## Deaths in Dexametomidine Clinical Studies
As Reported by: October 5, 1999

### Number of Deaths

<table>
<thead>
<tr>
<th></th>
<th>By Treatment</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dex</td>
<td>Placebo</td>
</tr>
<tr>
<td><strong>Phase I</strong></td>
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<tr>
<td>Abbott</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Orion</td>
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<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Phase II - Abbott</strong></td>
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<td></td>
</tr>
<tr>
<td>W97-249</td>
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</tr>
<tr>
<td>W98-263</td>
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<td>0</td>
</tr>
<tr>
<td>W98-264</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>W98-274</td>
<td>0</td>
<td>1</td>
</tr>
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<td><strong>Total</strong></td>
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<td><strong>Phase II - Orion</strong></td>
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</tr>
<tr>
<td><strong>Phase II - Abbott + Orion</strong></td>
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<tr>
<td><strong>Phase III - Abbott</strong></td>
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<tr>
<td>DEX95-002</td>
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<td>DEX95-004</td>
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<td>DEX95-014</td>
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<td>7</td>
<td>3</td>
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<td><strong>Total</strong></td>
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<td><strong>Phase III - Orion</strong></td>
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<td><strong>Phase III - Abbott + Orion</strong></td>
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<td><strong>Phases I, II, III</strong></td>
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<td>Abbott</td>
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<td>17</td>
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<tr>
<td>Orion</td>
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<td><strong>Academic - GNI99-102</strong></td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

* Treatment is 'None' if death occurred prior to treatment

### SOURCES:
- Abbott Studies - SAGE Report 05Oct99
- Orion Studies - Synopse
ABBOTT
Hospital Products Division
200 Abbott Park Rd.
Abbott Park, IL 60064-3537

To: Dr Susmita Samanta

Company: ________________________

FAX #: 301-480-8639

Date: 10/5/99

No. of Pages: 4 (including cover page)

From: Jean Conaway
Regulatory Affairs D389/AP30

(847) 937-3413 (telephone)
(847) 938-7867 (fax)

Here is a working draft copy of the cover letter only.
The original will be double-expressed in (5/24/99) and
attached on the letter.
October 5, 1999

CENTER FOR DRUG EVALUATION AND RESEARCH
ANESTHETIC, CRITICAL CARE & ADDICTION DRUG PRODUCTS, HFD #170
Attn: DOCUMENT CONTROL ROOM #9B-23
5600 Fishers Lane
Rockville, Maryland 20857-1706

ATTENTION: Cynthia McCormick, M.D.                    Fax: Dr. Susmita Samanta
                Director                              301-480-8682

Re: NDA 21-038 Dexmedetomidine Hydrochloride Injection

Abbott Laboratories hereby amends the above-referenced new drug application for the
subject drug product to provide for Case Report Forms (CRFs) and a table for the nine
specified patients. We are responding to the teleconference on October 4, 1999
between Dr. Patricia Hartwell and Dr. Susmita Samanta, FDA and Dr. Thomas Willer,
Abbott Laboratories.

The Agency requested the following:

REQUEST: Please provide CRFs for all nine deaths specified in the
teleconference between the Agency and Abbott Laboratories on
September 28, 1999 and reported in the amendment dated
October 1, 1999.

RESPONSE: The nine patients reported in the amendment dated October 1, 1999 are
as follows:
Cynthia McCormick, M.D.  
Page Two  
October 5, 1999

<table>
<thead>
<tr>
<th>Study No.</th>
<th>Patient Number</th>
<th>CRF Available</th>
<th>PCA No./ Related or Unrelated</th>
<th>Study Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>W97-245</td>
<td>#01001*</td>
<td>Yes</td>
<td>9906355- Unrelated</td>
<td>Placebo-died 5 days post-study</td>
</tr>
<tr>
<td>W97-245</td>
<td>#10401*</td>
<td>Yes</td>
<td>9907455- Unrelated</td>
<td>Placebo-died 12 days post-study</td>
</tr>
<tr>
<td>W97-245</td>
<td>#105</td>
<td>No</td>
<td>9905913- Unrelated</td>
<td>None received</td>
</tr>
<tr>
<td>W97-245</td>
<td>#6301</td>
<td>No</td>
<td>9906688- Unrelated</td>
<td>None received</td>
</tr>
<tr>
<td>W97-245</td>
<td>No # assigned**</td>
<td>No</td>
<td>9906525- Unrelated</td>
<td>None received</td>
</tr>
<tr>
<td>W97-246</td>
<td>#704</td>
<td>No</td>
<td>9907483- Unrelated</td>
<td>None received</td>
</tr>
<tr>
<td>W97-246</td>
<td>#12406*</td>
<td>Yes</td>
<td>9907027- Unrelated</td>
<td>Placebo- died 35 days post-study</td>
</tr>
<tr>
<td>W97-246</td>
<td>#11601</td>
<td>Yes</td>
<td>9906654- Unrelated</td>
<td>Dexmedetomidine- died 5 days post-study</td>
</tr>
<tr>
<td>3005003</td>
<td>#0901</td>
<td>Yes</td>
<td>9904548-Probably not related</td>
<td>Placebo- died 1 month post-study</td>
</tr>
</tbody>
</table>


**Consent form signed, but patient was not randomized prior to the start of surgery. Patient died intraoperatively.

Provided in EXHIBIT I are Case Report Forms for the following five patients:

01001, 010401, 012408, 011601, 0901.

The Case Report Forms for the remaining four patients will be sent to the Agency as soon as available.

REQUEST: Please provide a table which includes the number of deaths according to the following:
1. Groups: dexmedetomidine, placebo and active control groups,
2. Sponsor: Abbott, Orion and total,
3. Clinical Study Phase: Phase I, II and III.

RESPONSE: The above request is acknowledged and will be provided as soon as available.
If you have any additional questions, please do not hesitate to contact me at (847) 937-3413 or after October 7, 1999, Dr. Thomas Willer at (847) 937-6845.

Sincerely,

ABBOTT LABORATORIES

Jean M. Conaway, R.Ph.
Manager, Regulatory Affairs
Hospital Products Division
Phone: (847) 937-3413
Fax: (847) 938-7867
October 1, 1999

CENTER FOR DRUG EVALUATION AND RESEARCH
ANESTHETIC, CRITICAL CARE & ADDICTION DRUG PRODUCTS, HFD #170
Attn: DOCUMENT CONTROL ROOM #9B-23
5600 Fishers Lane
Rockville, Maryland 20857-1706

ATTENTION: Cynthia McCormick, M.D.
Director

Re: NDA 21-038 Dexmedetomidine Hydrochloride Injection

Abbott Laboratories hereby amends the above-referenced new drug application for the subject drug product. The FDA and Abbott Laboratories conducted a teleconference on September 28, 1999. Participating for the FDA were the following individuals: Dr. R. Rapaport, Assistant Division Director; Dr. P. Hartwell, Medical Reviewer; and Dr. S. Samanta, Project Manager. Participating for Abbott Laboratories were Ms. J. Sayre, Senior Operations Manager; Ms. R. Tiehen, Senior Regulatory Affairs Associate; and Dr. T. Willer, Associate Director, Regulatory Affairs. The Agency requested explanations for why the deaths of nine patients were duly noted in the 1999 Annual Progress Report but did not appear in NDA 21-038.

Please refer to Section 11 of the Integrated Summary of Safety (Additional Serious Adverse Event Reports from Abbott-Sponsored Studies) in the NDA. It reads as follows:

"Abbott Laboratories maintains a centralized database of serious adverse global events (SAGE). This database includes all serious adverse events reported for subjects/patients from the time informed consent is signed to at least 30 days after participation in an Abbott-sponsored study.

Serious adverse events reported for subjects/patients within 24 hours (48 hours for Study DEX-95-004) of participation in an Abbott-sponsored dexmedetomidine study were to have been included in the clinical database for the specific study and consequently in the overall safety database, in addition to their inclusion in the SAGE database. Serious adverse events reported for subjects/patients 24 hours (48 hours for Study DEX-95-004) after participation up to 30 days in an Abbott-sponsored dexmedetomidine study were to have been included in the SAGE database, but may not have been included in the clinical database for the specific study or in the overall safety database."

In order to accurately reflect the number of serious adverse events reported during the Abbott-sponsored dexmedetomidine clinical program, a reconciliation of the overall safety database and the SAGE database was performed (presented in Section 11 of the ISS, Tables 35 and 36).
The nine patients specified in the teleconference of September 28, 1999 are presented in tabular form, as follows:

<table>
<thead>
<tr>
<th>Study No.</th>
<th>Patient Number</th>
<th>CRF Available</th>
<th>PCA No./Related or Unrelated</th>
<th>Study Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>W97-245</td>
<td>#1001*</td>
<td>Yes</td>
<td>9906355- Unrelated</td>
<td>Placebo-died 5 days post-study</td>
</tr>
<tr>
<td>W97-245</td>
<td>#10401*</td>
<td>Yes</td>
<td>9907455- Unrelated</td>
<td>Placebo-died 12 days post-study</td>
</tr>
<tr>
<td>W97-245</td>
<td>#105</td>
<td>No</td>
<td>9905913- Unrelated</td>
<td>None received</td>
</tr>
<tr>
<td>W97-245</td>
<td>#6301</td>
<td>No</td>
<td>9906686- Unrelated</td>
<td>None received</td>
</tr>
<tr>
<td>W97-245</td>
<td>No # assigned**</td>
<td>No</td>
<td>9906525- Unrelated</td>
<td>None received</td>
</tr>
<tr>
<td>W97-246</td>
<td>#704</td>
<td>No</td>
<td>9907483- Unrelated</td>
<td>None received</td>
</tr>
<tr>
<td>W97-246</td>
<td>#12406*</td>
<td>Yes</td>
<td>9907027- Unrelated</td>
<td>Placebo-died 35 days post-study</td>
</tr>
<tr>
<td>W97-246</td>
<td>#11601</td>
<td>Yes</td>
<td>9906654- Unrelated</td>
<td>Dexmedetomidine-died 5 days post-study</td>
</tr>
<tr>
<td>3005003 (Orion)</td>
<td>#901</td>
<td>Yes</td>
<td>9904548-Probably not related</td>
<td>Placebo-died 1 month post-study</td>
</tr>
</tbody>
</table>


**Consent form signed, but patient was not randomized prior to the start of surgery. Patient died intraoperatively.

Please note that four patients (105, 6301, patient from W97-245 for whom no number was assigned, and 704) died intraoperatively and never received study drug (either placebo or dexmedetomidine). These patients were never considered part of the study because they never entered the ICU and received study drug. Therefore, these patients were not included in the NDA safety database or in the clinical study reports.

Three patients (1001, 10401, and 12406) received placebo, but all died at least five days after the end of study drug infusion (5, 12 and 35 days, respectively). The study follow-up period defined by the protocols was 24 hours. Because these three deaths occurred more than 24 hours after completion of the study, they were not included in the NDA safety database. As noted above, they were included in the SAGE database and in narratives, which appeared in Appendix B of the ISS (Volume 301 of 726, page 8/10-239-162).

One Abbott patient (11601) who received dexmedetomidine died 5 days after study completion. Since the death occurred more than 24 hours after study completion, this patient was not included in the clinical study database. It would appear, however, that this patient was inadvertently omitted from Appendix B of the ISS.

One Orion patient (901) who received placebo died one month after study completion. This patient was submitted as part of NDA-21-038, Volume 541 of 726, page 8/10-237-263.
Cynthia McCormick, M.D.  
Page Three  
October 1, 1999

All patients were noted as "unrelated" or "probably not related" with regard to study drug causality.

If you have any additional questions, please do not hesitate to contact me.

Sincerely,

ABBOTT LABORATORIES

Thomas F. Willer

Thomas F. Willer, Ph.D.  
Associate Director, Regulatory Affairs  
Hospital Products Division  
Phone: (847) 937-6845  
Fax: (847) 938-7867  
Internet: WILLET@hpd.abbott.com

APPEARS THIS WAY  
ON ORIGINAL

TFW:tw

g:10-99f.tw/18
EXHIBIT I

(1) ONGOING CLINICAL STUDIES
- DEXMEDEPOMIDINE HYDROCHLORIDE

(2) COMPLETED CLINICAL STUDIES SINCE SUBMISSION OF NDA (12/98)
- DEXMEDEPOMIDINE HYDROCHLORIDE
ONGOING CLINICAL STUDIES-DEXMEDETO MIDINE HYDROCHLORIDE

Protocol Number: W98-263
Study Title: A Pilot Phase II, Multi-Center, Randomized, Placebo-Controlled, Double-Blind Study Evaluating the Safety and Efficacy of Dexmedetomidine in Medical ICU Patients (France, Canada, and U.K.)
Estimated Study Completion Q4, 2000
Estimated Final Report: Q1, 2001
Summary:
Part I: 16 of 21 patients complete. Part II: 0 of 24 patients complete.

The objective of the study is to evaluate the safety and efficacy of dexmedetomidine in medical patients being intubated and ventilated for a minimum of six hours and not more than 24 hours. Patients admitted to the ICU for pulmonary disease requiring intensive treatment (i.e., pneumonia, asthma, chronic obstructive airway disease (COPD), smoke inhalation, or postoperative patients [≥72 hours postoperatively] who develop pulmonary or chest infections), patients with pancreatitis, myasthenia gravis, or neuropathy, such as Guillain-Barre syndrome are eligible for the study.

Patients enrolled in Part I of the study will receive open label dexmedetomidine, and patients enrolled in Part II of the study will be randomized to either dexmedetomidine or placebo. All patients may receive propofol and morphine if required as additional medication for sedation or analgesia respectively.

All patients will receive a loading dose of 1.0 mcg/kg over 10 minutes followed by a maintenance infusion at an initial rate of 0.4 mcg/kg/hr. Following the initial rate, patients will be maintained within the range of 0.2 – 0.7 mcg/kg/hr (France and Canada), titrated to maintain a Ramsay sedation score of ≥3 while intubated, and ≥2 after extubation. Four patients in the UK were completed under this dosing regimen, and it was decided to expand the range of maintenance infusion. Patients in the UK will be maintained within the range of 0.2 – 2.5 mcg/kg/hr, and may receive additional boluses of 12 mcg (3 ml) of dexmedetomidine if needed.

Patients requiring sedation beyond 24 hours will be enrolled into study W98-264.

Protocol Number: W98-264
Study Title: A Phase II, Multi-Center, Open-Label Study Evaluating the Safety and Efficacy of Dexmedetomidine in Medical ICU Patients (France, Canada, and U.K.)
Estimated Study Completion Q4, 2000
Estimated Final Report: Q1, 2001
Summary:
6 patients of 32 complete

Patients completing the 24 hour infusion in study W98-263 are eligible for study W98-264, in which all patients receive open-label dexmedetomidine for up to an additional 6 days.
Protocol Number: W98-266  
Study Title: Phase I Single-Center, Open-label Study Evaluating the Pharmacokinetics and Pharmacodynamics of Dexmedetomidine in Pediatric Patients (Canada)  
Estimated Study Completion: Q3, 2000  
Estimated Final Report: Q4, 2000  
Summary:  
1 of 18 patients complete  

The objective of this study is to evaluate the pharmacokinetics and safety of a single intravenous dose of dexmedetomidine in pediatric patients between two and twelve years of age. Pediatric patients undergoing urological, abdominal, or other surgeries requiring general and epidural anesthesia and overnight stay in the hospital are eligible for the study.  

A 10 minute infusion of dexmedetomidine will be administered 2 hours before induction of anesthesia. Dosing will be administered in an ascending dose-ranging fashion in three dose groups: 2.0 mcg/kg/hr for Group I, 4.0 mcg/kg/hr for Group II, and 6.0 mcg/kg/hr for Group III. In each group, four patients will receive dexmedetomidine, and two will serve as controls.

Protocol Number: W99-302  
Study Title: A Phase IIIb, Multi-Center, Open-Label, Randomized Study Comparing the Safety and Efficacy of Dexmedetomidine to Propofol-Based Standard of Care, for ICU Sedation Following Coronary Artery Bypass Graft Surgery.  
Estimated Study Completion: Q2, 2000  
Estimated Final Report: Q4, 2000  
Summary:  
49 of 300 patients complete  

Patients undergoing CABG surgery are eligible for this study in which patients are randomized to either dexmedetomidine or standard of care treatment with propofol. Dexmedetomidine infusion is initiated at time of last sternal wire, with a loading dose of 3.0 mcg/kg/hr for 20 minutes followed by an initial maintenance infusion of 0.4 mcg/kg/hr which is titrable between 0.2 and 0.7 mcg/kg/hr. Infusion will continue for at least 6 hours following extubation, for up to 24 hours total.

Protocol Number: W99-294  
Study Title: European Study in Post-Op Patients in the ICU; Open study w/Dex  
Estimated Study Completion: Q2, 2000  
Estimated Final Report: Q4, 2000  
Summary:  
00 of 500 patients complete  

Patients undergoing major surgery requiring general anesthesia are eligible for this study, in which two loading doses of dexmedetomidine are compared. Dexmedetomidine infusion will be initiated at time of first suture. Patients in Group I will receive a loading dose of 6.0 mcg/kg/hr for 10 minutes, and patients in Group II will receive a loading dose of 3.0 mcg/kg/hr for 20 minutes. Both groups will receive an initial maintenance infusion of 0.4 mcg/kg/hr which is titrable between 0.2 and 0.7 mcg/kg/hr.  

Infusion will continue through extubation and after extubation, for a recommended minimum of 6 hours. Maximum total infusion duration is 24 hours.
Protocol Number W99-314
Study Title CABG study in Latin America and S. Africa
Estimated Study Completion Not started

Summary

Patients undergoing CABG surgery are eligible for this study in which patients are randomized to either dexmedetomidine, or standard of care treatment with propofol. Dexmedetomidine infusion is initiated at time of last sternal wire, with a loading dose of 3.0 mcg/kg/hr for 20 minutes followed by an initial maintenance infusion of 0.4 mcg/kg/hr which is titratable between 0.2 and 0.7 mcg/kg/hr. Infusion will continue for at least 6 hours following extubation, for up to 24 hours total.
Protocol Number W98-272
Study Title: A Phase I, Single-Center, Double-blind, Randomized, Placebo-Controlled, Crossover Study Evaluating Dexmedetomidine as a Sedating Agent in Healthy Volunteers

Summary:
Eight healthy adult volunteers were to be enrolled. Each subject was to receive IV infusion of 0.2 mcg/kg/h dexmedetomidine HCl (low dose), 0.6 mcg/kg/h dexmedetomidine HCl (high dose), and a corresponding placebo via a standard syringe pump. Following an eight hour fast, subjects were to receive a 10-minute loading dose of 6.0 mcg/kg/h, followed by a 50-minute maintenance infusion of the designated study drug. Subjects randomized to placebo were to receive a loading dose of 0.9% sodium chloride solution.

The primary objectives of this study were to determine the sedative properties of low doses of dexmedetomidine in young, healthy volunteers, and to evaluate the effects of these low doses on analgesia, sedation, and cognitive function.

Final Report Submitted to FDA on May 12, 1999.

Protocol Number W98-273
Study Title: A Phase I, Placebo-controlled, Double-blinded, Dose Ranging Study to Evaluate the Effects of Dexmedetomidine on Sedation in Japanese Subjects.

Summary:
This trial designed as a two-part, Phase I, placebo-controlled, double-blinded trial in healthy subjects of ethnic Japanese origin. Part I was to consist of a dose-ranging study in approximately 40 subjects, 8 subjects per dose, to receive a 1-hour infusion. Part II was to consist of four long term infusion, dosing sessions in approximately 32 subjects, 8 subjects randomly assigned to each treatment group. Infusion times of 12 & 24-hours were to be studied.

The primary objectives were 1) to identify the dose/response relationship for sedation for single intravenous doses of dexmedetomidine, 2) to select and include 3 doses for the long term infusion portion of Part II of this study, and 3) to investigate the effects of long term infusions (12 & 24 hours) of dexmedetomidine on the sedative profile compared to single doses.


Protocol Number W98-274
Study Title: A Phase II Study entitled, "Alpha2-Agonists as Components for Analgesic Sedation in Intensive Care: Bispectral Index (BIS) Guided Sedation with Dexmedetomidine. A Randomized, Placebo-Controlled, Double-Blinded, Prospective Study".

Summary:
The objective the study was to evaluate the safety and efficacy of dexmedetomidine in patients requiring ventilation, sedation and intensive care for a minimum of 6 hours following surgery.

The primary efficacy variable for this study is the total dose of propofol required, in addition to study drug, to achieve adequate sedation, as deemed clinically necessary and as assessed by BIS, to achieve and maintain a BIS Score of 60 to 70 (indicating deep sleep) and a BIS Score of 85 to 95 after extubation (equivalent to a Ramsay Score of 2-3).

Study drug will be administered for a minimum of 6 hours prior to extubation and a minimum of 6 hours post-extubation. The investigator may continue the infusion at his/her discretion for a maximum of 72 hours total study drug infusion.

Estimated Final Report: December, 1999
Protocol Number DEX-96-017
Study Title: Beta Blocker Interaction: A Phase II, Single-Center, Double-Blind, Randomized, Placebo-Controlled Study Evaluating the Effect of Esmolol on the Pharmacodynamics of Dexmedetomidine in Patients Undergoing Elective Cardiac Surgery.
Summary:
The primary objective of this study was to evaluate the impact of dexmedetomidine on hemodynamics following administration of a beta-blocker (esmolol) to patients undergoing elective cardiac surgery.

At least 40 adult, ASA Class II – IV patients (four in the esmolol dose-verification portion of the study and 12 per treatment group in the double-blind, placebo-controlled portion) scheduled for cardiac surgery were to be enrolled.

0.3 or 0.6 ng/ml of dexmedetomidine was to be administered from approximately 1 hour prior to the induction of anesthesia until 6 hours after the end of surgery.
Estimated Final Report: October, 1999
ABBOTT
Hospital Products Division

To: DR S SAMANTA

Company: FDA

FAX #: 301-480-8682
     443-7068

Date: 9/21/99

No. of Pages: __________ (including cover page)

From: Dr. Tom Willer
      Regulatory Affairs

      (847) 937-6845 (telephone)
      (847) 938-7867 (fax)
Hospital Products Division
Abbott Laboratories
D-399, Bldg. AP30
200 Abbott Park Road
Abbott Park, Illinois 60064-6157

September 16, 1999

CENTER FOR DRUG EVALUATION AND RESEARCH
ANESTHETIC, CRITICAL CARE & ADDICTION DRUG PRODUCTS, HFD #170
Attn: DOCUMENT CONTROL ROOM #9B-23
5600 Fishers Lane
Rockville, Maryland 20857-1706

ATTENTION: Cynthia McCormick, M.D.
Director

Re: NDA 21-038 Dexmedetomidine Hydrochloride Injection

Abbott Laboratories hereby amends the above-referenced new drug application for the subject
drug. We are responding to two telephone requests from the FDA to Abbott Laboratories.

(1) FDA-Abbott Laboratories Teleconference, September 14, 1999

FDA request (b) was for information pertaining to the collection of PK data in ongoing and future
clinical studies. Pharmacokinetic data will be obtained from the following ongoing studies: W98-
266 (Pediatric), W98-263 (Medical ICU Patients) and W98-264 (Medical ICU Patients). Final
reports may be available in mid-2000. Abbott Laboratories is not in a position to project, at this
time, what future studies will be conducted and which ones will or will not incorporate the
collection of pharmacokinetic data.
(2) FDA-Abbott Laboratories Teleconference, September 16, 1999

A teleconference was held on September 16, 1999 among the following individuals: Dr. P. Hartwell, FDA Medical Reviewer; Dr. S. Samanta, FDA Project Manager; and from Abbott Laboratories: Dr. T. Willer Associate Director, Hospital Products Regulatory; Ms. P. Scaman, Associate Director, International Regulatory; Ms. R. Tiehen, Senior Regulatory Affairs Associate, International Regulatory; and Ms. J. Sayre, Senior Operations Manager, Dexametomidine Venture. The FDA requested that the paragraph pertaining to "Perioperative Studies" on page 5 of the annotated package insert be revised to remove all references to study Dex-96-012. The references deleted or modified include the following items:

- Evaluated in 7 studies; Total of "1199" patients; With "761" receiving i 
  Target concentrations of "0.15"; Infusions of 15 minutes(002, 004, 012,.....); "1-hour (012)"

Dr. Hartwell further requested that a caveat be added to the last sentence of the paragraph mentioning that although the drug is "well tolerated," an increase in hypotension may be seen with dexametomidine, as stated in other sections of the package insert. Per FDA request, the paragraph entitled "Perioperative Studies" has been revised and now reads as follows:

__________ has been evaluated in 6 clinical trials involving a total of 1165 patients, with 752
receiving ______ A loading dose followed by a maintenance infusion was administered
to achieve target concentrations of 0.3 or 0.6 ng/mL using continuous infusions of
15 minutes (002, 004, 014, 015, 016, and 021) prior to induction of anesthesia and
continued until determination of MAC response (016), the end of surgery (002), 2 hours (014
and 021), 6 hours (004), or 12 hours (015) postoperatively. _______ X was well tolerated
during pre-, intra-, and postoperative administration. However, reports of hypotension have
been associated with _______ infusion.

We recognize that the Agency has not accepted a brand name for this product and we will
update the package insert once that occurs. If you have any additional questions, please do not
hesitate to telephone me.

Sincerely,

ABBOTT LABORATORIES

Thomas F. Willer

Thomas F. Willer, Ph.D.
Associate Director, Regulatory Affairs
Hospital Products Division
Phone: (847) 937-6845
Fax: (847) 938-7867
Internet: WILLET@hpd.abbott.com

TFW:tw

g:9-991.tw/59
<table>
<thead>
<tr>
<th>To:</th>
<th>Company:</th>
</tr>
</thead>
<tbody>
<tr>
<td>DR. SAMANTHA</td>
<td>ABBOTT Hospital Products Division</td>
</tr>
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<table>
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<tr>
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<th>No. of Pages:</th>
<th>From: Dr. Tom Willer</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Regulatory Affairs</td>
</tr>
</tbody>
</table>

| (847) 937-6845 (telephone) | (847) 938-7867 (fax) |
To: DR. S. SAMANTHA

Company: FDA

FAX #: 301-480-8682

Date: 9/10/99

No. of Pages: 26 (including cover page)

From: Dr. Tom Willer
Regulatory Affairs

(847) 937-6845 (telephone)
(847) 938-7867 (fax)
Hospital Products Division
Abbott Laboratories
D-369, Bog. AP30
200 Abbott Park Road
Abbott Park, Illinois 60064-6157

September 10, 1999

CENTER FOR DRUG EVALUATION AND RESEARCH
ANESTHETIC, CRITICAL CARE & ADDICTION DRUG PRODUCTS, HFD #170
Attn: DOCUMENT CONTROL ROOM #9B-23
5600 Fishers Lane
Rockville, Maryland 20857-1706

ATTENTION: Cynthia McCormick, M.D.
   Director

Re: NDA 21-038 Dexametomidine Hydrochloride Injection

Abbott Laboratories hereby amends the above-referenced new drug application for the subject drug product. We are responding to a teleconference on September 9, 1999 between FDA: Dr. Patricia Hartwell and Dr. Susmita Samanta and Abbott Laboratories: Ms. Patricia Scaman, Ms. Rita Tiesen, and Dr. Thomas. Willer. The FDA requested a translated copy of a Case Report Form – Adverse Event Information for Patient No. 9, dated August 9, 1995. We were able to telephone Japan late yesterday and the requested translation was faxed to Abbott today. Please see Exhibit I.

We trust that this submission is complete. If additional information or clarification is needed, please telephone me at your earliest request.

Sincerely,

ABBOtT LABORATORIES

Thomas F. Willer, Ph.D.
Associate Director, Regulatory Affairs
Hospital Products Division
Phone: (847) 937-6845
Fax: (847) 938-7867
Internet: WILLETTF@hpd.abbott.com

TFW:tw

g:9-99f.thw/36
Attachment
EXHIBIT I

CASE REPORT FORM

ADVERSE EVENT INFORMATION FOR PATIENT NO. 9

DATED AUGUST 9, 1995

APPEARS THIS WAY
ON ORIGINAL

NOTE

WE PROVIDE THE ORIGINAL JAPANESE AE FORM.

THE ENGLISH TRANSLATION HAS BEEN TYPED IN BELOW THE JAPANESE WORDING.

FOR THE CONVENIENCE OF THE AGENCY, SINCE THE TYPE IS RATHER SMALL, WE PROVIDE A TYPED COPY FOLLOWING EACH ORIGINAL PAGE.
### Adverse Event

**Subject Admission**

**Study Period**

Subject No.: 09

#### Any Adverse Event Observed?

1. **☑️ Yes**
2. **☐ No**

If Yes, Complete One Column Per Event.

---

**Onset Date**

<table>
<thead>
<tr>
<th>Year (yr)</th>
<th>Month (mth)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>8</td>
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</tbody>
</table>

**Grade**

1. **☑️ Slight**

**Outcome**

1. **☐ Continuous**
2. **☑️ Discontinued**

Event Resolved at End of Study

---

**Event Course**

1. **☐ Yes**
2. **☑️ No**

If No, Number of Episodes: 01

---

**Medical Officer**

Physician in Charge: [Signature]

Date: 19 01 5 03 31

---

(Translation notes: Continuous was observed during the period from 3 minutes (06:00) after the start of all drugs, lasting till 5 hours and 20 minutes (13:30) after completion of the study drug infusion. The subject was able to open his eyes easily when instructed to verbally but began falling asleep again in the absence of such instructions.)
Adverse Event (1)

Study No.: CPC95-05

Subject # 09    Subject Initials: __________

Any Adverse Event Observed? Yes

Onset Date: 08:08, 24 August, 1995

Observed Events:
Drowsiness was observed during the period from 8 minutes (08:08) after the start of study drug dosing till 5 hours and 20 minutes (13:30) after completion of the study drug infusion. The subject was able to open his eyes easily when instructed to verbally but began falling asleep again in the absence of such instructions.

Grade: 1. Slight, Outcome: Event Continuing    2. No

Event Course: Continuous    2. No    If No, Number of Episodes    1

Onset Date: 11:05, 24 August, 1995

Event Observed:
The subject complained of nausea at the completion of blood sample collection and vital sign monitoring (immediately after removing the used to monitor vital signs), 2 hours 50 minutes (11:00) after completion of the infusion. The subject's posture was changed from semi-supine to one where the upper limbs were allowed to hang vertically with the lower extremities raised. Blood pressure at this time was 67/27mmHg. After i.v. administration of 0.5mg atropine sulfate, blood pressure increased and the nausea disappeared. Bradycardia (minimum 23 bpm) was also observed when the blood pressure decreased, however the subject's pulse rate gradually increased after receiving the atropine sulfate. Blood pressure and pulse rate had almost reverted to baseline values at 11:22.

Grade: 3. Severe, Outcome: Event Continuing    2. No

Event Course: Continuous    2. No    If No, Number of Episodes    1
### Adverse Event

#### Subject: Admission
- Study Period: Follow-up Study

#### Subject: Initials

<table>
<thead>
<tr>
<th>Event Observed</th>
<th>Date and Time</th>
<th>Relation to Investigational Drug</th>
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</thead>
<tbody>
<tr>
<td>Drowsiness after dosing with the study drug</td>
<td>9/5 0:18 2:14</td>
<td></td>
</tr>
<tr>
<td>Nausea, decreased BP, and bradycardia after dosing with the study drug</td>
<td>9/5 0:18 2:14</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>End Date and Time</th>
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</thead>
<tbody>
<tr>
<td>11/1 11:22</td>
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<table>
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<tr>
<th>Present Before Dosing</th>
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<tr>
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<tr>
<td>1.</td>
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<table>
<thead>
<tr>
<th>Action Taken on Study Drug Dosage</th>
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</thead>
<tbody>
<tr>
<td>None</td>
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<tr>
<td>None</td>
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<table>
<thead>
<tr>
<th>Corrective Therapy</th>
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<tr>
<td>Yes</td>
</tr>
<tr>
<td>1.</td>
</tr>
</tbody>
</table>

### Action Taken

- Drug Withdrawn

### Physician in Charge

- [Signature]

- Date: 9/5 0:18 2:14

---

CPC Clinic

Subject: Admission

Study No.: CPC 95-05

Subject No.: 09

End Date and Time:
- 9/5 0:18 2:14
- 11/1 11:22

Relation to Investigational Drug:
1. Not related
2. Probably not related
3. Probably related
4. Related

Present Before Dosing:
- Yes | No
- 1.  | 2.  |

Action Taken on Study Drug Dosage:
- None | Dose Changed
- None | Dose Changed

Corrective Therapy:
- Yes | No
- 1.  | 2.  |
Onset Date: 13:30, 24 August, 1995

Event Observed:
Drowsiness after dosing with the study drug.

Relationship to Investigational Drug: 4. Related, Present Before Dosing: 2. No

Action Taken on Study Drug Dosage: 1. None, Corrective Therapy: 2. No

Onset Date: 11:22, 24 August, 1995

Event Observed:
Nausea, decreased BP, and bradycardia after dosing with the study drug

Relationship to Investigational Drug: 4. Related, Present Before Dosing: 2. No

Action Taken on the Study Drug Dosing 1. None, Corrective Therapy: 2. Yes

APPEARS THIS WAY
ON ORIGINAL
<table>
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<th>観察された</th>
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<td>Adverse Event</td>
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<tr>
<td>1. 写(1)</td>
<td>郡で血圧下降と顔面虚血</td>
</tr>
<tr>
<td>2. 写(2)</td>
<td>郡で血圧下降と顔面虚血</td>
</tr>
<tr>
<td>3. 写(3)</td>
<td>郡で血圧下降と顔面虚血</td>
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<td>4. 写(4)</td>
<td>郡で血圧下降と顔面虚血</td>
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<td>7. 写(7)</td>
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<tr>
<td>8. 写(8)</td>
<td>郡で血圧下降と顔面虚血</td>
</tr>
</tbody>
</table>

### Description

**CPC Clinic**

**Subject Admission**

**Study Period**

**Follow-up Study**

**Subject Number:** 09

**Event Observed**

1. 死亡 (Death)
2. 死亡に付かもおそれがある (Life-threatening)
3. 永久的身体障害 (Any event which is permanently disabling)
4. 入院 (Any event which requires or prolongs inpatient hospitalization)
5. 発癌 (Case of Carcinogenesis)
6. 先天性異常 (Congenital abnormality)
7. 滅多投与 (Overdose of the test drug)
8. その他 (Other)

**Physician in Charge:**

**Date:** 19(95) 05 31

**年 (yr) 月 (min) 日 (day)**

**日付:** 19(95) 05 31
Event Observed:

Drowsiness after dosing with the study drug.

Does the adverse event fall into any of the following categories? Pick more than one if necessary.: 8. Others

Event Observed:

Nausea, decreased blood pressure, and bradycardia after dosing with the study drug.

Does the adverse event fall into any of the following categories? Pick more than one if necessary.: 8. Others

Appears this way on original
シービーシーキャンパス
CPC Clinic

有症事象 (4)
Adverse Event

被験番号：CPC 95-05
Study No.

被験者番号：99
Subject No.

安全事象に対する総合評価
(General comment on safety)

<p>| | | |</p>
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<td></td>
<td>(No problem)</td>
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<tr>
<td>2：</td>
<td>☐ 悪影響あり</td>
<td>2：</td>
</tr>
<tr>
<td></td>
<td>(Slightly problematic)</td>
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</tr>
<tr>
<td>3：</td>
<td>☐ 悪影響あり</td>
<td>3：</td>
</tr>
<tr>
<td></td>
<td>(Pretty problematic)</td>
<td></td>
</tr>
<tr>
<td>4：</td>
<td>☐ 悪影響あり</td>
<td>4：</td>
</tr>
<tr>
<td></td>
<td>(Very problematic)</td>
<td></td>
</tr>
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</table>

有症事象に関する主治医のコメント（Comment of physician in charge）

渇食、下痢の薬理作用（薬効適効）に基づく事象と特定されはなかった。

Nausea, decreased BP and bradycardia were also all expected events given the known pharmacological effect of DEX. Since these events were temporary and quickly reversed with no serious outcome, these events were judged as clinically meaningful in terms of safety.

コメントから、主治医（劇薬師）

Drowsiness was the expected event based on the known pharmacological effect (sedative effect of DEX) and its intensity is mild (Mild drowsiness is an expected event given the known pharmacological effect of this drug (sedative effect of DEX). Thus this event was not judged as clinically significant in terms of safety.

Nausea, decreased BP and bradycardia were also all expected events given the known pharmacological effect of DEX. Since these events were temporary and quickly reversed with no serious outcome, these events were judged as somewhat clinically significant in terms of safety.

主治医担当医師
Physician in Charge

Date: 1995年3月10日

Comments from physician (Pharmacist)

Drowsiness was an expected event based on the known pharmacological effect (sedative effect of DEX) and its intensity is mild. This event was not judged as clinically meaningful in terms of safety.
Event Observed:

Drowsiness after dosing with the study drug.

General comment (Global assessment) on safety: No problems

Event Observed:

Nausea, decreased BP, and bradycardia after dosing with the study drug.

General comment (Global assessment) on safety: Slightly problematic

Comments from physician (investigator) at site:

Drowsiness was to be expected event based the known pharmacological effect (sedative effect of DEX) and its intensity is mild. (Mild drowsiness is an expected event given the known pharmacological effect of this drug (sedative effect of DEX)) Thus this event was judged not to be clinically meaningful in terms of safety.

Nausea, decreased BP and bradycardia were also all expected events given the known pharmacological effect of DEX. Since these events were temporary and quickly reversed with relevant treatment • such as atropin injection, an anti-chonnergenic agent), there were no serious outcome. However in the case of an emergency requiring medical intervention, sufficient equipment and drugs should be available where DEX is used. Therefore these events were judged as somewhat clinically significant in terms of safety.
### CPC Clinic
#### Adverse Event

**Subject No.:** CPC 95-05

**Subject Initials:** C P

**Study No.:**

**Study Period:**

**Subject Admission**

---

**Any Adverse Event Observed?**

1. **Yes**
2. **No**

**If Yes, Complete One Column Per Event.**

---

**Event Observed:**

**Onset Date:**

- **Date:** 9/15
- **Time:** 14:41

**Duration:**

- **Duration:** 24hr: 15min

**During blood sample collection at 11:00, atrioventricular junctional rhythm was observed on the ECG while monitoring the subject for bradycardia. The ECG after lunch showed that this event had resolved.**

---

**Event Continuing:**

1. **Yes**
2. **No**

**Slight**

**Moderate**

**Severe**

---

**Outcome:**

1. **Resolved**
2. **No Resolved**

**Event Resolved at End of Study:**

- **Yes**
- **No**

---

**Event Course:**

1. **Yes**
2. **No**

**Number of Episodes:**

- **10**

---

**Physician in Charge:**

**Date:** 9/15

---

**Other notes:**

- **Specified notes:** any additional information or notes related to the event or the subject's condition.
Onset Date: 14:47, 24 August, 1995

Event Observed:

After lunch, two episodes of single ventricular extrasystole were observed in the ECG (14:47, 14:49). These events occurred when the subject was walking up and down the stairs between the 2nd and 3rd floors. The subject has intended to go to the lounge on the 3rd floor and returned to the ECG monitoring room at the onset of the event. The heart rate was 75 to 76 bpm; ECG was continuously monitored until 16:00. No further episodes of ventricular extrasystole or arrhythmia were observed.

Grade: 1. Slight, Outcome: Event Continuing 2. No

Event Course: Continuous 2. No If No, Number of Episodes 1

Onset Date: 11:13, 24 August, 1995

Event Observed:

During blood sample collection at 11:00, atrioventricular junctional rhythm was observed on the ECG while monitoring the subject for bradycardia. The ECG after lunch showed that this event had resolved.

Grade: 1. Slight, Outcome: Event Continuing 2. No

Event Course: Continuous 2. No If No, Number of Episodes 1

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<th>Anti-ventricular junctional rhythm</th>
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<td>(Probably not related)</td>
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<tr>
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<tr>
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<tr>
<th>治療担当医師</th>
<th>Date</th>
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<tr>
<td></td>
<td>19/15/08 31</td>
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<tr>
<th>CPC Clinic</th>
<th>Adverse Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study No.</td>
<td>Study Period</td>
</tr>
<tr>
<td>Subject No.</td>
<td>Follow-up Study</td>
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<tr>
<td>09</td>
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</table>
End Date and Time: 14:49, 24 August, 1995
Event Observed:
Ventricular extrasystole
Causality: Probably not related Present Before Dosing: No
Action taken on study drug dosing: None Corrective Therapy (Medical intervention):
No

End Date and Time: 14:47, 24 August, 1995
Event Observed:
Atrioventricular junctional rhythm
Causality: Related Present before Dosing: No
Action taken on study drug dosing: None Corrective Therapy (Medical intervention):
Yes
<table>
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<th>2.</th>
<th>3.</th>
<th>4.</th>
<th>5.</th>
<th>6.</th>
<th>7.</th>
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<td>Any event which is permanently disabling</td>
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<td>Any event which requires or prolongs inpatient hospitalization</td>
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</tr>
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有効事象は右記のどれに分類されるか（あてはまるものは全てチェック）

Dose The Adverse Event: Fall into Any of the Following Categories.
Tick More Than One If Necessary.
Event Observed:

Ventricular extrasystole

Does the adverse event fall into any of the following categories? Pick more than one if necessary.: 8. Others

Event Observed:

Atrioventricular junctional rhyme

Does the adverse event fall into any of the following categories? Pick more than one if necessary.: 8. Others
表題：シービーシーニックス
CPC Clinic

有効事象(4)
Adverse Event

検査番号：CPC 95-05
Study No.

被験者番号：09
Subject No.

検査事象：有効事象
Event Observed

<table>
<thead>
<tr>
<th>安全性に対する総合評価</th>
<th>Ventricular extrasystole</th>
<th>Atrioventricular junctional rhythm</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: □問題なし</td>
<td>(No problem)</td>
<td>1: □問題なし</td>
</tr>
<tr>
<td>2: □やや問題あり</td>
<td>(Slightly problematic)</td>
<td>2: □やや問題あり</td>
</tr>
<tr>
<td>3: □かなり問題あり</td>
<td>(Pretty problematic)</td>
<td>3: □かなり問題あり</td>
</tr>
<tr>
<td>4: □非常に問題あり</td>
<td>(Very problematic)</td>
<td>4: □非常に問題あり</td>
</tr>
</tbody>
</table>

有効事象に関する検査担当医のコメント
（Comment of physician in charge）

There was a long period between the onset of ventricular extrasystole and DEX dosing (about 1 week after dosing). Results from non-clinical studies and overseas clinical studies did not report any association between arrhythmia and DEX properties. Ventricular extrasystole was also not reported in studies with clonidine, a compound similar to DEX. Therefore this event is not likely to be a DEX related event. In addition to this, ventricular extrasystole is sometimes observed even in healthy subjects. In cardiac impairment tests where no organopathy is indicated in his basic condition, this event is not considered to be clinically meaningful. Thus based on the above, this event was not judged to be clinically significant in terms of safety.

With respect to atrioventricular junctional rhythm, this event is sometimes observed even in healthy subjects who are vagusoni. In cardiac impairment cases where no organopathy is indicated in the his basic condition, this event is not considered to be clinically meaningful. Thus based on the above, this event was judged not to be clinically significant in terms of safety.

検査担当医：
Physician in Charge

日付：19年6月15日 8時31分
Event Observed:

Ventricular extrasystole

General comment (Global assessment) on safety: No problems

Event Observed:

Atrioventricular junctional rhythm

General comment (Global assessment) on safety: No problems

Comments from physician (Investigator) at site:

There was a long period between the onset of ventricular extrasystole and Dex dosing (about 3.5hrs after dosing). Results from non-clinical studies and overseas clinical studies did not report any association between arrhythmia and DEX properties. Ventricular extrasystole was also not reported in studies with clonidine, a compound similar to DEX. Therefore this event is not likely to be a DEX related event. In addition to this, ventricular extrasystole is sometimes observed even in healthy subjects. In cardiac impairment cases where no organopathy is indicated in his basic condition, this event is not considered to be clinically meaningful. Thus based on the above, this event was judged not to be clinically significant in terms of safety.

With respect to atrioventricular junctional rhythm, this event is sometimes observed even in healthy subjects who are vagotonic. In cardiac impairment cases where no organopathy is indicated in the his basic condition, this event is not considered to be clinically meaningful. Thus based on the above, this event was judged not to be clinically significant in terms of safety.
CPC Clinic

Adverse Event

CPC 93-05
Study No.

Subject No.

subject initials

有無の有無
Any Adverse Event Observed?
Yes
No

1. 有り
2. 無し

存在された事件

Event Observed

Decrease in RBC and Hb were observed 24 hrs after dosing with the study drug. Both RBC and Hb reached minimum values 1 week after dosing. At 11 days after dosing both values had increased.

出現日時
Onset Date

年 (yr) 08 25
月 (mth) 08:00
日 (day) 01
時 (24hr) 分 (min)

程度
Grade

1. Slight
2. Moderate
3. Severe

有無が変化
Event Continuing

1. 持続 (Yes)
2. 消失 (No)

有無が変化
Event Continuing

1. 持続 (Yes)
2. 消失 (No)

經過
Event Course

1. Yes
2. No

行動 

Continuous

No の時のエピソードの回数
If No, Number of Episodes

01

治療担当医師
Physician in Charge

- 20 -
Onset Date: 08:00, 25 August, 1995

Observed Events:

Decreases in RBC and Hb were observed 24 hrs after dosing with the study drug. Both RBC and Hb reached minimum values 1 week after dosing. At 11 days after dosing both values had increased.

Grade: 1. Slight, Outcome: Event Continuing 2. No

Event Course: Continuous 2. No If No, Number of Episodes 1
<table>
<thead>
<tr>
<th>評価された 有効事象</th>
<th>有効事象出現最終日時</th>
<th>治療薬との因果関係</th>
<th>投薬前に存在したか</th>
<th>治療の変更</th>
<th>治療の有無</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event Observed</td>
<td>End Date and Time</td>
<td>Relation to Investigational Drug</td>
<td>Present Before Dosing</td>
<td>Action Taken on Study Drug Dosage</td>
<td>Corrective Therapy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>有効事象</th>
<th>例1: 白血球数の減少（Decreases in RBC and Hb）</th>
</tr>
</thead>
<tbody>
<tr>
<td>95年09月04日 12時10分</td>
<td></td>
</tr>
<tr>
<td>1. ☑ 関連なし (Not related)</td>
<td></td>
</tr>
<tr>
<td>2. ☑ 関連ないともいえない (Probably not related)</td>
<td></td>
</tr>
<tr>
<td>3. ☑ 多分、関連あり (Probably related)</td>
<td></td>
</tr>
<tr>
<td>4. ☑ 明らかに関連あり (Related)</td>
<td></td>
</tr>
<tr>
<td>1. ☑ 関連なし (Not related)</td>
<td></td>
</tr>
<tr>
<td>2. ☑ 関連ないともいえない (Probably not related)</td>
<td></td>
</tr>
<tr>
<td>3. ☑ 多分、関連あり (Probably related)</td>
<td></td>
</tr>
<tr>
<td>4. ☑ 明らかに関連あり (Related)</td>
<td></td>
</tr>
</tbody>
</table>

1. ☑ はい 2. ☑ いいえ Yes 3. ☑ 不明 Unknown

1. ☑ はい 2. ☑ いいえ Yes 3. ☑ 不明 Unknown

1. ☑ 治療の終絶 None 2. ☑ 治療の減量 Dose Changed

3. ☑ 治療の中止 Drug Withdrawn

1. ☑ 有 Yes 2. ☑ 無 No 1. ☑ 有 Yes 2. ☑ 無 No

治験担当医師：
Physician in Charge

日付：95年11月10日 22
End Date and Time: 12:00, 4 September, 1995

Event observed:
Decreases in RBC and Hb

Causality: Probably not related  Present Before Dosing: No

Action taken on study drug dosing: None  Corrective Therapy (Medical intervention):
No
CPC Clinic

Adverse Event

Subject No.: 69

<table>
<thead>
<tr>
<th>Event Observed</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. □ 死亡</td>
<td>1. □ 死亡</td>
</tr>
<tr>
<td>Death</td>
<td>Death</td>
</tr>
<tr>
<td>2. □ 死亡につながるおそれがある</td>
<td>2. □ 死亡につながるおそれがある</td>
</tr>
<tr>
<td>Life-threatening</td>
<td>Life-threatening</td>
</tr>
<tr>
<td>3. □ 永久的身体障害</td>
<td>3. □ 永久的身体障害</td>
</tr>
<tr>
<td>Any event which is permanently disabling</td>
<td>Any event which is permanently disabling</td>
</tr>
<tr>
<td>4. □ 入院</td>
<td>4. □ 入院</td>
</tr>
<tr>
<td>Any event which requires or prolongs inpatient hospitalization</td>
<td>Any event which requires or prolongs inpatient hospitalization</td>
</tr>
<tr>
<td>5. □ 発癌</td>
<td>5. □ 発癌</td>
</tr>
<tr>
<td>Case of Carcinogenesis</td>
<td>Case of Carcinogenesis</td>
</tr>
<tr>
<td>6. □ 先天性異常</td>
<td>6. □ 先天性異常</td>
</tr>
<tr>
<td>Congenital anomaly</td>
<td>Congenital anomaly</td>
</tr>
<tr>
<td>7. □ 过量投与</td>
<td>7. □ 过量投与</td>
</tr>
<tr>
<td>Overdose of the test drug</td>
<td>Overdose of the test drug</td>
</tr>
<tr>
<td>8. □ その他</td>
<td>8. □ その他</td>
</tr>
<tr>
<td>Other</td>
<td>Other</td>
</tr>
</tbody>
</table>

Dose The Adverse Events Fall into Any of The Following Categories. Tick More Than One If Necessary.

日付: 11月10日

Physician in Charge: 田

Date: 11/10/96

医師: 田

Date: 11/10/96
Event observed:

Decreases in RBC and Hb

Does the adverse event fall into any of the following categories? Pick more than one if necessary.: 8. Others

APPEARS THIS WAY
ON ORIGINAL

25
<table>
<thead>
<tr>
<th>Event Observed</th>
<th>Decrease in RBC and Hb</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: □</td>
<td>□ 問題なし</td>
</tr>
<tr>
<td>2: □</td>
<td>□ やや問題あり</td>
</tr>
<tr>
<td>3: □</td>
<td>□ かなり問題あり</td>
</tr>
<tr>
<td>4: □</td>
<td>□ 非常に問題あり</td>
</tr>
</tbody>
</table>

Comments from physician (investigator) on site:
Though these events were not judged as "completely unrelated", these decreases in RBC and Hb can most likely be attributed to the relatively large blood sampling volume. These decreases were mild, and no conditions related to anemia were observed. Therefore, these events were judged not to be clinically significant in terms of safety.
Event Observed:

Decreases in RBC and Hb

General comment (Global assessment) on safety: No problems

Comments from physician (Investigator) at site:

Though these events were not judged as 'completely not related', these decreases in RBC and Hb can most likely be attributed to the relatively large blood sampling volume. These decreases were mild, and no conditions related to anemia were observed. Therefore, these events were judged not to be clinically significant in terms of safety.
ABBOTT
Hospital Products Division

To:  DR S SAMANTA

Company:  FDA

FAX #:  381-486-8682

Date:  9/10/99

No. of Pages:  2 (including cover page)

From: Dr. Tom Willer
        Regulatory Affairs

(847) 937-6845 (telephone)
(847) 938-7867 (fax)
September 9, 1999

CENTER FOR DRUG EVALUATION AND RESEARCH
ANESTHETIC, CRITICAL CARE & ADDICTION DRUG PRODUCTS, HFD #170
Attn: DOCUMENT CONTROL ROOM #9B-23
5600 Fishers Lane
Rockville, Maryland 20857-1706

ATTENTION: Dr. Susmita Samanta, M.D. FAX 301-480-8682
Project manager

Re: Request for Guidance - Stability.

Regarding NDA 21-038 (xmedetomidine HCl) for Infusion, Abbott Laboratories would like to submit a new container size, a 5 ml vial, after this NDA is approved. We are making plans now to put this proposed new size on stability. It is the same product formulation. There are no changes in the manufacturing procedures, manufacturing site, etc. The only changes are the larger size vial and fill volume. We currently have under Agency review an...

In support of this vial supplement, we propose submitting three lots of product placed on three months accelerated stability at 40ºC/75% RH. We would do testing at zero, one, two, and three months. We will test for: physical appearance, color, particulate matter, sterility, BET, dexmedetomidine assay, optical purity, related substances, pH, sodium chloride. This testing conforms to the previously submitted marketed product stability protocol in terms of the terms to be performed.

Please contact me at your earliest convenience with comments and/or approval of our proposed stability plan for the...

Sincerely,

ABBOTT LABORATORIES

Thomas F. Willer, Ph.D.
Associate Director, Regulatory Affairs
Hospital Products Division
Phone: (847) 937-6845
Fax: (847) 938-7887
Internet: WILLETF@hpd.abbott.com

TFW:tw
Hospital Products Division
Abbott Laboratories
D-389, Bldg. AP30
200 Abbott Park Road
Abbott Park, Illinois 60064-6157

September 2, 1999

CENTER FOR DRUG EVALUATION AND RESEARCH
ANESTHETIC, CRITICAL CARE & ADDICTION DRUG PRODUCTS, HFD #170
Attn: DOCUMENT CONTROL ROOM #9B-23
5600 Fishers Lane
Rockville, Maryland 20857-1706

ATTENTION: Cynthia McCormick, M.D.
Director

Re: NDA 21-038 (dexmedetomidine HCl) for Infusion

Abbott Laboratories hereby amends the above-referenced new drug application for the subject drug product. The FDA and Abbott Laboratories conducted a teleconference on September 1, 1999. Participating for the FDA were the following individuals: Dr. C. McCromick, Division Director; Dr. R. Rapaport, Assistant Division Director; Dr. P. Hartwell, Medical Reviewer; and Dr. S. Samanta, Project Manager. Participating for Abbott Laboratories were Dr. M. Etropolski, Medical Director; Ms. J. Sayre, Senior Operations Manager; and Dr. T. Willer, Associate Director, Regulatory Affairs. The Agency requested several items of safety data: (1) case report forms (CRFs) for three patients who died in studies 3005006 — W98-263 (Abbott) and W98-264 (Abbott), (2) information and CRFs regarding three subjects in the Japanese Phase I study (J-DEX-9501) who experienced hematological changes, (3) CRF for subject #9 in Japanese Phase I study (J-DEX-9501) who experienced an SAE, (4) an explanation of why the and Japanese studies were not included in the Integrated Summary of Safety in the NDA, (5) breakdown of adverse incidences by study for the ISS Supplement, including and Japanese studies.

To comply with request number 1, please find enclosed as Exhibit I case report forms for the following: study 3005006, patient #211; Abbott study W98-263, patient #104; and Abbott study W98-264, patient #101.

Please find enclosed as Exhibit II selected pages from the J-DEX-9501 final clinical report Appendix and the case report forms for the three subjects who experienced hematological changes.

In the Phase I Japanese trial (J-DEX-9501), dexmedetomidine was infused intravenously for 10 minutes at doses of 0.1, 0.3, and 0.6 mcg/kg to 9 healthy Japanese male, adult volunteers. There were no SAEs or AEs leading to discontinuation and none of the subjects died. Although not reported originally as a serious adverse event by the Investigator, one subject (#9) experienced bradycardia, hypotension, atrioventricular rhythm, ventricular extrasystole, and nausea during administration of dexmedetomidine 0.6 mcg/kg that resolved after IV injection of atropine sulfate. Notation of this event appeared in the original ISS (Volume 301 of 726, 8/10-239-121) contained in NDA 21-038 (filed December 18, 1998). Subject #9 was also reported by Abbott Laboratories as a Serious Adverse Event (PCA #9902934).
The Japanese J-DEX-9501 final report stated the following regarding hematological changes: “Hematology showed a tendency of slight decreases in RBC and hemoglobin value in one subject (#1) of the 0.1 mcg/kg group and all subjects of the 0.3 and 0.6 mcg/kg groups. These changes might be attributed to blood collection in a relatively large volume specified in this study, but the involvement of the test drug cannot be completely ruled out. Therefore, the causal relationship with the drug was judged as 'possibly related'. In addition, it should be noted that red blood cell counts and hemoglobin values, although reduced, are within normal ranges at 24 hours after study drug administration in the 0.6 mcg/kg group (with the exception of subject #9 who had an RBC of 431 - normal range = 438 to 577 x 10,000/ml), and are therefore not considered clinically significant. Additionally, the changes in this group were in the range of 4% to 8% for the first 24 hours evaluation as compared to the 0.1 mcg/kg group where changes in RBCs measured 5% to 11%.

Please find enclosed as Exhibit III selected pages from the J-DEX-9502 final clinical report Appendix.

In the Phase II trial (J-DEX-9502), dexmedetomidine was infused intravenously for 5 minutes at doses of 0.2, 04, 0.6 and 0.8 mcg/kg to 139 Japanese patients undergoing surgical procedures under inhalation anesthesia. No SAEs were reported during the conduct of this perioperative study. There were no SAEs or AEs leading to discontinuation; none of the subjects died as referenced in the original ISS (Volume 301 of 726, 8/10-239-121) contained in NDA 21-068 (filed December 18, 1998).

Abbott Laboratories is most appreciative of the opportunity to work with the FDA via teleconferences. We are rapidly working to assemble the additional requested information in response to FDA Questions No. 3-5 above, which should be available in the immediate future.

If you have any additional questions, please do not hesitate to contact me.

ABBOTT LABORATORIES

Thomas F. Wiler, Ph.D.
Associate Director, Regulatory Affairs
Hospital Products Division
Phone: (847) 937-6845
Fax: (847) 938-7867
Internet: WILLETTF@hpd.abbott.com

TFW:tw

g:R-997.fw/17
Attachment
ABBOTT
Hospital Products Division

To: Dr. S. Samanta

Company: FDA

FAX #: 312-480-8682

Date: 9/2

No. of Pages: 3 (including cover page)

From: Dr. Tom Willer
Regulatory Affairs

(847) 937-6845 (telephone)
(847) 938-7867 (fax)
MEETING MINUTES

MEETING DATE: December 1, 1999

Division of Anesthetics, Critical Care and Addiction Drug Products (HFD-170)

NDA 21-038
DRUG: dexmedetomidine HCl
Proposed Indication: Short-term (24 hours or less) ICU sedation in patients 18 years of age and older.

SPONSOR/APPLICANT: Abbott Laboratories

TYPE of MEETING: Briefing meeting for Dr. Jenkins including discussion of pre-approval safety issues

ODE II PARTICIPANTS:
John Jenkins, Director

REVIEW DIVISION PARTICIPANTS:
Suresh Doddapaneni, Biopharm Reviewer
A. D'Sa, CMC Team Leader
Harry Geyer, Pharm/Tox reviewer
Belinda Hayes, Pharm/Tox reviewer
Lucy Jean, Pharm/Tox Team Leader
Mike Klein, CSET Team Leader
Jonathan Ma, Biostatistical Reviewer
Cynthia McCormick, Director
Tom Permutt, Biostatistical Team Leader
Bob Rappaport, Deputy Director
Susmita Samanta, PM
Cathie Schumaker, CPMS
Ramana Uppoor, Biopharm Team Leader

OPDRA PARTICIPANTS:
Mary Dempsey, PM
Carol Pamer, Safety Evaluator

DDMAC PARTICIPANTS:
Mark Askine, DDMAC reviewer
MEETING OBJECTIVES:

To provide a routine, formal mechanism for communications between the Office of Drug Evaluation (ODE) review divisions and the Office of Post-Marketing Drug Risk Assessment (OPDRA) risk evaluation divisions prior to the approval of a new chemical entity (NCE) or certain other applications in order to:

(1) Ensure that OPDRA is aware of potential post-marketing safety problems of drugs about to be approved,

(2) Consider, jointly, the need for any special post-marketing analyses or post-marketing safety studies or other evaluations to be implemented by or agreed to by the sponsor prior to the approval of a drug product, and

(3) Determine if there is any special information or feedback that the ODE review division would like from the OPDRA risk evaluation division during the immediate post-launch life of the soon-to-be-approved drug product.

Each discipline presented an overview of the data base reviewed for this NDA.

The safety data base indicates that hypertension, hypotension, and bradycardia are the most common adverse events. Multi-organ failure as a result of the cardiac effects would be the signal that the division would be most interested in having OPDRA monitor. Other signals that are important include: potential for diversion and abuse, liver toxicity with prolonged infusion, and adrenal suppression with long term infusion. Phase 4 commitments will be solicited regarding the long-term infusion and adrenal suppression issues.

The trade name for this product has not been approved. Abbott has provided an argument for Precedex. The consult regarding nomenclature is being reviewed by OPDRA.

ACTION ITEMS:

Carol Pamer will provide final consult on the nomenclature issue.

/Signature/
Cathie Schumaker
NDA 20-138
Briefing/Pre-Approval Safety Conference
Meeting Minutes
Page 3

cc:
Original NDA 21-038
HFD-170/Div File
HFD-170/Attendees
HFD-(430/440)/Division Director
  /Deputy Director
  /Safety Evaluator
  /Safety Evaluator Team Leader
  /Epidemiologist
  /Project Manager
HFD-042/MAskine

MEETING MINUTES – Briefing/Pre-Approval Safety Conference

APPEARS THIS WAY
ON ORIGINAL
Clinical Pharmacology and Biopharmaceutics Review

NDA: 21-038
Name: (Dexmedetomidine HCL)
Sponsor: Abbott Laboratories, 200 Abbott Park, Abbott Park, IL 60064
Submission Type: Original NDA
Submission Date: December 18, 1998
Reviewer: Suresh Doddapaneni, Ph.D.

45-Day Filing Review

Abbott Laboratories submitted NDA 21-038 seeking marketing approval for (Dexmedetomidine HCL for Infusion) for continuous intravenous infusion use in intensive care setting for providing sedation and analgesia. It is a sterile, non pyrogenic solution suitable for intravenous infusion following dilution. Dexmedetomidine HCL is not approved for marketing in any other country.

Overall, following information pertinent to this indication was provided in the Human Pharmacokinetics and Bioavailability section of NDA 21-038;

2. Protein binding:
   Dexmedetomidine is 89 to 92% bound to plasma proteins.
3. Metabolic inversion:
   Chiral inversion of dexmedetomidine to its inactive levo-enantiomer is minimal (LOQ of 0.02 ng/mL).
4. Metabolic Pathways:
   The metabolic pathways for dexmedetomidine were described. Roughly 62% of the AUC0-24h radioactivity was comprised of N- glucuronides of dexmedetomidine (G-Dex-1 and G-Dex-2), N-Methyl-O-glucuronide, O-glucuronide. Another 15% of the AUC0-24h radioactivity was accounted for by parent drug. The H-3 metabolite, the result of hydroxylation at the methyl position on the methylene bridge, accounted for another 11% of the AUC0-24h radioactivity. In vitro metabolism studies showed that the formation of the OH and H-3 metabolites is mediated largely by CYP2A6, although other CYP forms (1A2, 2E1, 2D6, and 2C19) may also be involved.
5. Mass Balance:
   Approximately 85% of the radioactivity was excreted within 24 hours (studies BA-91-04 & DEX-96-018). Approximately 3% of the dosed radioactivity was excreted in the feces while the rest was excreted in the urine as metabolites (no unchanged drug was excreted in the urine).
6. Dose-Proportionality:
   Dexmedetomidine clearance is approximately constant within the anticipated therapeutic range, resulting in dose-proportionality. This includes steady state drug plasma
concentrations expected to result from maintenance infusions of up to 0.7 μg/kg/hour (upper limit of maintenance infusion stated in the dosage and administration section of the package insert).

7. Renal Impairment:
Dexmedetomidine pharmacokinetics were not different in the two groups of severe renal impairment subjects and normal healthy subjects studied (study DEX-95-008).

8. Hepatic Impairment:
The mean clearance values for subjects with mild, moderate, and severe hepatic impairment were 74%, 64%, and 53% of those observed in the normal healthy subjects (study DEX-95-009).

9. Age assessment:
Dexmedetomidine pharmacokinetics were not different between young (18 to 40 years), middle-age (41-65 years), and elderly (>65 years) groups (study DEX-96-013).

10. Gender assessment:
Dexmedetomidine pharmacokinetics were not different between male and female subjects in the age assessment study (study DEX-96-013).

11. Drug-Drug Interactions:
No clinically relevant in vivo pharmacokinetic drug-drug interactions were reported between dexmedetomidine and midazolam (DEX-95-005), dexmedetomidine and propofol (DEX-96-019), and dexmedetomidine and alfentanil (DEX-95-011).

12. Analytical Methodology:

13. Package Insert:
The pharmacokinetics section of the package insert is annotated and contains the usual information on the ADME aspects of dexmedetomidine and pharmacokinetics of dexmedetomidine in special populations.

Recommendation
A cursory review of New Drug Application 21-038 did not reveal any obvious deficiencies that would preclude its filing. Therefore, NDA 21-038 can be filed from the viewpoint of Office of Clinical Pharmacology and Biopharmaceutics.

Suresh Doddapaneni, Ph.D.
Clinical Pharmacologist
DPE II/OCPB

FT initialed by John Hunt

CC:
NDA 21-038, HFD-170 (Division File, Morgan), HFD-850 (Lesko), HFD-870 (Doddapaneni, Mei-Ling Chen, Hunt, Uppoor), Barbara Murphy (CDR).
Filing Meeting February 3, 1999   (10:00 a.m. 11:30 a.m.)

NDA: 21-038

Sponsor: Abbott Laboratories
Drug: (dexmedetomidine HCl)

Indication: Provides for sedation in the adult ICU setting.

FILEABILITY:

On initial overview of the NDA application:   YES   NO

PHARMACOLOGY:

1. On its face, is the pharmacology section of the NDA organized in a manner to allow substantive review to begin?  X

2. Is the pharmacology section of the NDA indexed and paginated in a manner to allow substantive review begin?  X

3. On its face, is the pharmacology section of the NDA legible so that substantive review can begin?  X

4. Are all required(*) and requested IND studies completed and submitted in this NDA (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute adult studies, chronic adult studies, maximum tolerated dosage determination, dermal irritancy, ocular irritancy, photocarcinogenicity, animal pharmacokinetic studies, etc)?  X

5. If the formulation to be marketed is different from the formulation used in the toxicology studies, has the sponsor made an appropriate effort to either repeat the studies using the marketed product or to explain why such repetition should not be required?  X

6. Are the proposed labeling sections relative to pharmacology appropriate (including human dose multiples expressed in either mg/m or comparative serum/plasma levels) and in accordance with 201.57?  X

7. Has the sponsor submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor?

   4. Yes (index of studies)
   5. No, but can recalculate
   6. No, no studies to request
8. On its face, does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted rationale to justify the alternative route? X

9. Has the sponsor submitted a statement(s) that all of the pivotal pharm/tox studies been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations? X

10. Has the sponsor submitted a statement(s) that the pharm/tox studies have been performed using acceptable, state-of-the-art protocols which also reflect agency animal welfare concerns? X

11. From a pharmacology perspective, is this NDA fileable? If "no", please state below why it is not. X

Reviewing Pharmacology Officer

Team Leader 2/2/99

need tox with ord to studies
Filing Meeting (2/3/99)

NDA 21-038
Drug name: (dexametomidine HCl) 100 mcg/mL fc
Applicant: Abbott Labs, Inc.
Drug class:
Indication: to provide sedation in the adult ICU setting

Volumes received: 1.1, 1.3, 8/10-1 to 242 dated 18 December 1998
(Received HFD-170 21 December 1998)
Reviewer: Z. Jonathan Ma, Ph.D., HFD-720
User fee date:

Project manager: David Morgan
Medical reviewer: Charles Cortinovis, M.D.

1. INTRODUCTION

Clinical studies with this NDA submission contains the study reports and summaries for the following Phase II/III studies conducted by the sponsor:

ICU Sedation Studies – W97-245 (Phase III), W97-246 (Phase III), and W97-249 (Phase II).


For this specific indication, the sponsor identified the three ICU sedation studies above as the pivotal studies.

2. Study Design of the Pivotal Studies

Phase II Study W97-249 was designed to evaluate response in a target clinical population titrated to a protocol-specified level of sedation. Thereafter, two Phase III studies, W97-245 and W97-246, were initiated and followed a common design, differing only in the allowed sedation rescue medication.

Study W97-249 was a one-center study which enrolled a total of 24 patients, 12 in the open-label part and 12 in the double-blind part. The study design was similar to those of studies W97-245 and W97-246, which are summarized in the following.
<table>
<thead>
<tr>
<th>Overall Design</th>
<th>W97-245</th>
<th>W97-246</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Multicenter, two-part</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Part I: open label</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Part II: randomized, double-blind, placebo-controlled</td>
<td></td>
</tr>
<tr>
<td>Study drug</td>
<td>Dex 0.2 to 0.7 mcg/kg/h</td>
<td></td>
</tr>
<tr>
<td>Indication</td>
<td>ICU sedation and analgesia in postop patients</td>
<td></td>
</tr>
<tr>
<td>Study Phase</td>
<td>III</td>
<td></td>
</tr>
<tr>
<td>Primary Endpoints</td>
<td>Total dose (mg) of midazolam/propofol* during intubation received as rescue medication for sedation during study drug administration</td>
<td></td>
</tr>
<tr>
<td>Secondary Endpoints</td>
<td>Total dose (mg/h) of morphine during study drug infusion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total dose (mg) of morphine by time period</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total dose (mg) of midazolam/propofol* during study drug administration</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Etc.</td>
<td></td>
</tr>
<tr>
<td>Rescue Medication</td>
<td>Midazolam for sedation (0.02-mg/kg IV boluses) and morphine for pain (2-mg IV boluses)</td>
<td>Propofol for sedation (0.2-mg/kg IV boluses) and morphine for pain (2-mg IV boluses)</td>
</tr>
<tr>
<td>Study Site</td>
<td>33 centers in 10 countries</td>
<td>36 centers in 11 countries</td>
</tr>
<tr>
<td>Sample Sizes</td>
<td>Part I: 85</td>
<td>Part I: 92</td>
</tr>
<tr>
<td></td>
<td>Part II: 178 Active and 175 Placebo</td>
<td>Part II: 203 Active and 198 Placebo</td>
</tr>
</tbody>
</table>

*Midazolam for Study W97-245 and propofol for Study W97-246.

Statistical Methods

Only patients from Part II of the two studies were included in the efficacy analyses. Intent-to-treat analyses and evaluable subsets analyses were performed. Descriptive statistics and ANOVA models were used to analyze the efficacy endpoints.

Filing Issues

1. Volume numbering is confusing, two sets of numbering systems

2. Indices are confusing and inadequate, e.g.:
   - lists of tables and figures do not have either volume # or page #
   - there are two numbering systems for source tables
   - indices for appendices do not have either volume # or page #
   - could not locate the original protocols of the pivotal studies.

3. Did not find efficacy analyses by age, gender and race.

4. No electronic data was submitted.
Filing Meeting February 3, 1999  (10:00 a.m. 11:30 a.m.)

NDA: 21-038

Sponsor: Abbott Laboratories
Drug: I ——— (dexmedetomidine HCl)

Indication: Provides for sedation in the adult ICU setting.

FILEABILITY:
On initial overview of the NDA application:  

YES  NO

BIOPHARMACEUTICAL:

1. On its face, is the biopharmaceutics section of the NDA organized in a manner to allow substantive review to begin?  
   yes

2. Is the biopharmaceutical section of the NDA indexed and paginated in a manner to allow substantive review to begin?  
   yes

3. On its face, is the biopharmaceutics section of the NDA legible so that substantive review can begin?  
   yes

4. Are the Phase studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?  
   yes

5. If several formulations of the product were used in the clinical development of the product, has the sponsor submitted biopharmaceutics data to allow comparison between the product to be marketed and the product(s) used in the clinical development?  
   N/A

6. From a biopharmaceutic perspective, is the NDA fileable? If "no", please state below why it is not?  
   yes

Reviewing Biopharmaceutics Officer  /S/  1/99

Team Leader  /S/  4/1/99