane cohort.
   c. The non-serious adverse events, other than the respiratory events, appeared matched in the desflurane and isoflurane cohorts and were typical of an inhaled anesthetic and in a post-surgical pediatric population.

Dosing

The dose [minimum alveolar concentration (MAC) or concentration at which 50% of people will tolerate an incision] had been established for desflurane, including the pediatric population. Therefore no changes to the Dosage and Administration section of the label are necessary.

Clinical Pharmacology and Biopharmaceutics

Not applicable.

Conclusions and Recommendations

1. Desflurane will not be indicated for the maintenance of anesthesia in non-intubated children although this use will not be contraindicated.
2. Data and warnings about the propensity of desflurane to irritate the respiratory tree will be added to labeling.
3. The Applicant has met the requirements of the Pediatric Written Request.

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/s/

Sharon Hertz

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