CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-038

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

N21038)n #21-038 HFD-170 K1.1

DRUG NAME: Precedex (dexmedetomidine hcl injection)

RLC 12/28/99

APPLICANT: ABBOTT LABORATORIES

CHEMICAL & THERAPEUTIC CLASS:1S

Review Cycles

Review Cycle: 1 Submission Date:12-18-98 Receipt Date:12-18-98 Goal Date:12-18-99 Action:AP	Review Cycle: 2 Submission Date: Receipt Date: Goal Date: Action:
Review Cycle: 3 Submission Date: Receipt Date: Goal Date: Action:	Review Cycle: 4 Submission Date: Receipt Date: Goal Date: Action:

CORE REVIEW TEAM MEMBERS

PROJECT MANAGER/ CSO :Susmita Samanta Phone # & Office Room #:301-827-7410, 9B-45
MEDICAL:Patricia Hartwell, M.D., M.B.A.
CHEMISTRY:Michael Theodorakis, Ph.D.
PHARM/TOX:Harry Geyer, Ph.D.
BIOPHARMACEUTICS:Suresh Doddapaneni, Ph.D.
BIOMETRICS: Z.Jonathan Ma, Ph.D.
ABUSE LIABILITY: BeLinda A. Hayes, Ph.D.
MICROBIOLOGIST: Patricia Hughes, Ph.D.

Volume 1 of 4

Administrative volume #(s): 1
Clinical volume #(s): 2
CMC volume #(s): 3
Pharmacology/Toxicology volume #(s): 4

ODE II ACTION PACKAGE TABLE OF CONTENTS

Application #21-038

Drug Name: Precedex (dexmedetomidine Hydrochloride injection), 2 mL ampule/2 mL vial, 100 mcg/mL

Applicant: Abbott Laboratories Chem./Ther. Type:1S

CSO/PM: Susmita Samanta Phone: 301-827-7410 HFD-170

Original Application Date: December 18, 1998 Original Receipt Date: December 18, 1998

CURRENT USER FEE GOAL DATE: December 18, 1999 DateTableofContentsCompleted:9/13/99

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Application #21-038 Drug Name: Dexmedetomidine HCL

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Section C:	Chemistry, Manufacturing, and Controls (CMC) Information	X (completed), N/A (not applicable), or Comment
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Section D:	Pharmacology/Toxicology Information	X (completed), N/A (not applicable), or Comment
Tab D-1	Pharmacology/Toxicology Reviews and Memoranda	X
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Tab D-3	CAC/Executive Committee Report	NA

ADDITIONAL NOTES:

ABBOTT

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

December 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

Via Fax 301-480-8682
(Paper Copy Via Mail)

Re: NDA 21-038 Dexmedetomidine Hydrochloride Injection

Abbott Laboratories amends the above-referenced new drug application for the subject drug product. The FDA and Abbott Laboratories had a teleconference on December 16, 1999 in which we discussed the proposed Phase 4 commitments for this drug. We attach the Phase 4 commitments in Exhibit I. The Agency faxed these revised Phase 4 commitments to Abbott Laboratories on December 16, 1999. Abbott Laboratories agrees to the proposed six points in the commitment.

Please telephone me at your earliest convenience if I can provide any additional information.

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: WILLETF@hpd.abbott.com

TFW:tw

g:12-99\tfw\57
Attachment

EXHIBIT I

PHASE 4 COMMITMENTS

FOR

NDA 21-038 DEXMEDETOMIDINE HYDROCHLORIDE INJECTION

NOTE

THIS DOCUMENT WAS FAXED TO ABBOTT LABORATORIES ON DECEMBER 15, 1999.

WE HAVE MADE NO CHANGES TO THE DOCUMENT.

Phase 4 Commitments for Dexmedetomidine

1. A two week study in dogs, followed by a two week recovery phase, should evaluate general toxicology and effects on the HPA axis. As the protocol has been prepared for this study and received agency approval, and as we assume that the actual study has been initiated, we request that your final study report be submitted to the Agency within six months approval.

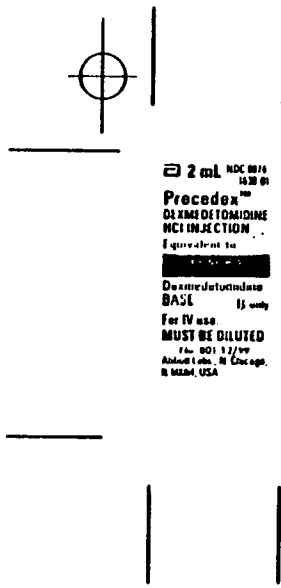
2. A two week study in dogs should evaluate changes in drug metabolism following two weeks of drug infusion. As the protocol has been prepared for this study and received agency approval, and as we assume that the actual study has been initiated, we request that your final study report be submitted to the Agency within six months from approval.

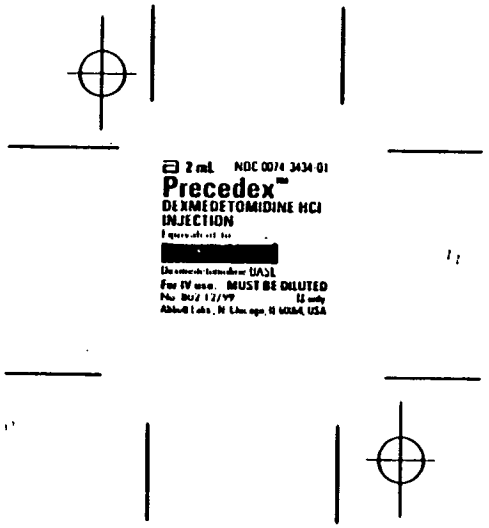
3. A study evaluating the effects of the three major human metabolites which are absent in the rat and the dog should be conducted in a human-relevant animal species or, alternatively, by direct administration of these metabolites in an appropriate animal species. We request that you start this study within six months from approval, and that you submit your final report within one year from approval.

4. Genotoxicity evaluations, including an in vitro human lymphocyte chromosomal aberration assay using the human liver S-9 fraction as the metabolic activation system and a study to assess the effect of temperature on the in vivo micronucleus assay in mice, should be conducted. We request that you start these studies within six months from approval and that you submit your final reports within one year from approval.

5. A long-term infusion study in patients should evaluate the pharmacokinetics, safety and extended effectiveness of dexmedetomidine in the ICU setting. We request that you start this study within one year from approval and that you submit the final study report within two years and six months from approval.

6. A second long-term, continuous infusion study should be performed in renal failure patients. This study should include an adequate number of patients with mild, moderate, and severe renal failure, to fully assess that patient population. Metabolite levels should be quantified to assess their accumulation with long-term use of dexmedetomidine in renal failure patients. We request that you start this study within six months from approval and that you submit the final study report within three years from approval.


2 mL
Precedex
DEXMEDETOMIDINE
HCl INJECTION
For IV use.
MUST BE DILUTED


2 mL NDC 0074 3434-01
Precedex™
DEXMEDETOMIDINE HCl
INJECTION
[redacted]
For IV use. MUST BE DILUTED
Rx only

2 mL Single-dose 5 Ampuls NDC 0074-3434-01

Preservative-Free

Precedex™

DEXMEDETOMIDINE HCl INJECTION

Equivalent to

[redacted]

Dexmedetomidine BASE

For IV use. MUST BE DILUTED

Each mL contains 100 mcg of dexmedetomidine base and 9 mg of sodium chloride in water for injection. The solution is preservative-free and contains no additives or chemical stabilizers. pH is 4.5 to 7.0. Usual dosage. See insert. Store at controlled room temperature 15° to 30°C (59° to 86°F). Rx only

Printed in USA

ABBOTT LABORATORIES, NORTH CHICAGO, IL 60064, USA

No. 803-12/99

2 mL Single-dose 25 Pharmacy Vials ~~Preservative-Free~~

NDC 0074-1638-01

Precedex™

DEXMEDETOMIDINE HCL INJECTION

Equivalent to [redacted] Rx only

For IV use. MUST BE DILUTED

Dexmedetomidine BASE

ABBOTT LABS., N. CHICAGO, IL 60064, USA

No.804-12/99

(01) 1 00074 163801 0

Printed in USA

Each mL contains 100 mcg of dexmedetomidine base and 9 mg of sodium chloride in water for injection. The solution is preservative-free and contains no additives or chemical stabilizers. pH is 4.5 to 7.0. Usual dosage: See insert.

Store at controlled room temperature 15° to 30°C (59° to 86°F)

Office of Postmarketing Drug Risk Assessment (OPDRA)

HFD-400; Parklawn Building Room 15B-03

FDA Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW:	**December 10, 1999**
NDA NUMBER:	**21-038**
NAME OF DRUG:	**Precedex™, ———— dexmedetomidine HCl injection)**
NDA HOLDER:	**Abbott Laboratories, Hospital Products Division, D-389, Building AP30, 200 Abbott Park Road, Abbott Park, Illinois 60064-6157**

I. INTRODUCTION

This consult was written in response to a request from the Division of Anesthetic, Critical Care, and Addiction Drug Products (HFD-170) for reassessment of the tradename (Precedex™) and an alternate ———— [1]) proposed by the sponsor.

———— ere initially submitted to the Labeling and Nomenclature Committee (LNC) and were found to be unacceptable. The sponsor contacted the Institute for Safe Medical Practices (ISMP), who provided an analysis of the name Precedex™ using the ERRS™ method, in addition to other analyses. Although their analysis yielded an overall ERRS score for Precedex of 3.5 (moderate trademark vulnerability), the ISMP disagreed with the LNC and did not believe that Precedex™ posed any safety issues as raised by FDA.

Precedex™ (dexmedetomidine HCl injection) is an alpha$_2$-adrenoreceptor antagonist that has been evaluated for use as a sedative with analgesic properties for use in an intensive care setting. The apparent patient population for which this product is intended for use is peri- or post-operative patients requiring intubation and assisted ventilation. The product is supplied as a 2mL vial or ampoule of a 100mcg/mL (base) solution, to be diluted for infusion prior to use. The usual adult dosage is initiated with a 1mcg/kg loading dose given over 10 minutes, followed by a maintenance infusion of 0.2 to 0.7mcg/kg/hr, titrated to the desired effect. Effects of the drug have not been studied beyond 24 hours.

II. SAFETY AND RISK ASSESSMENT

A. Product name search, product availability and dosing comparison, and focus group

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts[i,ii,iii] as well as several FDA databases[iv] for existing drug names which sound alike or look alike to **Precedex™** [redacted]™ to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[v]. Some consideration and review were also given to sound-alike and look-alike names previously noted by LNC and ISMP. An internal focus group discussion was conducted to review all findings from the searches.

A number of product names were identified in the OPDRA focus group, by LNC, and by ISMP that were thought to have potential for confusion. These products are listed in Table 1 (see Attachment 1), along with the dosage forms available, usual FDA-approved dosage, and other pertinent information. Most of these product names were considered less likely sources of confusion, given that dexmedetomidine will be used in intubated patients who cannot take oral products and the majority of these are oral products. Usual dosing is also quite dissimilar.

However, two products were identified by OPDRA as having considerable potential for confusion, one with each proposed name, [redacted] (Precedex™) [redacted]™). All three products are dosed based on body weight, must be prepared as infusions, and have a similar time for infusion of the initial dose (all less than one hour). The potential for serious adverse outcomes with inadvertent use (or non-use) of any of these products is also high.

B. Handwritten and verbal analysis of proposed names

A study was conducted within FDA employing health care professionals to evaluate potential errors in handwritten and verbal communications of the names Precedex and [redacted] This exercise was conducted in an attempt to simulate usual clinical practice settings. One of the following prescriptions was communicated per each FDA reviewer. Each reviewer was then requested to provide an interpretation of this prescription via email.

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTIONS
Precedex IV 70mcg in 50mL (total) 0.9 NaCl over 10 minutes, followed by 1.4mcg/hr for 24 hours. (n=21)	Precedex 70mcg in normal saline given IV over 10 minutes, followed by 1.4mcg per hour for 24 hours. (n=24)
[redacted] (n=24)	[redacted] per hour for 24 hours (n=23)

[i] MICROMEDEX Healthcare Intranet Series, 1999, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Emergindex, Reprodisk, Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 1999).

[ii] American Drug Index, 42nd Edition, 1999, Facts and Comparisons, St. Louis, MO.

[iii] Facts and Comparisons. Updated October 1999, Facts and Comparisons, St. Louis, MO.

[iv] Drug Product Reference File [DPR], the Established Evaluation System [EES], the AMF Decision Support System [DSS], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, and the electronic online version of the FDA Orange Book.

[v] WWW location http://www.uspto.gov/tmdb/index.html.

Results of this exercise are provided in Tables 2, 3, 4, and 5. A low response rate to this survey occurred, presumably due to the short time for review (<1 week), which makes interpretation of these data difficult. The majority of respondents provided misspelled variations of the drug names but these responses generally were phonetic variations of the name. Although ——— as most consistently spelled correctly from verbal prescriptions, one respondent to the verbal surveys independently noted the potential for confusion with Zenapax™, given the similarity in name and dosing regimen to ———

III. DRUG NOMENCLATURE ISSUES

A. The established drug name chosen by the manufacturer for this product, "dexmedetomidine HCl for infusion" is a pharmaceutical dosage form that is not officially recognized by the United States Pharmacopeia in their official compendia. Including the phrase "for infusion" in the established drug name is also a safety concern in that the user may assume that the undiluted product is ready for infusion, the reverse of the likely intent of the manufacturer.

We suggest that the established name be revised, based upon the USP/NF[vi], to "dexmedetomidine injection", with appropriate labeling specifying that the product must be diluted.

B. The current USP/NF standards also apply when specifying strength of the product for a drug that is an HCl salt but dosing is specified in terms of base equivalents. We recommend the following revised statement:

"Each 1 mL of Precedex ——— s dexmedetomidine hydrochloride equivalent to 100 mcg of dexmedetomidine and 9 mg of sodium chloride in water."

IV. LABELING, PACKAGING AND SAFETY RELATED ISSUES

In reviewing the draft product package insert, container labels, and carton labeling for ——— the previously proposed trade name of this product, OPDRA has attempted to focus on safety issues relating to potential medication errors. Many of the items discussed in this consult involve issues normally reviewed by the chemist and medical officer.

We reviewed the draft product labeling f——— and identified several labeling, packaging, and safety concerns.

A. CARTON and CONTAINER LABELING (2 mL vials, 2 mL ampoules)

1. We suggest that ——— be replaced with "———

We are recommending that the TOTAL drug content of the ampoule or vial be specified on the label instead of the mcg per mL content. Numerous medication error reports have been received where the entire contents of a parenteral drug product container have been administered, instead of the prescribed quantity of drug and its associated volume.

[vi] USP 24/NF 19: U.S. Pharmacopeia and National Formulary, 1999, The United States Pharmacopeial Convention, Inc., Rockville, MD, p.2112, "Injections".

2. We recommend that " For I.V. infusion only after dilution" be replaced with "MUST BE DILUTED".

3. Revise the content statement to "Each mL contains dexmedetomidine hydrochloride, equivalent to 100 mcg of dexmedetomidine and 9 mg of sodium chloride in water for injection."

4. We recommend that the statement "Licensed from Orion Corporation, Espoo, Finland" be deleted. CFR 201.1 sets forth various recommendations on the expression of relationship between a distributor, manufacturer, and/or labeler. The regulations do not allow others (e.g., licensors) to be included. This information appears in the draft package insert. On the carton labeling, it provides unnecessary distraction in reading carton labels.

5. "Preservative-free" and the statement "This solution is preservative-free and contains no additives or chemical stabilizers" is not necessary, as the content is apparent from listed ingredients.

B. PACKAGE INSERT

1. Delete all terminal zeros as they appear in the draft package insert under "Clinical Pharmacology. Clinical Trials, ICU Sedation" and especially under DOSAGE AND ADMINISTRATION when specifying the dose of dexmedetomidine. Specifically, "1.0 mcg/kg" should appear as "1 mcg/kg" in the package insert. Including terminal zeros increases the likelihood of 10-fold dosing errors occurring under usual clinical practice settings.

2. [redacted]

3. [redacted]

4. See also comments under CARTON and CONTAINER LABELING.

APPEARS THIS WAY
ON ORIGINAL

V. RECOMMENDATIONS

A. From a safety perspective, we do not recommend use of the proprietary names Precedex™ or [redacted] product.

B. OPDRA recommends the above labeling and packaging revisions to encourage the safest possible use of this product. We are willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.

C. OPDRA recommends that the Labeling and Nomenclature Committee be advised of our comments concerning the established name of the product.

OPDRA would appreciate feedback on the final outcome of this consult (e.g., copy of revised labels/labeling). We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Carol Pamer, R.Ph. at 301-827-3245.

Carol Pamer, R.Ph.
Safety Evaluator
Office of Postmarketing Drug Risk Assessment (OPDRA)

Concur:

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Postmarketing Drug Risk Assessment (OPDRA)

cc: NDA 21-038
HFD-170; Division Files/Laura Governale, Project Manager
HFD-170; Cynthia McCormick, Division Director
HFD-400; Janos Bacsanyi, Safety Evaluator, DDREII, OPDRA
HFD-400; Carol Pamer, Safety Evaluator, OPDRA
HFD-400; Jerry Phillips, Associate Director, OPDRA
HFD-400; Peter Honig, Deputy Director, OPDRA
HFD-002; Murray Lumpkin, Acting Director, OPDRA

ATTACHMENT 1

TABLE 1: Product availability and dosing of potential sound-alike, look-alike products

Product Name	Dosage form(s)	Usual dose*	Other
Precedex	100mcg/mL (base) clear, colorless solution. 2mL vials or ampoules.	Loading: 1 mcg/kg over 10minutes. Maintenance: 0.2 to 0.7mcg/kg/hr for 24hrs. Dilute to total volume 50mL NS.	ICU use for sedation of intubated patients.
Feridex I.V.	11.2mg Fe/mL. 5mL single dose vial of black to reddish-brown liquid. Contains dextran.	0.05ml/kg or 0.56mg Fe/kg, diluted in 100mL D5W and infused over 30 minutes with filter.	Contrast agent prior to MRI. Look-alike (L/A) potential per OPDRA.
Decadron	4mg/mL, 24mg/mL. Clear, colorless sol'n in 1mL,25mL vials (4mg/mL); 5mL vial (4&24mg/mL)	Shock: 1 to 6mg/kg IV, infused or single dose, as well as various other doses.	L/A per ISMP.
Casodex	Oral 50mg tablets.	50mg once daily	Sound-alike (S/A) per ISMP.
Cedax	Oral capsules 400mg or suspension 90mg/5mL, 180mg/5mL ceftibutin.	Adults: 400mg per day for 10 days. Children: 9 mg/kg per day for 10 days.	S/A per ISMP.
Percocet	Oral tablet analgesic.	One tablet every 6 hours as needed.	L/A, S/A per LNC.
Percodan	Oral tablet analgesic.	One tablet every 6 hours as needed.	L/A, S/A per LNC.
Peridex	Oral dental rinse only.	Oral rinse	S/A per ISMP, LNC.
Precose	Oral 25mg,50mg,100mg tablets.	25 to 100mg three times a day.	L/A per ISMP.
Prevacid	Oral 15mg, 30 mg capsules.	15 to 30mg once daily	L/A, S/A per LNC.
Prilosec	Oral 10mg,20mg,40mg capsules.	20 to 40mg once daily	L/A per ISMP.
Procardia	Oral 10mg, 20mg capsules.	10 to 30mg up to 4 times a day	L/A per ISMP.
		hrs.	
Zantac	Parenteral: 25mg/mL sol'n IM,IV; premix 50mg/50mL Oral:150,300mg caps, tabs; Syrup 15mg/mL.	50mg IV or IM every 6 to 8 hours. Oral: 150mg once or twice daily or 300mg daily	L/A, S/A per OPDRA.
Zenapax	25mg/5mL single dose vials	1mg/kg diluted in 50mL NS, given over 15minutes. Total of 5 doses at 14 day intervals.	L/A, S/A per OPDRA.
Xanax	Oral tablets 0.25, 0.5, 1, 2mg	0.25 to 0.5mg three times daily, up to 4mg total daily dose	L/A, S/A per OPDRA.
		*Frequently used, not all-inclusive.	

Table 2: Verbal Prescription:

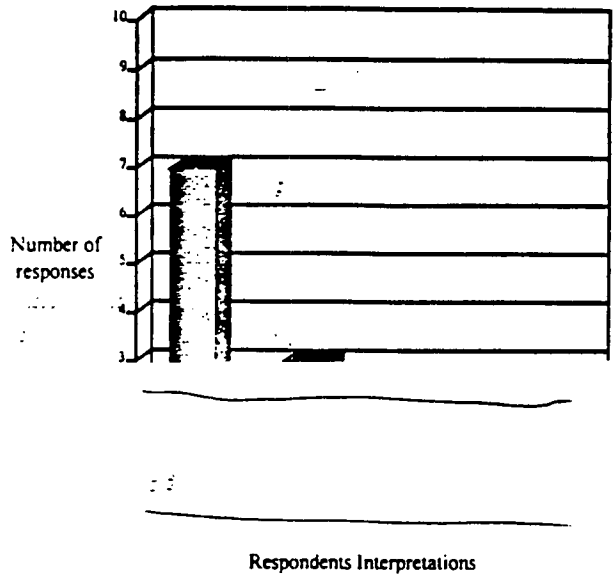


Table 3: Verbal Prescriptions (Precedex)

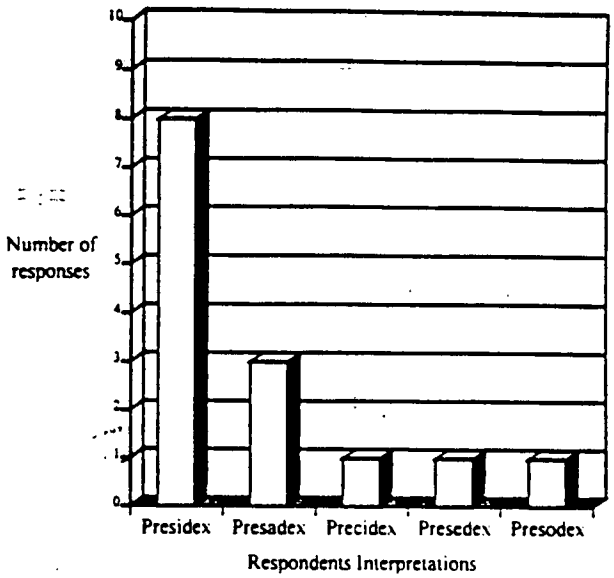


Table 4: Written Prescriptions

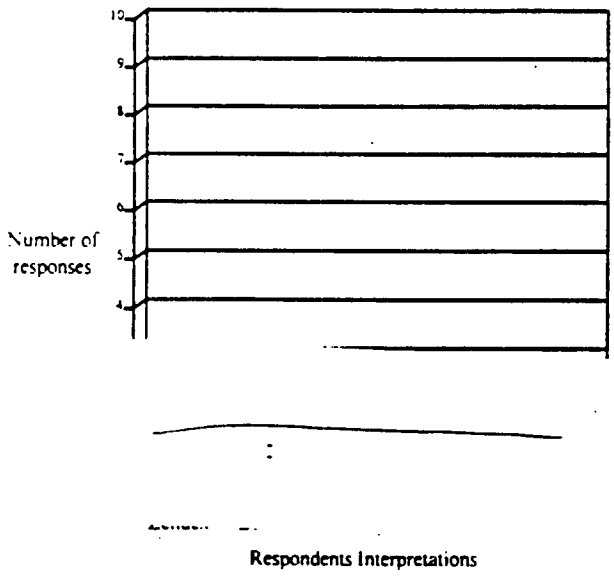
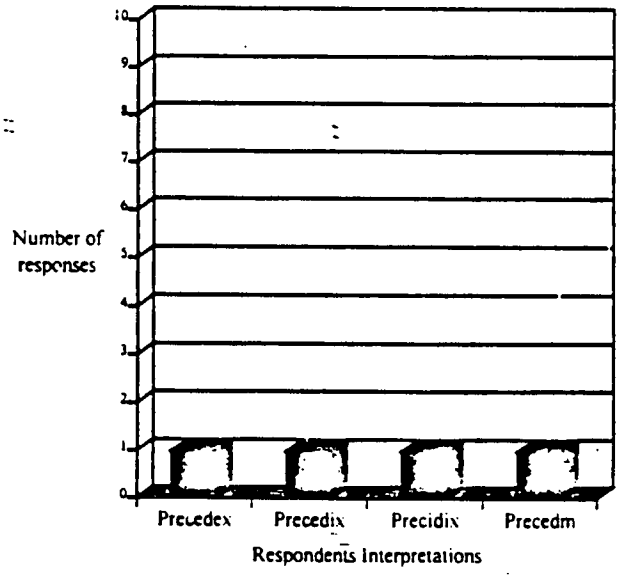


Table 5: Written Prescriptions (Precedex)



ABBOTT

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

November 17, 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

Via Fax 301-443-7068
(Paper Sent Via Mail)

Re: NDA 21-038 Dexmedetomidine Hydrochloride Injection

Abbott Laboratories hereby amends the above-referenced new drug application to submit two proposed brand names for this drug product. The Agency sent us a letter dated October 28, 1999 concerning its review of our proposed brand name, PRECEDEX. This brand name is not acceptable. The Agency made the following comment:

COMMENT: **"We have reviewed your proposed proprietary names PRIMEDEX and PRECEDEX and have concluded that these names are unacceptable. The name PRECEDEX could present look-alike/sound-alike confusion with drug products "PERIDEX", "PREVACID", "PERCOCET", and "PERCODAN".**

Please provide alternatives (we suggest three) to your proposal for the proprietary name, and/or the rationale for retaining the proprietary name PRECEDEX."

RESPONSE: In response to the Agency's consideration and non-acceptance of the proposed brand name PRECEDEX, Abbott Laboratories contacted the Institute for Safe Medical Practices (ISMP). We requested that ISMP evaluate PRECEDEX in light of the Agency's observations and concerns for look-alike / sound alike drug names. Dr. Michael Cohen, President, issued a report on the Institute's findings. For the convenience of the Agency, here is a summary using extracts/quotes from the ISMP report. Based on the ISMP detailed evaluation using a computer model, we believe that the proposed brand name of PRECEDEX does not pose safety issues raised by the Agency.

ERRS™
Error Recognition and Revision Strategies
Trademark Evaluation

The trademark vulnerability evaluation was performed using the ERRS™ Model, which is a modification of Failure Mode and Effects Analysis (FMEA). FMEA, a technique also used by other industries such as the automobile and aerospace industries, can uncover design flaws or other product defects in such a way as to limit the consequences of human error.

ERRS™ Model for Evaluating Trademark Vulnerability

Practitioners who are likely to use the product in their practice setting performed a safety assessment for each trademark candidate. After the proposed trademarks were scripted, respondents reviewed the handwritten trademarks and pronounced each name according to pronunciation guidelines. While considering the environment and conditions under which the product will be used, respondents identified potential problems arising from look-alike, sound-alike and other types of nomenclature problems. Respondents also rated the overall suitability of each trademark proposed for the new product.

A combination of Internet e-mail and FAX was used to assemble data for analysis. Respondents included a total of 25 health care practitioners from the United States. In addition to being reviewed by health care practitioners, each proposed trademark was evaluated by the ISMP health professional staff under the supervision of Michael R. Cohen, MS, FASHP, president. Careful consideration was given to how and where the drug will be used as well as the patient population that will be using the product. Also, factors related to drug procurement, storage, dispensing, handling and administration were considered.

Additionally, each trademark candidate was reviewed from the perspective of FDA Labeling and Nomenclature Committee and USAN criteria.

The ERRS™ model also incorporates a highly sensitive automated computer screening method to make predictions about look-alike and sound-alike medication errors. This method, which was developed by Dr. Bruce Lambert of the University of Illinois School of Pharmacy, relies on computerized measures of word to word similarity using the USP-DI and USAN dictionary databases for comparison. ISMP staff examined all names with an edit distance to the proposed trademark of 3 or less, or trigram similarity of 0.3 or greater. Only those names deemed significant by ISMP staff are included in the analysis. For practical purposes, trademarks have been excluded if used for OTC items or multi-source products unless the mark was used for the originator's product. ***Automated computer screening is used only to supplement practitioner review.*** As such, the process helps to assure that important name similarities are not overlooked during practitioner review.

Scoring methods

Overall trademark ratings were determined using a five point scale with 1 poorest and 5 best. Trademarks with a "high vulnerability" rating (1-2) are those with significant risk of patient harm if confused with similar drug names or medical terminology. ISMP recommends that proposed trademarks with "high vulnerability" ratings not be considered for a medical product. Trademarks with a "low vulnerability" rating (4-5) are those with a lower risk of patient harm if confused with similar drug names or medical terminology. From a safety perspective, ISMP recommends that the trademark selected for the medical product be chosen from those proposed names with a "low vulnerability" rating. Trademarks rated as "moderate vulnerability" (2.5-3.5) may also be considered for use with medical products. However, their use should be carefully examined in light of the information revealed in the report that follows.

Note: No trademark is completely free of possible confusion with another trademark in the complex health care system. The ERRS™ Model offers insights into possible problems that can help to identify trademarks that could be error prone, but it cannot guarantee that trademarks are error proof as long as humans are part of the process.

Results

PRECEDEX Overall score = 3.5 (moderate vulnerability)

There is slight look-alike confusion with DECADRON (dexamethasone; antiemetic and antiinflammatory agent) which is available as an injection, is dosed on a mg/kg basis (somewhat similar to PRECEDEX's mcg/kg dosing) and can be used in an intensive care setting like PRECEDEX. Several other products were reported to have some potential for look-alike confusion. PERCOCET (oxycodone/acetaminophen combination; analgesic) and PERCODAN (oxycodone/aspirin combination; analgesic) might look similar to PRECEDEX when handwritten. However, they are both combination products, which are taken orally, and have a different dosing schedule. The different environments in which these products are used reduces the chance of confusion. Some similarity also exists with PRECOSE (acarbose; antidiabetic agent), PRILOSEC (omeprazole; used to treat various GI conditions) and PROCARDIA (nifedipine; used to treat hypertension and angina). These agents are also oral products, and with different dosing schedules and dosage strengths, the risk of mix-up with PRECEDEX is lessened.

Sound-alike confusion exists with PERIDEX (chlorhexidine; used as a skin disinfectant and to treat gingivitis). It is available in liquid form, used as a "swish and spit" agent or as a topical agent. Its clinical indications and method of ordering are very different from PRECEDEX, with little chance of confusion. CEDAX (ceftibuten; antibiotic) can sound somewhat similar when spoken. However, it is available only in oral form, either as a capsule or powder for oral suspension, and it is administered at a set dose and dosing interval (not dosed on a mcg or mg/kg basis). CASODEX (bicalutamide; antiandrogen used to treat prostate cancer) has the potential for sound-alike confusion, but it is a 50 mg oral tablet, used in a different clinical setting.

CONCLUSION BY ISMP
Based on the above information, this trademark can be considered a good candidate for this product."

ADDITIONAL ABBOTT COMMENT ON BRAND NAMES

Based on this third party evaluation, we request an expedited review to reconsider the proposed brand name of PRECEDEX. The Agency has also recommended that Abbott Laboratories submit other brand names for Agency consideration. While PRECEDEX remains our primary choice, we also submit the following brand name for consideration:

[redacted]

Also, on an expedited basis, we request Agency evaluation for this additional brand name. If the Agency upon reevaluation, accepts the PRECEDEX name, we also request consideration of [redacted] so that we can choose either of these names. We appreciate the Agency's consideration of this important aspect to the NDA approval process.

Please telephone me at your earliest convenience if I can provide an additional information.

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: WILLETF@hpd.abbott.com

APPEARS THIS WAY
ON ORIGINAL

TFW:tw

g:11-99f.tfw/31

REQUEST FOR TRADEMARK REVIEW

To: Labeling and Nomenclature Committee
Attention: Dan Boring, Chair (HFD-530) NLRC

From: Division of	ANESTHETICS, CRITICAL CARE & ADDICTION	HFD-170
Attention:	SUSMITA SAMANTA	Phone: 301-827-7410
Date:	9-27-99	
Subject:	Request for Assessment of a Trademark for a Proposed New Drug Product	
Proposed Trademark:	PRECEDEX	NDA/ANDA# 21-038

Established name, including dosage form:

Dexmedetomidine Hydrochloride Injection

Other trademarks by the same firm for companion products:

NA

Indications for Use (may be a summary if proposed statement is lengthy):

ICU SEDATION

Initial Comments from the submitter (concerns, observations, etc.):

LNC did not approve TM

Note: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible. {Rev. August 95}

ABBOTT

Hospital Products Division
Abbott Laboratories
D-369, Bldg. AP30
200 Abbott Park Road
Abbott Park, Illinois 60064-6157

September 20, 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 a telephone request on September 17,1999 from Dr. S. Samanta, FDA, to Dr. T. Willer, Abbott Laboratories. The Agency requested the following: 1) a list of ongoing dexmedetomidine clinical studies along with a summary of each study; and 2) a list of all studies completed since submission of the NDA (December, 1998), including a summary of each study. We provide the requested information in Exhibit I.

We also submit a proposed brand name for this product. We have evaluated the Agency's comments concerning the pronunciation (sound-alike) of our two previous proposals. We believe that this brand name will meet those criteria while retaining the –dex suffix. We suggest:

PRECEDEX™

We look forward to your early review and acceptance of this brand name. If you have any 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: WILLETF@hpd.abbott.com

TFW:tw

g:9-99f.tfw/
Attachment

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

JUN 9 1999

NDA 21-038

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

Attention: Thomas F. Willer, Ph.D.
Associate Director, HPD Regulatory Affairs

Dear Dr. Willer:

Please refer to your pending December 18, 1998 New Drug Application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ——— (dexmedetomidine) Injection.

We have reviewed your proposed proprietary nam· ——— and have concluded that the name could present look-alike/sound-alike confusion with the approved drug product "DEMADEX".

Please provide alternatives (we suggest three) to your proposal for the proprietary name, and/ or the rationale for retaining the proprietary name ———

If you have any questions, contact David Morgan, Regulatory Project Manager, at (301) 827-7410.

Sincerely,

/S/

Cynthia McCormick, M.D.
Director
Division of Anesthetic, Critical Care,
and Addiction Drug Products, (HFD-170)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

CDER LABELING AND NOMENCLATURE COMMITTEE

CONSULT #	HFD#	PROPOSED PROPRIETARY NAME:	PROPOSED ESTABLISHED NAME:
1141	170	PRIMADEX	dexmedetomidine hydrochloride injection

ATTENTION: Michael C. Theodorakis

A. Look-alike/Sound-alike

	Potential for confusion:		
Primaxin	XXX Low	____ Medium	____ High
Primacor	XXX Low	____ Medium	____ High
Primatene	XXX Low	____ Medium	____ High
Primidone	XXX Low	____ Medium	____ High
Primaquin	xxx Low	____ Medium	____ High

B. Misleading Aspects:

C. Other Concerns:

D. Established Name

____ Satisfactory

XXX Unsatisfactory/Reason

There isn't an official dosage form category "for infusion"

Recommended Established Name

dexmedetomidine hydrochloride injection

E. Proprietary Name Recommendations:

XXX ACCEPTABLE ____ UNACCEPTABLE

F. Signature of Chair/Date /S/ 4/9/99

REQUEST FOR TRADEMARK REVIEW

Date: February 5, 1999

To: Dan Boring, Chair, Labeling and Nomenclature Committee, CRP2 / S447/ HFD-530

From: Michael C. Theodorakis, Ph.D. Senior Reviewing Chemist, Division of Anesthetic, Critical Care, and Addiction Drug Products HFD-170 Phone: 443-3741

MCT 2/8/99

Subject: Request for Assessment of a Trademark for a Proposed New Drug Product

JS 2/8/99

Proposed Trademark: ———

Established name, including dosage form: **dexmedetomidine hydrochloride injection**

Other trademarks by the same firm for companion products:

Indications for Use (may be a summary if proposed statement is lengthy): **ICU Sedation**

Initial Comments from the submitter (concerns, observations, etc.):

Please note that in the labeling the established name and dosage form appear as "(dexmedetomidine HCl) for Infusion". The USP does not provide for an injection to be described as infusion. Also, infusions in USP are limited to suspension administered intramammary in large animals.

Note: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHETICS, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS

HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857
Tel:(301) 827-7410

MEMORANDUM

to: John K. Jenkins, MD
Director,
Office of Drug Evaluation II

Division File: NDA # 21-038

from: Cynthia G. McCormick, MD
Director, Division of Anesthetics, Critical Care and Addiction Drug Products

subject: Dexmetetomidine NDA, Addendum to Division Memo

date: December 17, 1999

Several outstanding issues were remaining at the time of the Division Memo of November 30,1999. These included mutagenicity, evaluation in the very elderly population, and trade name.

Mutagenicity

The mutagenicity studies performed during development included a full battery of tests for genotoxicity and clastogenicity. Dexmedetomidine was not found to be mutagenic in the Ames test or the mouse lymphoma assay. Dexmedetomidine was, however, shown to be clastogenic in the *in vitro* human lymphocytes chromosomal aberration assay with metabolic activation using rat hepatic tissue incubation, resulting in exposure of the human bone marrow cells to metabolites specific to the rat but not necessarily human. Since the human metabolic profile has not yet been not completely established these results cannot be fully interpreted. Before drawing further conclusions about these findings, the human metabolic profile must be further defined or the studies repeated in an appropriate setting to obtain less equivocal results. An *in vitro* human lymphocyte chromosomal aberration assay using the human S-9 fraction as the metabolic activation system was requested and agreed to by the sponsor. This study will be initiated within 6 months of approval and the final study reports are expected within one year of approval.

In addition to the above finding, the in *in vivo* mouse micronucleus also demonstrated evidence of chromosomal breakage but only under conditions of hypothermia. These results are not conclusive. A new study designed to assess the effect of temperature on the *in vivo* micronucleus assay in mice has been requested and agreed to by the sponsor.

Insofar as there is no incidence of clastogenicity in competing products, the results of these studies will be included in the label for the sake of full disclosure when more definitive results are obtained

Possible Pharmacodynamic differences in the Elderly

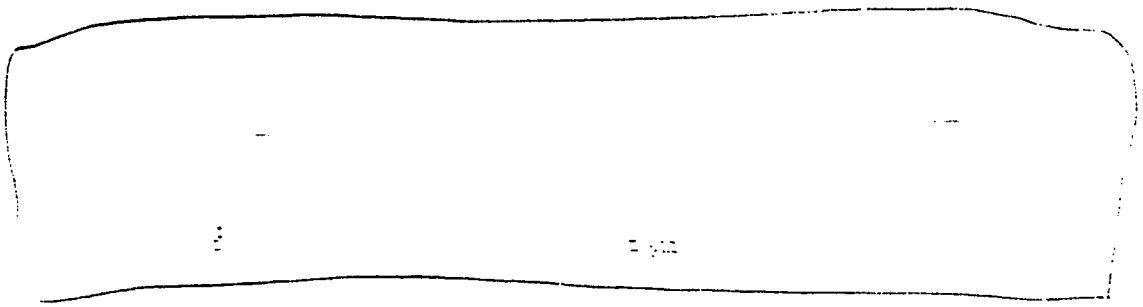
Approximately 531 patients over 65 years of age have been studied in this NDA. A total of 129 subjects in the clinical studies were 75 years of age and over. The pharmacokinetic profile of dexmedetomidine was not altered by age. There were no differences in the pharmacokinetics of dexmedetomidine in young (18-40 years), middle-age (41-65 years), and elderly (>65 years) subjects. The elderly patients >75 years in general received shorter duration infusions than those between the ages of 65 and 75 years of age.

To assess whether dosage adjustment may be needed in the very elderly patients based on anticipated PD differences associated with sedative agents, the treatment-emergent adverse events were analyzed which differed significantly from placebo. When treatment-emergent adverse were analyzed it was found that bradycardia and hypotension were more common in the >75 year old patients. These findings will be reflected in the package insert with an additional precaution that dosage adjustment may be required in patients over 65 years of age. In addition, because elderly patients are more likely to have decreased renal function, care should be taken in dose selection in elderly patients, and it may be useful to monitor renal function.

Tradename

The sponsor has proposed the tradename Precedex. A consultation obtained by OPDRA suggested that there might be a possible source of confusion with Feredex, a contrast agent administered prior to MRI. The likelihood of these agents, even if one were to make the case that they were sound-alike or look alike products in hospital orders, have a number of features which mitigate against this possibility of confusion. Those mitigating features are as follows: the difference in color, the vastly different clinical setting, and the difference in the dispensing practices in the hospitals. Precedex is a colorless concentrate stored in vials and ampules for dilution. Feredex, the potentially confusing product is reddish brown in color, unlikely to be confused on that basis. Feredex is an IV contrast agent for use in the radiological suite. Imaging agents are not normally dispensed through hospital pharmacies, and therefore would not be expected to be confused with a sedative dispensed by the hospital pharmacy and administered by infusion in the ICU. For these reasons, I agree with the sponsor that the Tradename PRECEDEX is appropriate and unlikely to lead to medication errors.

Morphine Potentiation Effect



APPEARS THIS WAY
ON ORIGINAL

EXCLUSIVITY SUMMARY FOR NDA # 21-038_____ SUPPL #_____

Trade Name _____ Generic Name: dexmedetomidine hydrochloride

Applicant Name: Abbott Laboratories HFD # 170_____

Approval Date If Known: December 17, 1999

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /_X_/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /___/

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /_X_/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES /___/ NO /_X__/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

_NO_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /___/ NO /_X__/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /_X__/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /_X__/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

_____

_____

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !

IND # YES /___/ ! NO /___/ Explain: _____

!

! _____

Investigation #2 !

!

IND # _____ YES /___/ ! NO /___/ Explain: _____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !

!

YES /___/ Explain _____ ! NO /___/ Explain _____

! _____

_____ ! _____

!

_____ ! _____

!

!

Investigation #2 !

!

YES /___/ Explain _____ ! NO /___/ Explain _____

!

_____ ! _____

!

_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

/S/ 11-30-99

Signature Date

Title: Reg. Project manager

/S/ 11-30-99

Signature of Office/ Division Director Date

cc: Original NDA Division File HFD-93 Mary Ann Holovac

APPEARS THIS WAY
ON ORIGINAL

13. PATENT INFORMATION

Product: [redacted] (dexmedetomidine HCl) [redacted]

Patent: US Patent 4,910,214

Expiration date: July 15, 2008

Type of patent: The above patent claims the drug, pharmaceutical compositions of the drug for use in sedation, and a method of sedation by administration of the drug.

Owner of patent: Farmos Yhtyma Oy

Certif [redacted]

[redacted]

(name) Gregory W. Steele
(title) Counsel

APPEARS THIS WAY
ON ORIGINAL

14. PATENT CERTIFICATION

The present NDA is being filed pursuant to Section 505(b)(1) of the Act and, therefore, no patent certification under 21 CFR 314.50(l)(1) is required.

(name) Gregory W. Steele
(title) Counsel

APPEARS THIS WAY
ON ORIGINAL

16. DEBARMENT CERTIFICATION

Abbott Laboratories hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

Etropolski

Mila Etropolski, M.D.
Associate Medical Director
Dexmedetomidine Venture

November 11, 1998
Date

APPEARS THIS WAY
ON ORIGINAL

ABBOTT
Hospital Products Division

To: DR. S. SAMANTA

Company: FDA

FAX #: 301-443-7068

Date: 10/25/99

No. of Pages: 8 (including cover page)

From: Dr. Tom Willer
Regulatory Affairs

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

ABBOTT

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

October 27, 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

ATTENTION: Cynthia McCormick, M.D.
Director

Via Fax 301-443-7068
(Paper Copy Via Mail)

Re: NDA 21-038 Dexmedetomidine Hydrochloride Injection

Abbott Laboratories hereby amends the above-referenced new drug application for the subject drug. We are following up on our response to a teleconference request on October 19, 1999 between Drs. Freeland, R. Rapapport, P. Hartwell, and S. Samanta, FDA, and Ms. R. Tiehen and Dr. T. Willer, Abbott Laboratories. Dr. Samanta faxed us on October 20, 1999, a proposed chart for organizational purposes. The Agency had requested additional elaboration on the extent of exposure information in the Integrated Safety Summary. We have assembled the requested treatment with dexmedetomidine information. Please see Exhibit I.

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: WILLETF@hpd.abbott.com

10-99f.tfw/127
Attachment

EXHIBIT I

ADDITIONAL INFORMATION ON

PATIENT EXPOSURE TO DEXMEDETOMIDINE

3

As requested at a teleconference between ..... on ..... the following tables are provided:

Exhibit 1: All Treated Dexmedetomidine Subjects in Phase I Continuous Infusion Studies/Table of Duration (hours) by Dose (mcg/kg)
Exhibit 2: All Treated Dexmedetomidine Subjects in Phase I Rapid Infusion Studies/Table of Duration (hrs) by Dose (mcg/kg)
Exhibit 3: All Treated Dexmedetomidine Subjects in Phase I Intramuscular Studies/Table of Doses (mcg/kg)
Exhibit 4: All Treated Dexmedetomidine Patients in Phase II/III Continuous Infusion Studies/Table of Duration (hrs) by Dose (mcg/kg)
Exhibit 5: All Treated Dexmedetomidine Patients in Phase II/III Rapid Infusion Studies/Table of Duration (hrs) by Dose (mcg/kg)
Exhibit 6: All Treated Dexmedetomidine Patients in Phase II/III Intramuscular Studies/Table of Doses (mcg/kg)

The tables in Exhibit 1-6 provide further detail for the data provided in tables supplied in the ISS Supplement, Appendix C, Tables 1.1.2, 1.2.2, 1.3.2, 2.1.2, 2.2.2.1, and 2.3.2, submitted on 08/16/99, respectively.

TABLE OF DURATION BY DOSE

DURATION / DOSE	0-2	>2-4	>4-6	>6-8	>8-10	>10-12	>18	Total
0-2	66	7	0	0	0	0	0	73
>2-4	13	3	1	3	0	2	0	22
>4-6	0	7	0	0	0	0	2	9
>6-8	0	10	0	0	0	0	0	10
>8-10	1	7	0	0	0	0	0	8
>10-12	0	4	5	1	0	0	0	10
>12-14	0	3	3	0	0	0	0	6
>18-20	0	1	3	0	0	0	0	4
>20-22	0	0	12	0	0	0	0	12
>22-24	0	0	7	0	6	0	6	19
>24	0	0	1	0	0	0	0	1
Total	80	42	32	4	6	2	8	174

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TABLE OF DURATION BY DOSE

DURATION	DOSE			
Frequency	0-0.5	>0.5-1.5	>1.5-2	Total
0-0.05	12	6	10	28
>0.05-0.10	0	6	16	22
>0.15-0.20	6	106	5	117
Total	18	118	31	167

DOSE	Frequency	Cumulative Frequency
0-2	22	22
>2-4	6	28
>8-10	8	36

TABLE OF DURATION BY DOSE

DURATION DOSE

Frequency	0-2	>2-4	>4-6	>6-8	>8-10	>10-12	>12-14	>14-16	>16-18	Total
0-2	151	12	1	0	0	0	0	0	0	164
>2-4	92	41	1	1	0	0	0	0	0	135
>4-6	57	195	1	0	0	0	0	0	0	253
>6-8	24	41	5	0	0	0	0	0	0	70
>8-10	24	35	17	0	0	0	0	0	0	76
>10-12	0	66	94	29	9	0	0	0	0	198
>12-14	0	32	42	55	33	5	0	0	0	187
>14-16	0	28	30	36	5	9	1	0	0	109
>16-28	1	19	27	32	10	4	5	0	0	98
>18-20	0	5	15	20	11	14	4	0	0	69
>20-22	1	1	9	13	5	1	2	4	0	36
>22-24	0	1	5	12	7	14	11	9	7	66
>24-26	0	1	0	3	2	0	2	0	0	8
>26-38	0	0	0	0	1	0	0	0	0	1
>28-30	0	0	0	0	1	0	0	0	0	1
>38-40	0	0	1	1	0	0	0	0	0	2
Total	350	477	268	202	84	47	25	13	7	1473

TABLE OF DURATION BY DOSE

DURATION / DOSE				
Frequency	>0.5-1	>1-1.5	>1.5-2	Total
0-0.05	7	4	67	78
>0.05-0.10	21	0	2	23
>0.10-0.15	2	0	2	4
>0.15-0.20	0	0	1	1
Total	30	4	72	106

DOSE	Frequency	Cumulative Frequency
0-0.5	15	15
>0.5-1	196	211
>1-1.5	32	243
>1.5-2	28	271
>2-2.5	391	662

FAX
TRANSMISSION

DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
5600 Fishers Lane
HFD-170, Rm. 9B-45
Rockville, Maryland 20857
Office: 301-827-7410
Fax: 301-480-8682/301-443-7068

To: DR. TOM WILLER

Date: 10-20-99

Fax #: 847-938-7867

Pages: 2 (INCLUDING THIS COVER SHEET)

From: DR. Susmita Gamanta

Subject: NDA 21-038

Comments: Attached is the format for dose/duration count.

PLEASE CALL (301) 827-7410 IF RE-TRANSMISSION IS NECESSARY

Example Only

these dose ranges are examples only. Should be at least this range.

Duration (Hours)*	Dose (mcg/kg)					
	<5	5-10	10-15	15-20	20-25	>25
<1						
1						
2						
3						
4						
5						
6						
7						
8						
9						
10			23			
11						
12						
13						
14						
15						
16						
17						
18						
19						
20						
21						
22						
23						
24						
>24						

*please explain handling of hourly increments

Each open space in grid filled with exact number of patients corresponding to that category, i.e. 23 patients receiving 10-15 mcg/kg total dose for 10 hours

Construct separate table for each route of administration for both Phase 1 and Phase 2/3 studies

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ABBOTT
Hospital Products Division

To: DR. S. SAMANTA

Company: FDA

FAX #: 301-443-2068

Date: 10/19/99

No. of Pages: 3 (including cover page)

From: Dr. Tom Willer
Regulatory Affairs

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

ABBOTT

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

October 19, 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

Via Fax 301-443-7068
(Paper Copy Via Mail)

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 a teleconference request on October 19, 1999 between Drs. Freeland, R. Rapapport, P. Hartwell, and S. Samanta, FDA, and Ms. R. Tiehen and Dr. T. Willer, Abbott Laboratories. The Agency requested additional elaboration on the extent of exposure information in the Integrated Safety Summary. We propose: Provide scatter plots of Exposure (mcg/kg) vs. Duration (hours) for dexmedetomidine patients (see attached Exhibit I of scatter plot -only 5 patients plotted on this example) for each route of administration: Continuous Infusion, Rapid Infusion, and IM Administration, for both Phase I and Phase II / III studies. Additionally, we can attach the data listings, which include the duration and total dose for each patient. We should be able to provide this within two days.

We have reviewed the Agency's request and request guidance before we initiate efforts to respond. We trust that this submission is complete. We await your expeditious review and will immediately commence work on the response upon your comments. Please telephone with your comments. If I do not immediately answer my telephone, please touch "0" for one of our staff to take your message.

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: WILLETF@hpd.abbott.com

TFW:tw

g:10-99f.tfw/33
Attachment

EXHIBIT I

EXTENT OF EXPOSURE – PHASE I CONTINUOUS INFUSION

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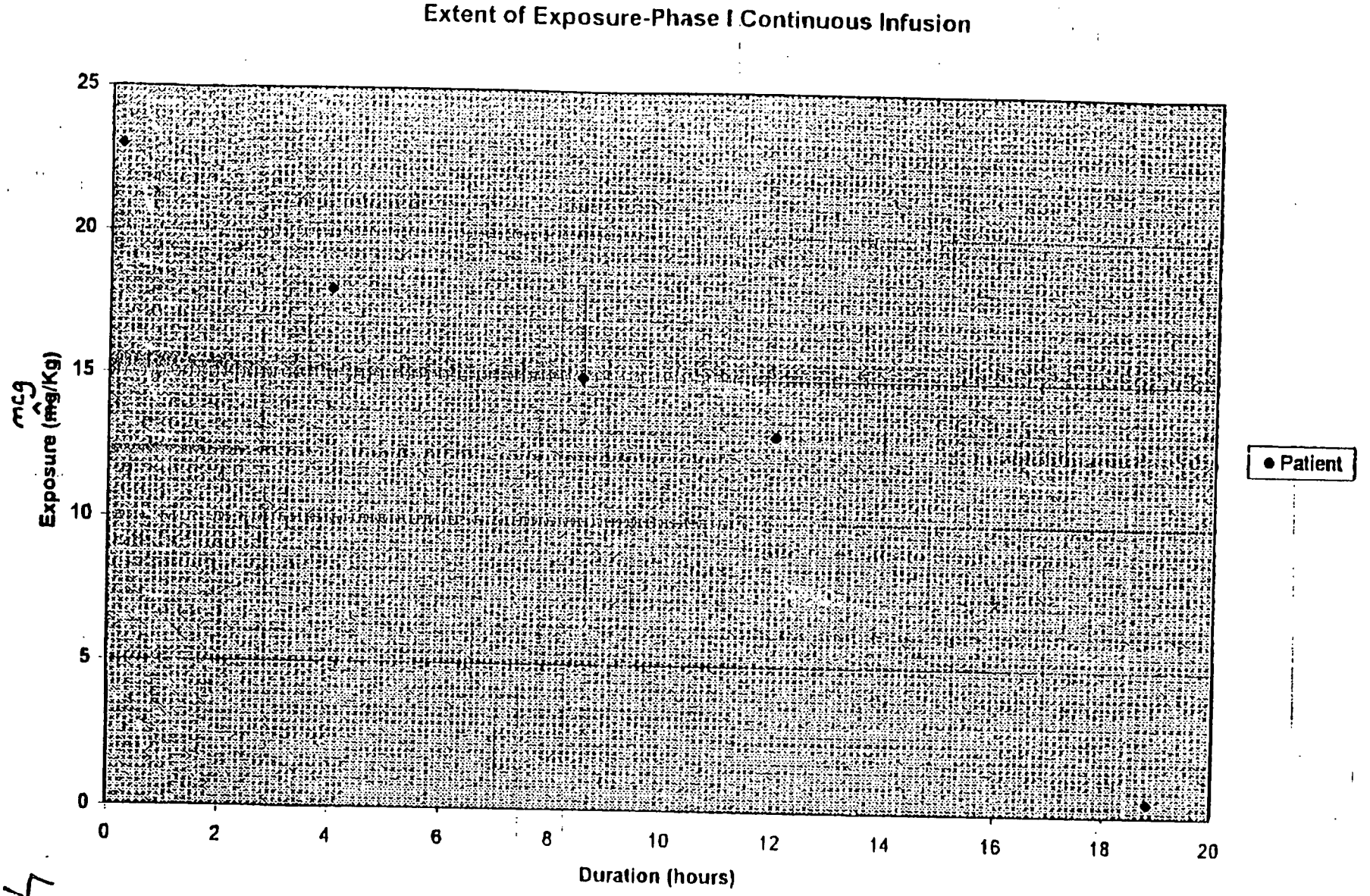
SAMPLE SCATTER PLOT



4

ABBOTT
Hospital Products Division

Hi - Well - I am finally back in the office. You will have the paper copy on Monday. TOM

To: DR S SAMANTA

Company: FDA

FAX #: 301-480-8682

Date: 10/8/98

No. of Pages: 6 (including cover page)

From: Dr. Tom Willer
Regulatory Affairs

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

ABBOTT

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

October 8, 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

Via FAX 301-480-8682
(Paper Copy via Mail)

Re: NDA 21-038 Dexmedetomidine Hydrochloride Injection

Abbott Laboratories hereby amends the above-referenced new drug application for the subject drug product. We are responding to an Agency telephone request on October 4, 1999 from Dr. S. Samanta, Program Manager, and Dr. P. Hartwell, Medical Reviewer, and Dr. Thomas Willer, Abbott Laboratories. We have previously responded on October 5, 1999. The information herein addresses these requests:

1. Provide a table of deaths by group: number of deaths in dex group, number of deaths in placebo group, and number of deaths in active control group.
2. Provide break out of deaths by Abbott, Orion, and total.
3. Provide break out by Phase I, II, or III.

We provide the requested patient information in Exhibit I. Please see spreadsheet one, which answers all three of the Agency's questions. In addition, we also provide a second spreadsheet in Exhibit II. As supplemental information, this is spreadsheet breaks down deaths by study.

If you have any questions, please do not hesitate to call.

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: WILLETF@hpd.abbott.com

TFW:tw

g:10-99f.tfw/21
Attachment

EXHIBIT I

SUMMARY OF PATIENT DEATHS

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

Number of Deaths

		By Treatment				Total
		Dex	Placebo	Active Control	None*	
Phase I						
	Abbott	0	0	0	0	0
	Orion	0	0	0	0	0
	Total	0	0	0	0	0
Phase II						
	Abbott	7	1	0	0	8
	Orion	1	2	0	0	3
	Total	8	3	0	0	11
Phase III						
	Abbott	15	16	0	4	35
	Orion	0	1	0	0	1
	Total	15	17	0	4	36
Phases I, II, III						
	Abbott	22	17	0	4	43
	Orion	1	3	0	0	4
	Total	23	20	0	4	47
Academic**		2	0	0	0	2

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

** Academic study is GBNI99-102; an ongoing study

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EXHIBIT II

ADDITIONAL PATIENT DEATH INFORMATION

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ON ORIGINAL