CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number 020615

Trade Name DURACLON 0.1mg/ml Injection

Generic Name Clonidine Injection

Sponsor Fujisawa

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

OCT 2 [illegible]

NDA 20-615

Fujisawa USA, Inc.
3 Parkway North, 3rd Floor
Deerfield, Illinois 60015-2548

Attention: Jerry D. Johnson, Ph.D.
Vice President, Regulatory Affairs

Dear Dr. Johnson:

Please refer to your August 8, 1995 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Duraclon™ (clonidine HCl), 0.1 mg/mL, Injection.

We acknowledge receipt of your ten amendments noted on page 3.

This new drug application provides for continuous epidural administration as adjunctive therapy with intraspinal opiates for the treatment of pain in cancer patients, tolerant to, or unresponsive to, intraspinal opiates alone.

We have completed the review of this application including the submitted draft labeling and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed draft labeling. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed draft labeling. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit sixteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-615. Approval of this labeling by FDA is not required before it is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

We remind you of your Phase 4 commitments specified in your submission dated August 30, 1996. These commitments, along with any completion dates agreed upon, are listed below.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to HFD-170 and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and
Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Millie Wright
Project Manager
(301) 443-4250

Sincerely yours,

Curtis Wright, M.D., M.P.H.
Acting Division Director
Division of Anesthetic, Critical Care
and Addiction Drug Products, HFD-170
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure: Draft Labeling

EXCLUSIVITY SUMMARY FOR NDA # 20--615 SUPPL OCT 11 1996

Trade Name: DURACLON Generic Name: clonidine hcl injection

Applicant Name: Fujisawa USA, Inc. HFD # 170

Approval Date:

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 /_X__/

   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.

   _____N/A_____

   _____

   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.

Form OGD-011347 Revised 8/7/95

cc: Original NDA 20-615 Division File/HFD-170 HFD-85 Mary Ann Holovac
HFD-170/M.Wright

d) Did the applicant request exclusivity?

YES /_X__/ NO /___/

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

7 (Sponsor granted orphan drug status 1/24/89/#88343)

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?

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)

N/A

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 /___/

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

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.)

N/A YES /___/ NO /___/

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

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**

**This is a new route of administration for clonidine HCL and has been granted orphan drug status

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 /X_ / 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.

For the purposes of this section, studies comparing two products with the same ingredients(s) are considered to be bioavailabilty studies.

(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 /_X__/ 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 /_X__/ 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 /_X__/

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 /__X_/

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:

Investigation #1, Study EC-001

_____

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 /_X__/

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:

NDA#_____ Study #_____

NDA#_____ Study #_____

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 /_X__/

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:

NDA#_____ Study #_____

NDA#_____ Study # _____

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"):

Investigation #___1_____, Study #_EC-001_____

Investigation # _____, Study #_____

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 /_X__/ 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 N/A

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 /_X__/

If yes, explain: _____

_____

Millie Wright
Signature

10/11/96
Date

Title: Project Manager

Curtis Wright
Signature of Office/
Division Director

10/11/96
Date

cc: Original NDA 20-615 Division File/HFD-170 HFD-85 Mary Ann Holovac
HFD-170/M.Wright

PATENT CERTIFICATION

Fujisawa USA Incorporated is the sponsor of the Orphan Drug Application for clonidine hydrochloride for epidural administration. The designated indication is for continuous epidural administration as adjunctive therapy with intraspinal opiates for the treatment of pain in cancer patients tolerant to, or unresponsive to, intraspinal opiates alone.

Fujisawa USA, Inc. does not have a partner or licensee for the development of clonidine hydrochloride for epidural administration, and there are no current U.S. patents on clonidine hydrochloride for epidural administration.

Jerry D. Johnson

Jerry D. Johnson, Ph.D.

July 21, 1995

Date

PATENT AND EXCLUSIVITY INFORMATION

There are no current US patents on clonidine hydrochloride for epidural administration. Approval of Orphan Drug Status for clonidine hydrochloride for epidural administration was received on January 24, 1989 under IND

This IND was transferred to the Sponsor (Fujisawa Pharmaceutical Company, a division of Fujisawa USA, Inc., Deerfield, Illinois) of this application on April 6, 1990, The Sponsor, therefore, requests marketing exclusivity for 7 years post-NDA approval.

Dennis Drehkoff

Dennis Drehkoff **Date** 11-17-94
Patent Counsel

JUL 29 1996

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 20-615 Trade (generic) names DURACLON (clonidine hcl inject)

Check any of the following that apply and explain, as necessary, on the next page:

____ 1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.

____ 2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.

____ a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.

____ b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)

✓ 3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).

____ a. The applicant has committed to doing such studies as will be required.

____ (1) Studies are ongoing.
____ (2) Protocols have been submitted and approved.
____ (3) Protocols have been submitted and are under review.
____ (4) If no protocol has been submitted, on the next page explain the status of discussions.

____ b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

____ 4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

____ 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items: _____

We have not yet discussed plans for commitments, including pediatric trials, with Sponsor

Signature of Preparer

7/29/96.
Date

cc: Orig NDA
HFD-___/Div File
NDA Action Package

Department of Health and Human Services Public Health Service

Division of Anesthetic, Critical Care and Addiction Drugs

Review of Pediatric Experience with Clonidine

NDA	~~20,076~~ 20615 LB 9/4/96
REVIEW DATE:	September 3, 1996
CSO:	M. Wright
REVIEWER:	Lillian Burke, M.D.
SECONDARY REVIEWER:	Curtis Wright, M.D.

Use of Clonidine in Children

This review summarizes the available information relating to clonidine and the use of clonidine in children[1]. Oral and transdermal clonidine have been used in children for various conditions including hypertension and attention deficit disorder[1]. The literature on the use of clonidine is limited. Based on these limited reports, the side effect profile and efficacy of clonidine in general, and of epidural clonidine in particular, appear to be similar in children and in adults.

Use of Epidural Clonidine in Pediatric Patients

Pediatric subjects were not included in the pivotal trial for the use of clonidine in patients with refractory cancer pain. The only reported use of epidural clonidine in children is the short-term use for analgesia during and after surgery. As in adults, analgesia is prolonged by the addition of clonidine to bupivacaine. Decreases in blood pressure and heart rates were noted, and mild respiratory depression was also seen. These surgical studies are summarized below.

Clonidine, 2 μg/kg, added to bupivacaine for intraoperative anesthesia, prolonged analgesia and decreased the use of other medications in 23 patients who were undergoing orthopedic surgery[2]. No further decreases in blood pressure or heart rates were seen as compared to bupivacaine

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[1] It is based on the manufacturer's articles submitted for the NDA, and searches of Medline and Sedbase. Comprehensive searches have not been rechecked due to the unavailability of the searching facilities on this date (September 3, 1996)

alone. Sedation was prolonged from 5.8±1.5 hours to 8.4±5.8 hours. Similarly, 2 μg of clonidine added to bupivacaine, provided adequate analgesia following hernia surgery in eight patients[3]. Clonidine 5 μg, added to bupivacaine, produced analgesia and was well tolerated in thirty patients who received it for postoperative analgesia[4].

In another study, 45 patients, 1 to 7 years old, received bupivacaine via caudal block with light general anesthesia for surgical anesthesia during hernia repair or urological surgery[5]. In these patients, pain scores and the number of patients requiring additional analgesia was reduced and the duration of analgesia was increased with clonidine. Clonidine did not increase sedation or cause respiratory depression.

Use of Epidural Clonidine in Pediatric Patients[2]

Sponsor #	First Author; yr	type study	dose/route	Total subjects	Clonidine subjects	Ages	Outcome
#58	Lee; 94	randomized; active control	2 μg/kg with bupivacaine	46	23	1 to 10 yrs	Blood pressure and respiratory effects were similar to those seen in adults.
#59	Jamali; 94	randomized, active control; caudal block during orthopedic surgery	1 μg/kg with bupivacaine	45	15	1 to 7 years	Clonidine decreased the number of subjects requiring additional analgesia and increased the duration of analgesia from 460±439 minutes to 987±573 minutes ($p<0.001$). Mild sedation, respiratory depression and sedation were seen.
#60	Klimscha	randomized, active control	2 μg/kg with bupivacaine	24	8	*	Hemodynamic parameters were reported to be less than those seen in adults at the equivalent doses. Pain relief was prolonged.
#61	Motsch; 93	randomized, active control	5 μg/kg with bupivacaine	45	30	4 to 8 yrs	Heart rate and blood pressure were lower in the clonidine group, but this effect did not occur until after emergence from anesthesia
	Totals			160	76		

Fetal Exposure

Several published studies document the use of clonidine during labor and delivery with intra partum exposure of at least 222 infants (see below). The condition of the infant is not always specifically documented. However, there is an absence of reports of a negative effect in infants for this short-term use. Given the extent of the exposure this indicates that if there are side

[2] Only short-term use during surgery has been reported.

effects peculiar to infants, they are uncommon or rare. Hypotension and mild respiratory depression may be seen in the mothers and these effects may potentially affect the fetus.

One case-controlled study looked at the effects of intrauterine long-term clonidine exposure on behavior. Restless sleep appeared to be more common in children who had been exposed to clonidine before birth (N=22) than in those not so exposed (N=21). Ten of 10 children whose mothers received more than 300 µg clonidine per day had sleep disorders as compared to approximately one third of those whose mothers received lower doses.

Effect on Infant When Clonidine Used for Obstetrical Anesthesia

Spons or Ref#	First Author;yr	type study	dose/route (if not epidural)	Total subjects	Clonidine subjects	Outcome
#9	Mendez; 90	randomized, placebo-control	400 to 800 µg ep +10 to 20 µg/hr	60	40	No mention of infant outcomes
#10	Huntoon; 92	rnadomized, active control	400 or 800 with bupivacaine or chloroprocaine	63	40	No mention of infant outcomes
#35	Cigarini; 92	randomized, active control	75 µg with bupivacaine	48	12	Fetal heart rate ("Krebs" score), "Apgar" score were the same. No changes were noted in infant glucose levels.
#36	Brichant; 94	randomized, active control	37.5, 75 or 150 µg with bupivacaine	60	45	Fetal heart rates were monitored and no ill effects were reported.
#37	O'Meara; 93	randomized, active control	120 µg	42	20	No specific mention of infant outcomes
#38	Le Polain; 93	randomized, active control	30 µg with bup + epi+sufen	50	25	No specific mention of infant outcomes
#45	Capogna; 95	randomized, placebo-controlled	75 or 150 µg; repeated prn (75 to 450 µg)	60	40	No specific mention of an infant outcome
	Totals			383	222	

Adverse Events Reported in Children

A comprehensive review of the literature of clonidine poisoning[6] in 146 children reported only the expected side effects including: depressed consciousness (86%), bradycardia (29%), hypotension (23%), respiratory depression (20%), miosis (19%), and hypertension (4%). Fifty-

five per cent of 11 subjects in whom temperature was reported were noted to be mildly hypothermic.

Bradycardia is consistently seen with therapeutic doses of epidural clonidine[7]. Clonidine slows conduction in the sinoatrial node and this effect responds to treatment with atropine. Cardiac arrhythmias including sinoatrial block and PVCs have been reported in both children and adults[8]. These conduction abnormalities resolve spontaneously with treatment.

Sudden death was reported in three children taking clonidine[9]. In each of these cases, there was no clear relationship to clonidine use. An eight-year-old child taking methylphenidate and clonidine vomited and died, but neither clonidine nor methylphenidate was detected in his blood therefore the relationship between clonidine and this death seems unlikely. A 7-year-old boy on these same medications died unexpectedly and an autopsy revealed extensive myocardial fibrotic scarring. This death was most probably due to an underlying congenital abnormality or was the sequelae of a previous, undiagnosed myocarditis. Another child taking clonidine died with seizures and had evidence for an intentional overdose of fluoxetine.

Respiratory depression requiring ventilatory support has been reported[10]. Other effects reported in children include seizures[11], hypoglycemia with seizures in a child with hypopituitarism[12], and exacerbation of self-injurious behavior[13] or tics[14] in children with La Tourette's disorder.

Pharmacokinetics

No specific information on pharmacokinetics in children is available in the literature submitted, nor is this information available in the pharmacokinetics review written by John Hunt, Ph.D. The pharmacokinetics of clonidine in children do not appear to have been studied.

Chemistry

Extremely small amounts of 2-,6- dichloroaniline are present in the final product and result from the production of clonidine. This compound is related to aniline, a known carcinogen. The mutagenic capability of 2-,6-dichloroaniline has not been well studied. Its 2-chloro structure tends to pull electrons from the phenyl ring and makes this compound less likely to be mutagenic than is aniline. The highest possible daily dose is many orders of magnitude less than that shown to cause mutagenesis. Based on these considerations, this contaminant is not likely to be of concern in patients in the target population, namely patients with refractory cancer pain. Nor is it likely to be a risk for patients who occasionally receive it off-label during surgery or for another short-term use. Long-term epidural high-dose use in a child could be of concern but such use would rarely, if ever, occur.

Summary

The use of epidural clonidine has been reported in 76 pediatric patients. These subjects exhibited approximately the same efficacy and side effects as those reported for adults. Hypotension, bradycardia and sedation are the most common side effects. One report suggested that the side effects in children were less than those seen in adults at equivalent doses[3]. The published literature documents that at least 222 infants were exposed to clonidine during labor and delivery. No adverse effects were reported in these infants although the status of the infants was not always systematically studied. In children there is evidence for prolongation of postoperative analgesia when epidural clonidine is used in conjunction with bupivacaine similar to that seen in adults. Cardiac arrhythmias have been reported in both children and adults. Although there have been reports of sudden death in children taking clonidine, the relationship of clonidine to these deaths is unclear and other possible etiologies for these deaths appear more likely. There is one report, a case-control study, suggesting that children who are exposed to long-term clonidine therapy *in utero* may be more likely to develop sleep disorders. This reviewer is unaware of any data on the pharmacokinetics of clonidine in children.

Conclusion

Review of the available literature suggests that epidural clonidine should not pose an unwarranted risk in children, especially for those with refractory cancer pain.

Addendum

Summary of References submitted with the NDA related to the use of epidural clonidine in children.

Ref #;Citation	**#58; Lee JJ, Rubin AP. Comparison of a bupvacaine-clonidine mixture with plain bupivacaine for caudal analgesia in children. Br J of Anaesthesia (1994) 72:258-262.**
Design:	Randomized, double-blind study of 46 children who received intraoperative caudal anesthesia during orthopedic surgery. **B: Bupivacaine 0.5% 1 ml/kg** **BC: Same + clonidine 2 µg/kg**
Efficacy Results: Pain relief:	Pain score based on criteria of Hannallah et al. (Crying, arterial pressure, movement, agitation and localization of pain. Given medication when pain score >4 on scale of 10.
Reduction in use of other medications:	Number of administrations of additional medication: 4 hours: B: 4, BC: 0 12 hours: B: 34, BC: 13 24 hours: B: 66, BC: 35
Safety Results: Blood pressure effects and fluid management:	Pre-op / Decrease / Time B: 81±4 / 19.2±6.3 / 44±5 BC: 82±3 / 19.6±8.2 / 70±9
Bradycardia:	Pre-op / Decrease / Time B: 103±10 / 22±2 / 71±10 BC: 106±13 / 19±3 / 83±9
Respiratory Depression:	No respiratory rates of <16 or S_pO_2<95% were noted.
Sedation:	Duration of sedation: B: 5.8 hours±1.5 BC: 8.4 hours±5.8
Other adverse events:	Vomiting / Urinary retention B: 13/23 / 1/13 BC: 11/23 / 0/13
Conclusions:	The addition of clonidine 2 µg/kg to bupivacaine prolonged analgesia in pediatric patients following orthopedic surgery. Side effects were not increased.

Ref #;Citation	**#59; Jamali SM, Monin S, Begon C, Dubousset A, Ecoffey C. Clonidine in pediatric caudal anesthesia. Anaesth Analg (1994) 78:663-6.**

Design: 45 patients , 1 to 7 years old, received bupivacaine via caudal block with light general anesthesia for surgical anesthesia during hernia repair or urological surgery.
B: Bupivacaine 0.25%, 1 ml/kg
BC: Same + clonidine 1 µg/kg
BE: bupivacaine + epinephrine 1/200,000

Efficacy Results:
Pain relief: Maximum objective pain scores:
B: 3.4±1.8 BC: 2.3±1.6 ($p<0.05$) BE: 3.4±1.4

Reduction in use of other medications: Patients requiring no additional analgesia:
B: 2/15 BC: 8/15 ($p<0.05$) BE: 1/15

Prolongation of analgesia: Duration of Analgesia (min):
B: 460±439 BC: 987±573 ($p<0.01$) BE: 377±341

Safety Results:
Blood pressure effects and fluid management: Systolic arterial pressure was lower in the BC group than in the B group, but did not differ from the BE group.

HR decreased by equivalent amounts in all groups.

Respiratory Depression:

	Resp Rate	Low S_pO_2	Oxygen required
B:	23(19-37)	97(94-100)	3/15
BC:	23(17-36)	97(94-99)	2/15
BE:	27(19-36)	97(95-99)	2/15

Sedation: Duration of Sleep in Recovery Room
B: 31±44 min BC: 36±47 min BE: 19±28 min

Nausea/ vomiting: 1/15 in BC and 1/15 in B groups.

Conclusions: 1. Clonidine, 1 µg/kg, added to bupivacaine, decreased the pain scores and prolonged analgesia. 2. Side effects were not significantly increased.

Ref #:Citation **#60; Klimscha W, Sauberer A, Lerche A, Langenecker S, Semsroth M. Caudal block with clonidine provides prolonged analgesia after ambulatory hernia repair in children.**

Design: 24 children, (N=8 in each group) were given the study medications following inguinal hernia repair:
B: Bupivaine 0.25%, 0.75 mg/kg
BC: Bupivaine + clonidine 2 µg/kg
BE: Bupivaine + epinephrine 3.75 µg/kg

Efficacy Results:
Pain relief: Parameters recorded every 15 minutes for 5 hours
Pain relief better in BC group than in B or BE
Analgesia "prolonged"

Safety Results:	
Blood pressure effects and fluid management:	Hemodynamic parameters "stable"
Sedation:	Increased sedation in BC group, compared to the others.
Conclusions:	1. The addition of clonidine to bupivacaine improved and prolonged analgesia. 2. Hemodynamic effects were less pronounced than that reported in adults at equivalent doses.

#61;

Ref #;Citation	**#61; Motsch J, Schreckenberger R, Skoberne Th, Böttiger, Bach A, Böhrer, Martin E. Effects of clonidine added to bupivacaine for combined caudal and general anesthesia in children. Regional Anesthesia (1993) 18:31 (Abstract)**
Design:	45 children, aged 4-8 years old, were given study medications following induction of general anesthesia:**N=15 in each group** **B0.1C: 0.1% Bupivacaine 1 ml/kg + clonidine 5 µg/kg** B0.175C: 0.175% Bupivacaine 1 ml/kg + clonidine **5 µg/kg** **B: 0.175% Bupivacaine 1 ml/kg**
Efficacy Results:	
Pain relief:	Pain relief (as measured by Tramadol by patient-controlled analgesia (PCA)) and duration of analgesia were significantly better in B0.175C than in B or B0.1C groups.
Safety Results:	During the postoperative period, blood pressure and HR were significantly lower in the subjects who received clonidine. However, there were no differences noted during anesthesia.
Conclusions:	1. Addition of clonidine 5 µg/kg to bupivacaine enhanced analgesia and prolonged its duration in children aged 4-8 years old. 2. BP and HR were decreased by the addition of clonidine, but this effect did not occur until the emergence from anesthesia.

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SEP 4 1996

Office of Drug Evaluation III
Room 13B45 Parklawn

CDE III

phone 301-827-3144
fax 301-480-3761

DATE: August 8, 1996

TO: Acting Director
Division of Anesthetic, Critical Care, and Addiction Drug Products

FROM: Acting Director
Office of Drug Evaluation III

SUBJECT: NDA 20,615. epidural clonidine HCl injection [Duraclon]
Fujisawa

Neuropathic vs. visceral/somatic pain

The conclusion that epidural clonidine is an effective analgesic, in cancer patients with pain resistant to morphine, only in the subgroup with neuropathic pain and not with visceral or somatic pain is not supported by enough evidence. I am not willing to conclude, based on the present evidence, that epidural clonidine should not be used in patients with visceral or somatic pain.

Reasons follow. I am not suggesting that these points be addressed in a review or the trial further evaluated. I am simply trying to articulate reasons why the present study alone is for me insufficient for differential findings in patients with different kinds of pain. The data base for this orphan disorder is tiny and the present study is sufficient for marketing approval. We are talking about the labeling, not the approval itself.

Findings from the single clinical trial available have not been confirmed in another trial.

The number of patients on which the finding rests is very small.

No assessment has been made of the adequacy of criteria used in the trial for neuropathic and non-neuropathic pains and no assessment has been made of the validity of the diagnosis in each patient. Neither the sponsor's summary of effectiveness nor FDA reviews discuss these problems of diagnosis. Misclassification of few patients would vitiate [or strengthen markedly] the conclusions reached about effectiveness in patients in the 2 pain subgroups.

The finding of effectiveness in patients only with neuropathic pain could actually be a finding of effectiveness in patients with more severe pain. The group of patients with neuropathic pain had more pain as judged from mean morphine use at baseline. [This isn't a very good measure of pain severity in this trial, but it's all I could do with the data I had.] I didn't find assessment in reviews of the relationship between effectiveness and severity of pain. Maybe it can't be done. ..... The FDA statistician's analysis which eliminated some patients with low morphine use or pain scores doesn't do the trick because it eliminated a couple of patients [espec. one] with substantial morphine use but no pain on morphine. These patients may not have met protocol criteria but may well have had substantial pain without morphine.

Effectiveness rests on a comparison of a patient's VAS or morphine use during baseline with these measures on treatment [or placebo]. A morphine titration period ranged between 1-7 days, and baseline was, as best I can tell, then taken as the day before patients were begun on active drug or placebo. It's not clear whether titration as short as one day is reliable, or what actual titration times were in each patient, or whether titration times ended up balanced in the various sets of patients.

5 clonidine patients and 2 placebo patients received radiation or chemo near the beginning of the trial--more patients in the clondine group that in placebo. Were their results included, and which type of pain did they have? If the 5 clonidine patients were wrongly considered clonidine responders and happened to have had neuropathic pain, they might have skewed the trial results in favor of patients with neuropathic pain.

Labeling

I'd prefer labeling to say that the drug is recommended:

in combination with opiates for the treatment of pain not adequately relieved by opiates alone in cancer patients. Epidural clonidine is more likely to be effective in patients with neuropathic pain than with somatic or visceral pain.

I recommend that the box warning be changed to:

...is not recommended for obstetrical, post partum, or peri-operative pain management. Hemodynamic instability, especially hypotension and bradycardia, from epidural clonidine is expected to be unacceptably high in these patients. In a rare patient, potential benefits may outweigh the serious risks.

I've left changes to you, and I'll revisit after you've made them.

I'm happy to discuss further.

Paula Botstein MD

Paula Botstein M.D.

cc:
NDA 20-615
HFD 170/MO/Scheinbaum/Barbera, Cerney, Randall
HFD 170/CSO/MWright
HFD ~~170/statistician~~ HFD-550/Leung
HFD 103/Collier
HFD 103/clonidine file
HFD 103/chron
HFD 103/sig
HFD-170/ Dio File

JUN 24 1996

MEDICAL OFFICER REVIEW
DIVISION OF ANESTHETIC, CRITICAL CARE & ADDICTION DRUG PRODUCTS

NDA#: 20,615 Orphan Drug Designation No. 88-80-343-6
NAME: Epidural Clonidine HCl for the Treatment of Pain Associated with Advanced Cancer
APPLICANT: Fujisawa USA **SUBMISSION DATE:** 7/95
REVIEWER: Monte L. Scheinbaum, Ph.D., MD, Medical Officer
PEER REVIEWER: Robert Bedford, MD **CSO:** Mildred Wright
DATE: 6/6/96

EFFICACY REVIEW OF EPIDURAL CLONIDINE

E-I. PIVOTAL STUDY EC-001

A. PLAN OF THE STUDY

1.OBJECTIVES: The objectives of the pivotal study were to evaluate the analgesic efficacy and clinical safety of epidurally administered clonidine compared to epidurally administered placebo in the treatment of intractable cancer pain.

2. DESIGN: The pivotal efficacy study for this NDA (EC-001 carried out under was a randomized, double-blind, placebo-controlled, multicenter (21 sites), 2-week trial of continuously infused epidural clonidine in advanced cancer patients with intractable pain (38 of 85 patients received clonidine). The study was divided into three periods: Morphine titration (one to seven days), study treatment administration (15 days) and washout (three days). Following the titration period with epidural morphine by patient-controlled analgesia (PCA), patients were randomized to a continuous epidural infusion of clonidine or placebo for 14 days as an add-on treatment to the titrated morphine dose. Randomization included stratification to one of four strata based on previous use of epidural narcotics (yes/no) and type of pain, i.e., primarily neuropathic or primarily nonneuropathic (somatic and/or visceral). Neuropathic pain is characterized by burning, shooting, electrical-like pain in a dermatomal or peripheral nerve distribution.

There was also a long-term extension associated with this trial (35 patients) which is discussed in section E-II.

3. SITES: **The principal investigator was James Eisenach, MD, of Bowman Gray School of Medicine (Winston Salem NC). Other investigators were: Robert Finnegan, MD (Houston TX); David Bryce, MD (Marshfield WI); Dermot Chamberlain, MD and Stuart Dupen, MD (Seattle WA); Richard Payne, MD (Cincinnati OH); Rafael Miguel, MD (Tampa FL); Ronald Kaplan, MD (Bronx NY); Luke Kitahata, MD (New Haven CT); Michel DuBois, MD (Washington DC); W. David Leak, MD (Westerville OH); Yasin Khan, MD (Allentown PA); Jonathon Skerman, DSc (Shreveport LA); Robin Slover, MD (Denver CO); Charles Hantler, MD (San Antonio TX); Gerald A. Burger, MD (San Diego CA); Richard Shildt, MD (Tulsa, OK); Richard Docherty, MD (Huntington Beach CA); Steven M. Rosen, MD (Philadelphia PA); Mark Lema, MD, PhD (Buffalo NY), and V. Lee, MD (Charlottesville VA).**

4. POPULATION: Patients eligible for participation were to have cancer with severe intractable pain located below the C4 dermatome, severe intractable pain being defined as severe pain not relieved by large doses of opiates (equivalent to 100 mg morphine/day systemically or 20 mg/day epidurally), or severe pain in individuals intolerant of opiates due to therapy-limiting adverse events. Patients were to be eighteen years of age or older, have a life expectancy beyond the 18 study days, and be willing and able to give informed consent. Pregnancy and lactation were exclusions. Women of childbearing potential were to have a negative pregnancy test at entry and be willing to use oral contraceptives as a method of birth control for the duration of the study and three months afterward. Also excluded were the following: Patients with serum creatinine $>$ 3.5 mg/dl, history of atrioventricular block greater than first degree, hypersensitivity to clonidine, alcoholism or drug abuse, or the presence of psychiatric disease, encephalopathy, emotional or intellectual problems that were likely to limit the validity of consent to participate in this study or, in the opinion of the investigator, would invalidate the data or increase the risk to the patient. Initiation of steroids or non-steroidal anti-inflammatory drugs, less than seven days before the onset of the study were to be excluded. (Patients in whom such drugs were given more than seven days before the onset of the study could be included provided the dose remained constant throughout the study). Use of chemotherapy or radiation therapy within less than 48 hours of randomization was excluded.

5. EPIDURAL MORPHINE TITRATION: During the titration period, epidural morphine usage and pain level as defined by visual analog scores were recorded twice daily. The objective was to switch the patient from alternative morphine dosing to epidural patient-controlled morphine dosing alone. An epidural catheter was inserted and morphine titrated over 1-7 days. For a minimum of 24 hours before randomization, the patient had to be on a single dose of morphine that was triggered by the patient approximately five to 15 times. This dosing schedule had to keep the patient in a pain category of moderate or less. Patients who continued to experience greater than moderate pain with epidural morphine could still be enrolled if no other reasonable analgesic alternative were identified.

6. TREATMENT: Treatment involved continuous infusion of either clonidine at 30 μg/hr or placebo for 14 consecutive days. Clonidine (or placebo), was delivered via an external ambulatory infusion pump (*CADD-1^R pump*). Clonidine hydrochloride, 100 μg/ml in a 10-ml vial, a package of 20 vials per patient, was supplied by Fujisawa Pharmaceutical Company. Matching placebo (0.9% sodium chloride for injection), was also supplied as twenty 10 ml vials per patient. In patients without a previously implanted epidural catheter, and epidural catheter was inserted and attached to an external or subcutaneous injection port. Prior to the study, the epidural location of the catheter was confirmed either by demonstration of appropriate sensory blockade to local anesthetic injection or by epidural injection of a radiopaque contrast medium followed by roentgenographic examination of the catheter site. During the treatment period the only allowable route of morphine administration was by an epidural patient controlled analgesia device (*CADD-PCA® pump*). All patients remained in the hospital for the first 24 hours following the onset of clonidine (or placebo) infusion. During this time, blood pressure, heart rate, temperature, respirations and epidural morphine use were monitored every four hours. Thereafter, inpatients were seen daily during the two-week trial by one of the co-investigators or a research nurse. Outpatients were seen in the clinic by one of the co-investigators at weekly intervals and daily at home by a research nurse during the two-week trial. All patients had access to epidural morphine delivered by ambulatory patient-controlled analgesia (PCA) device (CADD-PCA® pump) set to deliver, on patient demand, the previously titrated dose. The maximal number of doses per day was set to be twice the titrated frequency. The lock-out period between doses was set at 45 minutes. Any changes in morphine dose or lock-out time had to be cleared with the FPC monitor. No morphine was given by continuous infusion, and no oral narcotics were allowed during the study. On study day 15, the study medication was discontinued. Daily observations were continued for three days following end of drug administration. Patients continued to have access to epidural morphine delivered only by an ambulatory PCA device (CADD-PCA® pump).

7. ASSESSMENTS: The primary efficacy parameters, pain level (using a 0-10 cm visual analog scale) and morphine use, were recorded: twice daily during the titration period, every four hours for the first 24 hours following the onset of study drug infusion, and daily during the treatment and 3-day washout periods. The following secondary efficacy parameters were evaluated at the end of the titration period, and at Days 8 and 15 of the treatment period: the Memorial Sloan-Kettering Pain Assessment Card score; pain character according to Arner categories using the short-form McGill Pain Questionnaire; Quality of life and effect of pain on quality of life, using the Spitzer and Eastern Clinical Oncology Group performance scales. Free plasma concentrations of morphine and clonidine were determined from blood samples analyzed by Harris Laboratories.

8. ANALYSIS OF DATA: The study was originally designed to have 90% power to detect a 28% change from baseline in the visual analog score for the clonidine group (assuming no change in the placebo group) and/or a 13% change in morphine use while maintaining an overall two-sided significance level of 0.05. A Bonferroni adjustment for multiple comparisons was to be used for a design involving interim analysis, requiring 120 patients (both arms combined). Evaluability was defined based on completion of at least seven days of drug therapy and the pain characterization for Study Day 8. Prior to the scheduled interim analysis and before breaking the study blind, the original statistical plan was modified in conjunction with FDA reviewers. Modifications to the original design included reliance on an intent to treat approach including all randomized patients regardless of protocol compliance or duration of therapy, and replacing the original sequential design with a single, final analysis of all randomized patients accrued through January, 1993. The primary efficacy analysis was also modified to use treatment success, defined as a decrease in either VAS pain scores or morphine rescue use with no increase in either variable, as the endpoint. Power calculations performed in the fall of 1992 suggested that based on the overall (blinded) frequency of treatment success observed at that time (approximately 25%) and assuming equal distribution of patients into clonidine and placebo treatment arms, a sample size of 80 randomized patients would provide approximately 80% power to detect odds ratios for treatment effects of at least 3.0 at the 5% significance level. Baseline comparability of treatment groups for demographic and prognostic factors were assessed by the sponsor using two-tailed (uncorrected) Chi-square and two-tailed t-tests as appropriate. A Cochran-Mantel-Haenszel Chi-Square test was used to evaluate the differences in the frequency of treatment success between the clonidine and placebo groups after control for previous epidural narcotic use and primary pain mechanism. A Breslow-Day test for homogeneity of odds ratios was calculated to evaluate the consistency of the drug effect across the four combinations of these two variables. The extent of treatment success was also examined based on the combined magnitude of changes from baseline in VAS pain scores and rescue morphine use. Patients were grouped into five categories of treatment success: (1) a 50% reduction in both VAS pain and morphine use, (2) some reduction in both VAS pain and morphine use, without a 50% reduction in both variables, (3) a reduction in either VAS pain or morphine use accompanied by an increase in the other variable, (4) some increase in both VAS pain and morphine use without a 50% increase in both variables, and (5) a 50% increase in both VAS pain and morphine use, and a Mantel-Haenszel Chi-Square statistic test for linear association was used to compare the proportion of patients by treatment arm in categories of increasing extent of success. Logistic regression analyses were used in most of the secondary analyses.

B. RESULTS

1. **Demographics:** All 85 patients enrolled received study medication. There were 38 patients who received clonidine and 47 were randomized to placebo. Table E1 tabulates baseline characteristics. There were no significant baseline differences between clonidine and placebo groups. Table E1a provides a further description of stratified clonidine and placebo patients with respect to prior use of epidural narcotics and primary pain of neuropathic origin.

TABLE E1 BASELINE CHARACTERISTICS

CHARACTERISTIC		CLONIDINE (n=38) n (%)	PLACEBO (n=47) n (%)	TOTAL (n=85) n (%)
Sex	Male	37 (71)	24 (51)	51 (60)
	Female	11 (29)	23 (49)	34 (40)
Race	White	35 (92)	37 (79)	72 (85)
	Black	3 (8)	7 (15)	10 (12)
	Other	0 (0)	3 (6)	3 (4)
Prior Epidural Narcotics		22 (58)	26 (55)	48 (57)
Worst Pain Neuropathic		18 (47)	18 (38)	36 (42)
Distant Metastases		28 (74)	38 (81)	66 (78)
Age(Years)	Mean (S.D.)	56.8 (11.6)	56.4 (11.8)	56.6 (11.6)
	Range			
Weight(kg)	Mean(S.D.)	71.5 (17.2)	68.4 (16.8)	69.8 (17.0)
	Range			
Height(cm)	Mean(S.D.)	173 (11)	169 (10)	171 (11)
	Range			
Total Morphine Usage (mg/24hr)	Mean(S.D.)	133 (155)	124 (149)	128 (151)
	Range			
Time from Cancer Diagnosis (months)	Mean(S.D.)	42 (34)	30 (34)	35 (34)
	Range			

TABLE E1a. Distribution of Patients into Baseline Strata
Table Entry: # of clonidine patients + # of Placebo Patients

	Prior Epidural Narcotics - Yes	Prior Epidural Narcotics - No	Total
Neuropathic Pain-Yes	10 + 9	8 + 9	18 + 18
Neuropathic Pain- No	12 + 17	8 + 12	20 + 29
Total	22 + 26	16 + 21	38 + 47

2. Protocol Variations: One patient (EC01-11-001) received fentanyl and another, EC01-12-001, was given dilaudid, rather than morphine, because these patients were intolerant to morphine. Fentanyl and dilaudid usages were converted to morphine equivalents, and data for these patients were included in all analyses. Patient EC05-12-004 had chemotherapy stopped two days prior to randomization. Patient EC10-12-001 had no baseline VAS pain scores collected. Baseline pain was defined using the pre-randomization MPAC VAS assessment, and this patient was included in all analyses. Patient EC10-12-007 was receiving radiation at time of enrollment. Therapy continued throughout study period. Patient EC11-12-007 was receiving oral clonidine for the treatment of hypertension at the time of randomization and throughout the study period. Patient EC11-22-002 had a history of alcoholism, inactive for three years prior to entry. Patient EC12-21-001 started prednisone 16 days prior to randomization and continued throughout study period. Two patients (EC05-12-003 and EC25-11-001) discontinued the study during first two days of treatment. No post-treatment pain assessments or morphine use data collected. These patients were classified as treatment failures for primary efficacy analyses.

3. Disposition of Patients Entered: Of the 85 patients randomized and treated, 66 (30 on clonidine and 36 on placebo) completed eight days; there were 50 patients (22 on clonidine and 28 on placebo) who completed the 15-day treatment period. Table 1c lists reasons for discontinuations.

TABLE E1c. REASONS FOR DISCONTINUATION

REASON	CLONIDINE	PLACEBO	TOTAL
Disease Progression	4	4	8
Death	0	2	2
Adverse Experience	4	3	7
Protocol Violation	2	2	4
Other	6	9	15
TOTAL	16	19	35

4. Primary Efficacy Analysis: Results from the primary efficacy analysis, comparing the frequency of treatment success (defined as a reduction in either VAS pain scores or rescue morphine use, with no increase in either variable) across treatment groups are summarized in Table E2. Overall, 27 of the 85 randomized patients (32%) met the definition of treatment success. The frequency of treatment success in the clonidine group was 45% (17/38) and 21% (10/47) in the placebo group. After control for prior epidural narcotic use and pain mechanism (primary pain neuropathic: yes/no) the odds of treatment success were significantly greater for patients receiving clonidine than for patients receiving placebo (Cochran-Mantel-Haenszel Odds Ratio = 3.3, p = 0.016). There were no significant difference in odds ratios among the four stratification levels defined by the combination of prior epidural narcotic use and primary pain mechanism.

TABLE E2. Treatment success for Randomized Patients
Table Entry: Proportion of Success (%) clonidine v. placebo

	Prior Epidural Narcotics - Yes	Prior Epidural Narcotics - No	Total
Neuropathic Pain (Primary) - Yes	C: 5/10 (50.0%) p: 1/9 (11.1%)	C: 5/8 (62.5%) p: 0/9 (0.0%)	C:10/18 (55.6%) p: 1/18 (5.6%)
Neuropathic Pain (Primary) - No	C: 2/12 (16.7%) p: 3/17 (17.7%)	C: 5/8 (62.5%) p: 6/12 (50.0%)	C: 7/20 (35.0%) p: 9/29 (31.0%)
Total	C: 7/22 (31.8%) p: 4/26 (15.4%)	C: 10/16 (62.5%) p: 6/21 (28.6%)	C: 17/38 (44.7%) p: 10/47 (21.3%)

a. Pain Mechanism: The difference in the proportion of treatment success between clonidine and placebo patients was much more pronounced in patients whose primary pain was neuropathic. Seven patients (5 on clonidine and 2 on placebo) received additional radiation or chemotherapy post-randomization. When these 7 patients were excluded from the primary efficacy analysis, the difference in treatment sucess remained statistically significant ($p = 0.038$).

b. Center and Baseline Effects: Treatment effects across clinical centers were evaluated for consistency by the comparing success rates among the only center with at least 12 patients (Swedish Hospital Medical Center, SHMC) and those for the other centers. The success rate was 2/14 (14.3%) for the SHMC and 25/71 (35.2%) for the remaining centers. The difference was not statistically significant due to the small sample size in SHMC. There were six centers with 6 to 11 patients other than the SHMC. Although the success rates varied from 11.1% to 42.9% in these 7 centers compared to 48.0% in the remaining pooled centers, the differences were again not statistically significant. The center effect was therefore dropped in all analyses. Logistic regression models were developed to assess effects of baseline imbalances between treatment groups (gender, race, height, and elapsed time since initial cancer diagnosis), using the stratification factors as covariates. Controlling only for the stratification factors, none of the four baseline factors exhibiting imbalances affected the outcome of the analysis. The FDA statistician agreed with the sponsor in this regard.

c. Outcome Categories: Patient outcomes were categorized to represent the extent of treatment success or failure. These are summarized in Table E3 below. Category A was defined as 50% or more reduction in both VAS pain and morphine consumption, category B as less than 50% reduction in both variables, category C as mixed outcome (reduction in one variable but increase in the other), category D as increase of less than 50% in both variables and category E as increase of 50% or more in both variables. The Mantel-Haenszel chi-square test produced a p-value of 0.031 after controlling for the two stratification factors. Categories B and E contributed most of the differences between clonidine and placebo.

Table E3. Magnitude of Treatment Success or Failure

	A	B	C	D	E	Total
clonidine	6(15.8%)	10(26.3%)	12(31.6%)	8(21.0%)	2(5.3%)	38
placebo	5(10.6%)	5(10.6%)	18(38.3%)	9(19.2%)	10(21.3%)	47
Total	11(12.9%)	15(17.6%)	30(35.3%)	17(20.0%)	12(14.1%)	85

d. Separate VAS Pain and Morphine Use Analyses: The sponsor also separately analyzed VAS pain scores and morphine use. Figures E1 and E2 show the daily mean VAS pain scores and mean daily morphine use by treatment group. The baseline mean VAS was slightly higher in the clonidine group than in the placebo group but the difference was not statistically significant ($p=0.79$). The baseline morphine use was also higher in the clonidine group than in the placebo group but the difference was also not statistically significant ($p=0.65$). In figures E1 and E2, Day 1 was the baseline day and W1, W2, and W3 were the washout days. Figure E1 shows that the VAS mean score of the clonidine patients was lower than that of the placebo patients on most days. Statistically significant differences occurred at Days 3 and 15. VAS mean scores for clonidine patients increased sharply during the washout. The mean daily morphine use was below baseline for both treatments during the 15-day period. Morphine use substantially increased during the washout for the clonidine patients compared to the placebo patients. Although there were no statistically significant differences in morphine use between the two treatments, the increase in morphine use for clonidine patients on washout Days 1 and 2 approached statistical significance ($p<0.10$). The sponsor also explored the differences in VAS pain scores during the first week of the study using a mixed model repeated measurement analysis of covariance. The baseline VAS score was used as a covariate. There was a significant treatment effect ($p=0.034$) and also a significant ($p=0.0034$) 3-way interactions of pain mechanism by treatment by day. A post hoc 2-way interaction of pain mechanism by treatment was also considered to be approaching significance ($p=0.09$), indicating difference in treatment effect depended on the pain mechanism (neuropathic primary pain or not). A similar analysis was performed on the rescue morphine use during the first week of the study. There were no statistically significant differences in either the main effects or interactions except for a 4-way interaction of treatment by pain mechanism by prior epidural narcotic use by day. This interaction term was considered too complicated to meaningfully interpret.

e. FDA Statistician Reanalysis: The sponsors' analysis used means of the last four daily measurements. The FDA statistician ignored prior epidural narcotic status (which had not been shown to play a role in outcome), varied the last number of daily measurements, stratified with respect to pain mechanism and obtained a set of results for treatment successes reproduced in Table E4. The table shows that had the sponsor chosen only the last day's measurements for comparisons, the result would not have been statistically significant. Averaging over any number of last daily measurements (except 11 days) would produce a statistically significant result. The treatment difference was contributed mainly from the subgroup of patients whose primary pain was neuropathic. For patients whose primary pain was somatic or visceral, the results were equivocal.

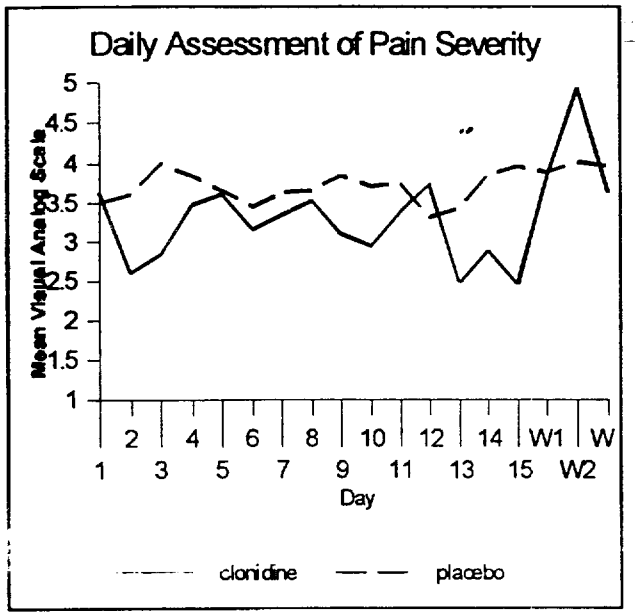


Figure 1

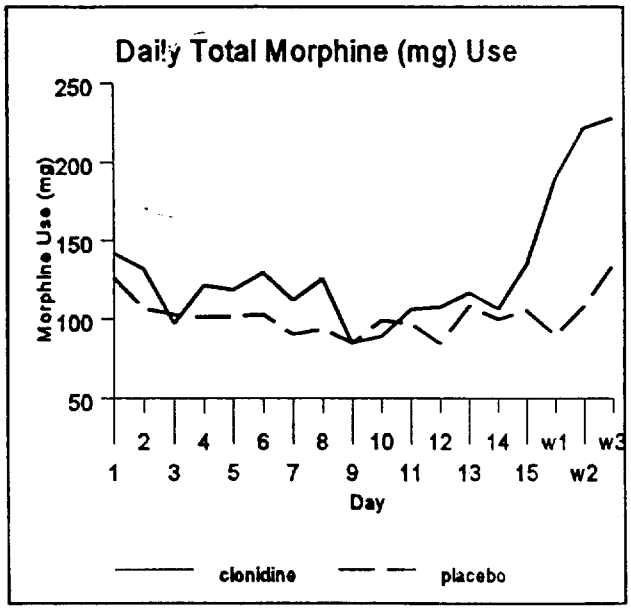


Figure 2

Figures E1 and E2

f. FDA Statistician Subgroup Reanalysis: An analysis was performed to excludeor patients with low morphine (15 mg or less) use combined with mild pain (2.5 cm or less on a 0 to 10 cm VAS) at the baseline. (The protocol had called for inclusion of patients with severe intractable cancer pain unrelieved by less than 20 mg/day of morphine or patients with at least moderate pain unable to tolerate high doses of morphine.) Seven placebo patients, but no clonidine patients, satisfied the above post-hoc exclusion rules; three of the seven had primarily neuropathic pain. Prior epidural narcotic use was ignored. Table E5 presents results, using varying number of last days of observation, for the subgroup remaining after the exclusions were applied. Results were similar to those in Table E4, however, the shaded cells in the somatic/visceral columns indicate that the placebo group was numerically better than the clonidine group when the last daily measurements or the average of the last week of measurements were used. Although success rates in clonidine patients were numerically better than for placebo patients in both subgroups in the sponsor analysis, the reanalyses suggest that statistically significant difference in success rates between clonidine and placebo were driven by the smaller subgroup with primarily neuropathic pain patients and not from the primarily somatic or visceral pain. Results from the re-analysis also showed that the outcome for patients with neuropathic pain was robust and the difference in treatment effects was substantial despite the smaller sample size compared to the other subgroup. Figures E3 and E4 show the mean daily pain intensity, and Figures E5 and E6 show the mean morphine usage for the two subgroups.

Table E4. Treatment Successes By Type of Pain

Pain	Neuropathic		Somatic/Visceral		
Days Avg.	Clonidine	Placebo	Clonidine	Placebo	p-value
1	9 (50.0%)	2 (11.1%)	5 (25%)	9 (31.0%)	0.174
2	9 (50.0%)	2 (11.1%)	7 (35.0%)	9 (31.0%)	0.049
3	10(55.6%)	2 (11.1%)	7 (35.0%)	9 (31.0%)	0.003
4	10(55.6%)	1 (5.6%)	7 (35.0%)	9 (31.0%)	0.016
5	10(55.6%)	1 (5.6%)	7 (35.0%)	9 (31.0%)	0.016
6	10(55.6%)	1 (5.6%)	7 (35.0%)	10(34.5%)	0.029
7	10(55.6%)	0 (0%)	7 (35.0%)	11(37.9%)	0.027*
8	11(61.1%)	1 (5.6%)	7 (35.0%)	11(37.9%)	0.029*
9	11(61.1%)	1 (5.6%)	7 (35.0%)	11(37.9%)	0.029*
10	11(61.1%)	2 (11.1%)	7 (35.0%)	10(34.5%)	0.030
11	10(55.6%)	2 (11.1%)	7 (35.0%)	10(34.5%)	0.053
12	11(61.1%)	2 (11.1%)	8 (40.0%)	10(34.5%)	0.016
13	10(55.6%)	0 (0%)	8 (40.0%)	10(34.5%)	0.007*
14	11(61.1%)	0 (0%)	8 (40.0%)	10(34.5%)	0.004*
Denominator	18	18	20	29	

*** The Breslow-Day test for homogeneity for odds ratios of the four strata was also statistically significant ($p < 0.05$) indicating non-homogeneous of odds ratios among the four strata.**
The deeply shaded cells indicated that placebo was numerically better than clonidine in success rate.
The lightly shaded row was the sponsor's choice in their analysis.

Table E5. Subgroup Analysis for Reduced Patient Population

Pain	Neuropathic			Somatic/Visceral		
Days Avg.	**Clonidine**	**Placebo**	**p-value**	**Clonidine**	**Placebo**	**p-value**
1	9(50.0%)	2(13.3%)	.028	5(26.3%)	9(34.6%)	.557
2	9(50.0%)	2(13.3%)	.028	7(36.8%)	9(34.6%)	.879
4	10(55.6%)	1(6.7%)	.003	7(36.8%)	9(34.6%)	.879
7	10(55.6%)	0(0%)	.001	7(36.8%)	11(42.3%)	.715
N	18	15		19	26	

The p-value was from a CMH chi square test.

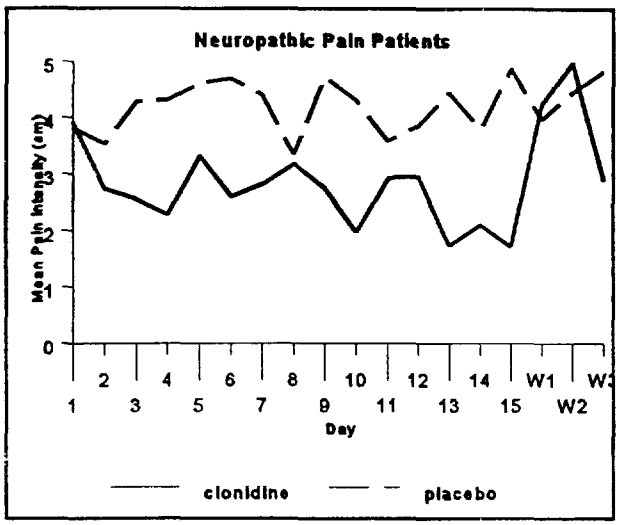


Figure 3

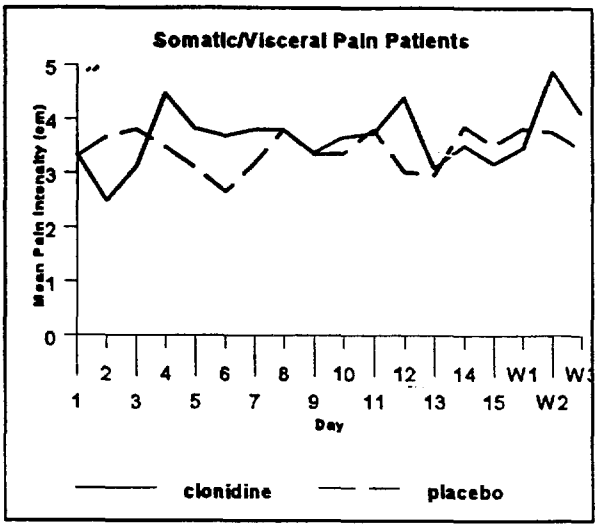


Figure 4

Figures E3 and E4

Figures E5 and E6

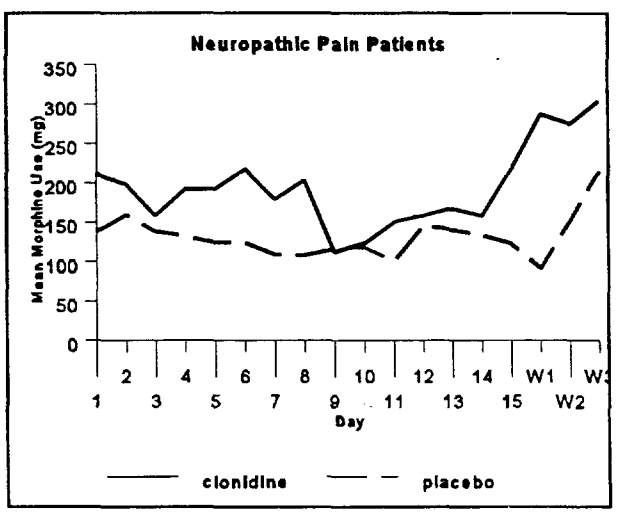


Figure 5

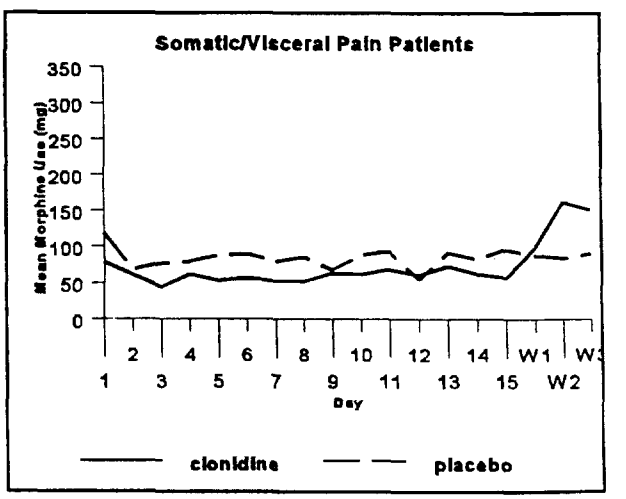


Figure 6

5. Secondary Efficacy Analysis: There were essentially no statistically significant differences between clonidine and placebo in other secondary variables such as free plasma morphine concentrations, MPAC, McGill, and Quality of Life Assessments (cf. Table E6).

TABLE E6

QUALITY OF LIFE, ECOG, MPAC AND McGILL SCORES BY STUDY DAY AND TREATMENT ARM

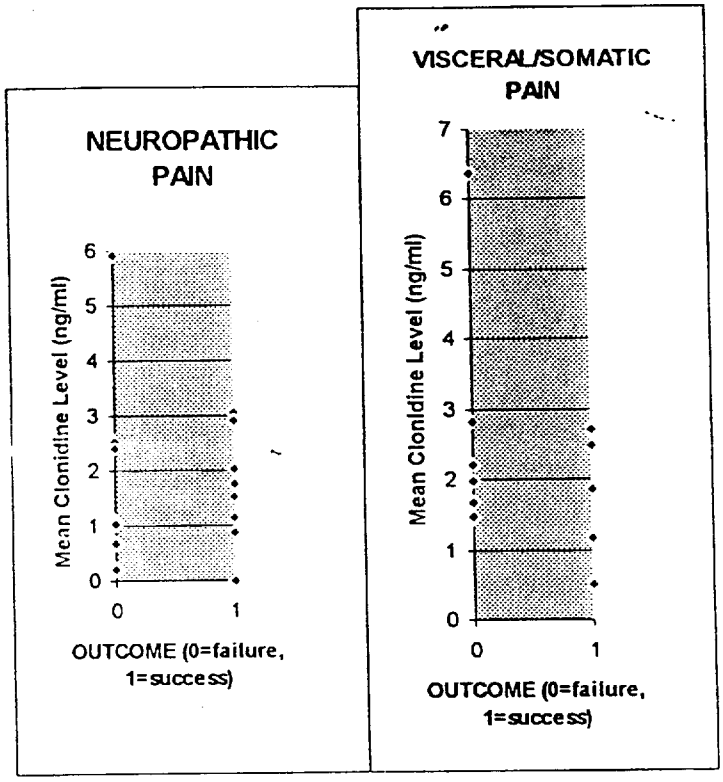
		------Clonidine Arm------			-------Placebo Arm-------			
		N	Mean	s.e.	N	Mean	s.e.	P-value
ECOG SCORE	Day 0	38	2.68	0.14	47	2.68	0.13	0.9860
	Day 8	32	2.59	0.16	39	2.31	0.16	0.2170
	Day 15	24	2.50	0.21	32	2.56	0.17	0.8180
SPITZER QOL	Day 0	37	4.59	0.28	47	4.77	0.28	0.6670
	Day 8	33	4.79	0.30	39	4.64	0.26	0.7120
	Day 15	24	5.29	0.39	33	4.91	0.32	0.4510
MPAC VAS PAIN	Day 0	37	3.94	0.46	46	4.28	0.38	0.5750
	Day 8	33	3.78	0.50	40	4.08	0.47	0.6670
	Day 15	24	3.18	0.52	31	4.63	0.52	0.0560
MPAC VAS RELIEF	Day 0	37	4.90	0.45	45	4.47	0.43	0.4960
	Day 8	33	4.32	0.54	40	4.70	0.46	0.5840
	Day 15	24	3.47	0.58	32	4.50	0.50	0.1820
MPAC VAS MOOD	Day 0	37	6.09	0.46	45	5.11	0.35	0.0880
	Day 8	33	5.40	0.48	39	5.25	0.42	0.8130
	Day 15	24	5.65	0.45	32	5.29	0.47	0.5990
MPAC DESCRIPTOR	Day 0	37	3.97	0.27	44	3.73	0.23	0.4880
	Day 8	33	3.82	0.32	38	3.79	0.33	0.9500
	Day 15	24	3.33	0.32	31	3.81	0.30	0.2890
MCGILL PRESENT PAIN INTENSITY	Day 0	37	1.78	0.19	47	2.09	0.18	0.2560
	Day 8	33	1.82	0.22	40	2.10	0.23	0.3940
	Day15	23	1.83	0.29	32	2.09	0.26	0.4960
MCGILL AFFECTIVE SCORE	Day 0	37	4.35	0.50	47	5.96	0.50	0.0280
	Day 8	33	3.82	0.54	40	4.58	0.53	0.3230
	Day 15	24	3.54	0.64	32	3.84	0.62	0.7410
MCGILL SENSORY SCORE	Day 0	37	12.86	1.19	47	13.09	0.94	0.8830
	Day 8	33	9.76	1.23	40	9.43	1.25	0.8520
	Day 15	24	9.21	1.44	32	8.75	1.37	0.8210
MCGILL TOTAL SCORE	Day 0	37	17.22	1.61	47	19.04	1.31	0.3760
	Day 8	33	13.58	1.64	40	14.00	1.69	0.8590
	Day 15	24	12.75	2.03	32	12.59	1.88	0.9560
O'BRIEN RANK SUM PAIN SCORE	Day 0	38	280.87	16.35	47	290.43	13.78	0.6540
	Day 8	33	251.68	16.39	40	259.59	15.43	0.7270
	Day15	24	186.23	14.70	32	204.20	12.31	0.3500

a. Free Plasma Morphine Concentrations: The baseline mean plasma free morphine concentration for 23 clonidine patients with processed samples was 109.7 ng/ml. with a standard error of 31.00, while the mean concentration for 34 placebo patients was 59.0 ng/mL with a standard error of 10.13. This difference was not statistically significant. Differences in plasma free morphine concentrations between treatment arms decreased during the post-treatment period, and variances became more homogeneous. On study day 8, the mean plasma free morphine concentration for 26 clonidine patients was 64.1 ng/mL with a standard error of 17.73, while the mean concentration for 34 placebo patients was 88.3 ng/mL with a standard error of 18.12. On day 15, the mean plasma free morphine concentration for 23 clonidine patients was 93.1 ng/mL with a standard error of 27.35, while the mean concentration for 30 placebo patients was 85.5 ng/mL with a standard error of 23.56. There were no significant differences in morphine concentrations between either treatment arms or assessment periods.

b. Free Plasma Clonidine Concentrations: Plasma concentrations of clonidine for 33 patients randomized to the active drug arm were measured on study days eight and 15. Results of plasma clonidine assays were maintained by Harris Labs and the Statistical Coordinating Center at Bowman Gray School of Medicine in blinded data files until the study blind was broken. The mean plasma clonidine concentration for 27 patients contributing data on study day eight was 2.06 ng/mL, with a standard error of 0.23. On study day 15, the mean plasma clonidine concentration for 24 patients contributing data was 2.29 ng/mL, with a standard error of 0.31. There were no significant differences between Day 8 and 15 values.

c. Plasma Clonidine Concentrations vs. Outcome: The FDA Medical Reviewer compared plasma clonidine levels where available with outcomes. Mean values for levels from Days 8 and 15 were calculated. When levels were not obtained on a particular time, the value measured at the other day (Day 8 or 15) was utilized. For patients with primary neuropathic pain, there were eight who were treatment failures. One had no levels measured, another was missing a Day 8 level and four missed Day 15 values. The calculated mean was 2.28 ng/ml. Ten patients with primary neuropathic pain had successful outcomes. Two had no levels measured, another was missing a Day 8 level and three missed Day 15 values. The calculated mean was 2.46 ng/ml. For patients with primary somatic or visceral pain, there were thirteen treatment failures. Six had no levels measured. The calculated mean was 2.57 ng/ml. There were seven successes with primary somatic or visceral pain patients; however, two had no clonidine measurements and one missed the Day 15 level. The mean was 1.75 ng/ml. Figure 7 contains plots of individual patients' mean plasma clonidine levels vs. outcome for each primary pain mechanism. No clear relationship between plasma clonidine levels and outcome are evident.

FIGURE E7


NEUROPATHIC PAIN
Mean Clonidine Level (ng/ml)
0
1
2
3
4
5
6
0
1
OUTCOME (0=failure, 1=success)
VISCERAL/SOMATIC PAIN
Mean Clonidine Level (ng/ml)
0
1
2
3
4
5
6
7
0
1
OUTCOME (0=failure, 1=success)

C. DISCUSSION

The medical reviewer is offering an hypothesis to attempt to explain the low placebo response in patients with primarily neuropathic pain.

1. Background: Naloxone is known to block placebo responses to pain (Levine JD et al, Lancet 1978;2(8091):654-7). This has been attributed to the narcotic antagonist's blockade of opioid receptors in the brain. Placebo does have analgesic properties. Placebo is thought to stimulate endogenous narcotic neuropeptides (e.g. endorphins) which cause analgesic effects via interaction with brain narcotic receptors. When these receptors are blocked by naloxone, the result is that the analgesic efficacy of placebo and certain nonpharmacological treatments of pain can be reduced.

2. Hypothesis for Clonidine and Morphine-Treated Neuropathic Pain: The hypothesis to explain the results of the subgroup analyses for this study is as follows: Patients in this study are all being treated with epidural morphine. Morphine acts at receptor sites to provide analgesia for the visceral and somatic pain. Increasing the dose of morphine or using placebo or clonidine (the latter appears to be no different that placebo for this type of pain) can afford more analgesia since receptor sites remain available. In the case of primarily neuropathic pain, brain morphine receptors that can provide analgesic responses to morphine or placebo may be more limited. Hence, morphine might be expected to be of limited efficacy in treating this type of pain. Also, morphine, in the setting of this study, may have blocked the relevant receptors for endogenous narcotic peptides and thereby inhibited the placebo response to neuropathic pain. The situation may be that placebo or clonidine has room to work in somatic or visceral pain by the mechanism of endogenous opioid peptide stimulation and receptor interaction, while morphine has blocked the ability of placebo to do the same for neuropathic pain. Clonidine, however, would be effectively treating neuropathic pain by a mechanism that does not involve narcotic receptors.

D. CONCLUSIONS

1. Continuous infusion of epidural clonidine (30 mcg/hr) as an adjunct to epidural morphine was effective compared with placebo in relieving severe intractable cancer pain (located below the C4 dermatome).

The frequency of treatment success (defined as a reduction in VAS pain scores or rescue morphine use, with no increase in either variable) according to intent to treat analysis was 44.7% (17/38) in the clonidine group and 21.3% (10/47) in the placebo group.

2. Post-hoc reanalysis of the intent to treat data suggests that epidural clonidine is particularly effective relative to placebo in patients with pain primarily of neuropathic nature.

For patients with primarily neuropathic pain, there were 56% (10/18) on clonidine and 6% (1/18) on placebo who were treatment successes. For patients primarily with somatic and/or visceral pain, there were 35% (7/20) on clonidine and 31% (9/29) on placebo who were treatment successes.

The FDA statistician's post-hoc reanalysis involved exclusion of patients with protocol violations related to inadequate baseline pain. When averaging VAS pain scores and rescue morphine use over seven days, for patients with primary neuropathic pain there were 56% (10/18) on clonidine and 0% (0/15) on placebo who were treatment successes. For patients primarily with somatic and/or visceral pain, there were 37% (7/19) on clonidine and 42% (11/26) on placebo who were treatment successes.

The hypothesis arising from these reanalyses is that the response of the patients with primarily neuropathic pain essentially accounts for the effectiveness demonstrated by epidural clonidine as an adjunct to epidural morphine in this study. There is no evidence from this trial that epidural clonidine is more effective than placebo in cancer patients with primarily somatic and/or visceral pain who are being treated with epidural morphine.

3. There were no statistically significant differences between clonidine and placebo in other secondary variables such as free plasma morphine, concentrations, MPAC, McGill, and Quality of Life Assessments.

4. There was no clear relationship between plasma clonidine levels and outcome.

E-II. EXTENSION STUDY EC-001LT

A. PLAN OF THE STUDY

1. OBJECTIVES: The primary objective of the extension study was to describe the safety profile of long-term use of epidural clonidine.

2. DESIGN: Following the 14-day controlled phase of pivotal study EC-001, 39 patients from 11 of the 21 centers were enrolled in the long-term, extension phase (EC001LT). Originally, the extension study remained blinded with patients continuing to receive what they had before; however, a protocol amendment developed early in the trial converted the study to an open-label one where all patients would receive clonidine. Patients were rehospitalized for one day following completion of EC-001, received epidural clonidine 30 mcg/hr by continuous infusion. Five patients received higher infusion doses (up to 41.7 mcg/hr) and four were administered doses below 25 mcg/hr at times during the trial. The pain level (defined using a 10-cm Visual Analog Scale was monitored twice-weekly for two weeks, then weekly thereafter. All patients had access to epidural morphine. Use of other forms of clonidine or beta-blockers or ganglionic blockers or alpha-methyldopa was prohibited.

B. RESULTS:

1. Demographics and Patient Disposition: Seventeen patients had received clonidine during the controlled phase and continued to receive clonidine during the extension phase; eighteen patients received placebo during the controlled phase and crossed over to clonidine during the extension phase, and four patients received placebo during the controlled phase and continued to receive placebo during the extension phase. A total of 56 patients received clonidine during the controlled and/or extension phase of the study (Table E-7). It should be noted that three patients who entered the extension phase and received clonidine were not included in the NDA data base; two were not brought to the sponsor's attention until after the data base was finalized, and there was no case report form available for the third one. The 32 clonidine patients were mostly male (41%) and white (84%). There were 9% black and 6% other races. Mean age was 57.3 years; most (59%) patients were 56 years old or over. Duration of dosing ranged from one to 94 weeks. The numbers of patients at different durations of treatment were: 21 at four weeks, 14 at eight weeks, 11 at 12 weeks, four at 26 weeks, two at 71 weeks and one thereafter.

2. Pain Scores: Figure E8 plots mean VAS pain scores and number of patients on clonidine for each of the first nine weeks of the extension. Figure E8a is similar, but only looks at patients who were originally on placebo in the pivotal trial and are new to clonidine in the extension study. In both plots, the number of patients still in the study is approximately halved by six weeks. The mean pain scores fluctuate; consistent changes are not apparent. The pain scores by themselves, i.e., without epidural morphine usage data, are inadequate measures of efficacy. Efficacy in this study is also complicated by worsening of metastatic disease, often with increasing pain and frequently leading to death. Most patients continued with the infusions until death or adverse events, including catheter problems resulted in termination. There was only one case of termination clearly labeled as due to drug being ineffective.

TABLE E7

FUSA-Sponsored Controlled Clinical Study of Epidural Clonidine For Intractable Cancer Pain

Protocol (Ref)	Control	Study Design	Total No. Pts.	No. Pts. Rec'd Clonidine	Mean Age &/or Range (Years)	Method of Dosing	Duration of Treatment (Days)		
EC-001: Extension (4)	None	Open-label phase	39 17 who rec'd clonidine in controlled phase; 18 who crossed over from placebo to receive clonidine; 4 who continued to receive placebo	35	-81.21875	Continuous infusion 30 mcg/hr	-657		
TOTAL PATIENTS			**85**						

C. CONCLUSIONS:

No conclusions regarding long-term efficacy can be made for the following reasons. Only VAS pain scores were measured, without clear baseline values and without morphine usage. There were no global ratings of efficacy, and there was no substantive placebo group.

Most patients were willing to continue the infusions until death or other problems unrelated to efficacy resulted in termination.

FIGURE E8 VAS PAIN AND PATIENTS DURING FIRST 9 WEEKS

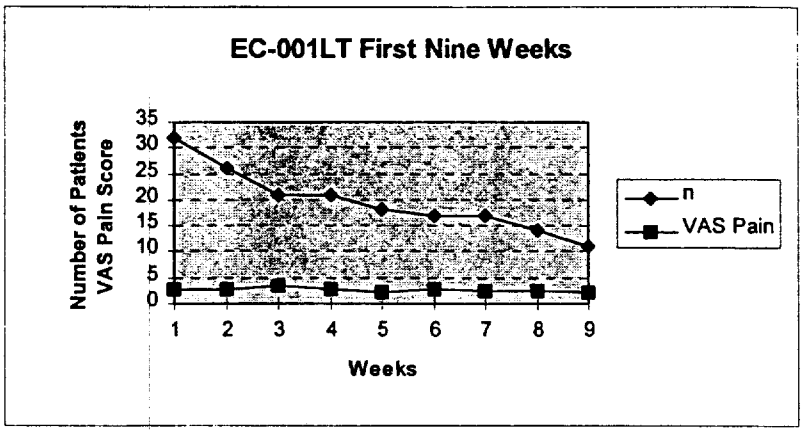
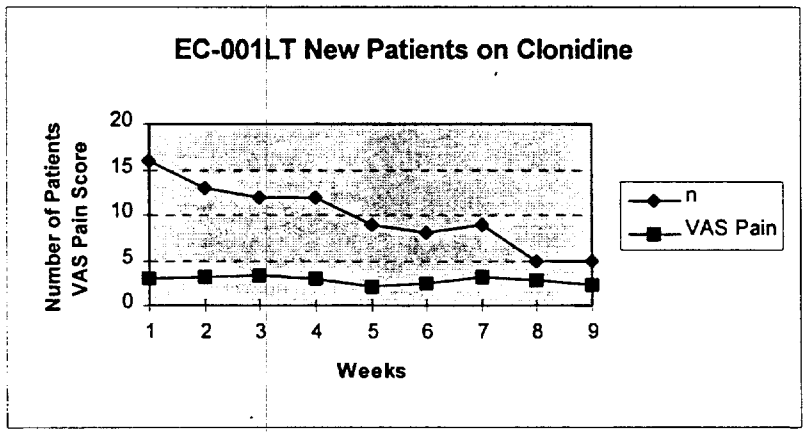


FIGURE E8a NEW PATIENTS ON CLONIDINE



E-III. OTHER STUDIES

A. OTHER PHASE I OR CANCER STUDIES SPONSORED BY FUJISAWA

1. Volunteer Study 92-3001

a. Design: This was an open-label, parallel-group study involving 19 healthy volunteers. Nine subjects (mean age 33; four men and five women) received single bolus dose, epidural administration of clonidine (700 mcg, infused over five minutes). Ten other volunteers received treatment with epidural alfentanil for comparison, but this aspect of the study is not discussed here. Arterial blood and CSF levels of clonidine were obtained, and finger and toe photoplethysmographic recordings and VAS pain measurements were carried out in conjunction with 60 second immersion of hands or feet in ice water at 0.5 hour intervals for two hours and again at three, four and six hours after epidural clonidine administration.

b. Results: Foot pain, but not hand pain, was significantly reduced for up to four hours by clonidine. Maximum effect was at one hour following epidural bolus infusion. VAS pain in the foot correlated better with CSF than with plasma clonidine; the calculated EC50 for CSF clonidine was 80$\pm$ 6 ng/ml. Clonidine reduced sympathetic outflow; plasma norepinephrine (but not epinephrine) was reduced. Epidural clonidine increased the amplitude of plethysmographic waveforms and reduced the decrease in these waveform amplitudes associated with ice-water immersion in both hand and feet. Both CSF and plasma clonidine correlated with these effects. (Cf. Eisenach J, Detweiler, D and Hood D, Hemodynamic and Analgesic Actions of epidurally Administered Clonidine, Anesthesiology 1993;78(2):277-287 for further details).

c. Conclusions: The authors postulated that the greater effect in the foot relative to the hand supports a local spinal mechanism of clonidine-induced analgesia. They also suggest that correlation of effect with CSF clonidine levels and minimal hysteresis may be in accord with rapid diffusion of clonidine to the superficial dorsal horn. Decrease in sympathetic tone and reflex activity may be owing to a central redistribution effect.

2. Study 87-3000

a. Design: This was an open-label, exploratory, dose-finding study involving nine patients (mean age 55; four men and five women) with intractable metastatic cancer pain treated with epidural clonidine. Two patients with metastatic breast cancer had pain of primarily neurogenic origin. One patient had primarily hepatic pain; six had primarily somatic pain. Patients received three escalating bolus doses of epidural clonidine on consecutive days. The first three received 100, 200 and 300 mcg, the next three received 400, 500 and 600 mcg, and the last three were administered 700, 800 and 900 mcg epidural clonidine. Supplemental analgesia was provided through Patient Controlled Analgesia with intravenous morphine. VAS pain scores, morphine usage and plasma levels of clonidine were measured at specific intervals during the first six hours following epidural injection. Seven patients also received clonidine under a compassionate use basis until their death by continuous infusion (12.5 to 70 mcg/hr) combined with morphine and by demand bolus for 21 to 140 days, but analgesia was not measured during this aspect of the study. Further details of the trial are found in the publication: Eisenach JC et al, Anesthesiology 1989:71:647-52.

b. Results: All patients had improvements in pain. There were dose-related reductions in VAS pain scores. Morphine usage was variable. Two patients in the middle dose group and all three in the high dose group were able to achieve complete relief of pain at the time of peak effects (two hours for the high dose group). Peak plasma levels occurred 15-127 minutes following injection; elimination half-lives were 2.3-27 hours.

c. Conclusions: The lack of placebo control and variability of morphine usage make any conclusions regarding efficacy highly speculative.

B. PUBLISHED STUDIES OF TREATING INTRACTABLE CANCER PAIN WITH EPIDURAL CLONIDINE

The published literature describe 32 other cancer patients treated with boluses of epidural clonidine. Petros, AJ and Bowen Wright, RM (Lancet 1987;(8540):1034) describe a patient with neuropathic, spinal deafferentation pain who improved after treatment with epidural clonidine150 μg q 12 hours + morphine. Strum, PJ et al. (Anaesthesia 1984;39:834-5) reported that a patient on morphine with pelvic pain failed to further improve on 300 to 900 μg ep clonidine. Lund C et al (Eur J Anaesthesiology 1989;6:207-13) studied twelve patients with abdominal pain who were not adequately treated with opioids alone. Pain medications were stopped 9-10 hours prior to treatment with clonidine150 μg ep. Mean VAS pain scores were reduced; six patients became pain-free. Ferit PA et al (Regional Anesthesia 1992;17:173) reported that fifteen patients improved on 750 μg ep. Germain H et al (Proceedings of the World Congress on Pain 1988;ch52:472-6) reported three patients improved on clonidine 4 to 10 μg/kg ep. These trials are discussed further in Dr. Burke's review (Appendix I). These publications were of open-label, uncontrolled studies. Although improvements in pain and narcotic usage were described, no firm conclusions regarding analgesic efficacy can be made from these trials.

C. OTHER INDICATIONS

Dr. Burke's review (Appendix I) also examines results for other indications, such as postoperative analgesia, deafferentation and other types of chronic pain. There is inadequate data available at this time to support the efficacy of these indication. The apparent analgesic effects of clonidine in postoperative pain may be owing to clonidine's prolongation of regional anesthetic effects. This is discussed further in the safety review (S-III-A-1). One literature report of placebo-controlled treatment of a neuropathic pain, namely refractory reflex sympathetic dystrophy, is worthy of mention. Rauck et al. (Anesthesiology 1993;79:1163-9). Epidural boluses of clonidine 300 and 700 mg were superior to placebo in reducing VAS pain. The data, however, is inadequate for serious review.

E-IV. OVERALL CONCLUSIONS REGARDING EFFICACY

Epidural clonidine in continuous infusion doses of 30 mcg/hour was an effective analgesic in a controlled trial as an adjunct to morphine in cancer patients with neuropathic pain. Evidence is lacking for any wider claim of efficacy.

MEDICAL OFFICER REVIEW
DIVISION OF ANESTHETIC, CRITICAL CARE & ADDICTION DRUG PRODUCTS

NDA#: 20,615 Orphan Drug Designation No. 88-80-343-6
NAME: Epidural Clonidine HCl for the Treatment of Pain Associated with Advanced Cancer
APPLICANT: Fujisawa USA **SUBMISSION DATE:** 7/95
REVIEWERS: Monte L. Scheinbaum, Ph.D., MD, Medical Officer
Igor Cerny, Pharm. D, Interdisciplinary Scientist
Lillian Burke, MD, Medical Officer
PEER REVIEWER: Robert Bedford, MD **CSO:** Mildred Wright
DATE: 6/6/96

6/6/96

SAFETY REVIEW OF EPIDURAL CLONIDINE

S-I. PIVOTAL STUDY EC-001 SAFETY

A. STUDY PLAN, DEMOGRAPHICS, EXPOSURE AND DISPOSITION

The objectives, design, population and specifications of investigators and sites of the pivotal study, EC-001, are discussed in Section E-I-A and in Dr. Cerny's review, attached as Appendix III. Table S-1 below summarizes selected baseline demographic characteristics of the 85 randomized subjects. All 38 patients who received clonidine were infused for at least 24 hours (0.72 mg total dose/patient); thirty (79%) completed at least one week of therapy (5.04 mg total) and 22 (58%) completed the 15-day study (10.8 mg total). Mean number of days on the study was 10.6 (S.D. 4.7). Reasons for discontinuation are listed in Table S-2.

TABLE S-1 Selected Demographics of Study EC-001

CHARACTERISTIC		Clonidine (N=38) N	Placebo (N=47) N	Total (N=85) N
SEX	Male	27	24	51
	Female	11	23	34
RACE	White	35	37	72
	Black	3	7	10
	Other	0	3	3
AGE (years), MEAN(S.D.)		56.8 (11.6)	56.4 (11.8)	56.6 (11.6)
WEIGHT (kg), MEAN(S.D.)		71.5 (17.2)	68.4 (16.8)	69.8 (17.0)
DISTANT METASTASES		28	38	66
MONTHS from cancer diagnosis, MEAN(S.D.)		42	30	35

Table S-2: Reasons for Discontinuation before Completion of the 14 Day Treatment Period

Reason for Discontinuation	Clonidine (N=38) (N)	(%)	Placebo (N=47) (N)	(%)	TOTAL (N=85) (N)	(%)
All Discontinuations	16	42.1%	19	40.4%	35	41.1%
Disease Progression	4	10.5%	4	8.5%	8	9.4%
Death	0	0.0%	2	4.3%	2	2.4%
Adverse Experience	5	13.2%	3	6.4%	8	9.4%
Patient Refused to Continue	2	5.3%	4	8.6%	6	7.1%
Physician refused to let patient continue	1	2.6%	0	0.0%	1	1.2%
Other	2	5.3%	5	10.6%	7	8.2%
Protocol Violation	2	5.3%	2	4.3%	4	4.7%

B. ADVERSE EVENTS

1. ADVERSE EVENTS LEADING TO DISCONTINUATION: Ten subjects (five in the clonidine group and five in the placebo group) discontinued treatment prior to completion of the 15-day study due to adverse experiences or death. These are summarized in Table S-3 below:

TABLE S-3: Summary of Discontinuations from the 15-day trial due to Adverse Reactions

Subject#	Age	Sex	Race	Group	Day	ADR
EC01-12-001	35	M	W	clonidine	3	somnolence and postural hypotension
EC01-21-001	35	F	W	placebo	6	severe drowsiness, nausea and vomiting
EC05-11-001	64	F	W	clonidine	3	severe confusion and hallucinations
EC06-22-002	65	M	B	clonidine	3	severe hypotension, postural hypotension and dizziness.
EC08-22-001	48	M	W	placebo	3	severe respiratory depression and confusion
EC08-22-002	51	M	W	placebo	14	severe dehydration, hypercalcemia and sedation
EC11-21-001	78	M	W	placebo	12	Death due to complications of malignant disease including pneumonia, shortness of breath, decreasing consciousness and decreased oxygen saturation
EC12-21-001	57	F	B	placebo	5	Death due to disease progression evidenced by tachypnea that required an increase in supplemental oxygen.
EC14-21-003	46	M	W	clonidine	5	severe pain associated with catheter infections
EC25-11-001	46	M	W	clonidine	2	severe pain associated with catheter infections^

2. DEATHS: Fourteen subjects (five in the clonidine group and nine in the placebo group) died during the study or within a 30-day period following the last administration of the study drug. None of the deaths was considered related to the study drug. All of the deaths were attributed to malignant disease except for a single death (placebo patient) attributed to stroke. Information relating to deceased subjects is summarized in Table S-4.

TABLE S-4: Summary of Deaths occurring either during the study or within a 30-day period following last administration

Subject#	Age	Sex	Race	Group	Days on Drug	Cause of Death
EC01-12-001	35	M	W	clonidine	3	died 24 hrs after last dose due to malignant disease.
EC02-12-001	45	M	W	clonidine	5	withdrew from the study after 5 days after dislodging the catheter and died the following day from cardiovascular failure related to malignant disease
EC03-11-004	73	F	W	placebo	14-complete	completed the study and died 3 days later related to malignant disease.
EC03-12-002	66	F	W	placebo	14-complete	completed the study and died 29 days later related to malignant disease
EC05-11-004	37	M	W	placebo	14-complete	completed the study and died 6 days later related to malignant disease.
EC06-22-001	49	M	W	placebo	14-complete	completed the study and died 14 days later related to malignant disease
EC07-11-001	44	F	A	placebo	14-complete	completed the study and died 14 days later due to septic shock and metabolic acidosis
EC07-22-005	79	F	W	placebo	14-complete	completed the study and died 21 days later from a stroke
EC08-22-002	51	M	W	placebo	13	withdrew from the study after 13 days due to severe dehydration, hypercalcemia and sedation. Death the following day was reported as related to malignant disease
EC10-12-003	63	M	W	clonidine	14-complete	completed the study and died 8 days later related to malignant disease
EC11-12-007	54	F	W	clonidine	13	withdrawn from the study after 13 days based on a misinterpretation of the study protocol. Death 13 days later was reported related to malignant disease
EC11-21-001	78	M	W	placebo	11	died on the 11th day of the study due to complicqtions of malignant disease including pneumonia, shortness of breath, decreasing consciousness and decreased oxygen saturation
EC12-21-001	57	F	B	placebo	4	died on the 4th day of the study secondary to disease progression evidenced by tachypnea that required an increase in supplemental oxygen
EC14-21-002	70	M	W	clonidine	7	withdrew from the study after 7 days because of disease progression. Death 24 days later was reported related to malignant disease.

3. FREQUENTLY OCCURRING ADVERSE EVENTS: The frequency of patients reporting one or more adverse experiences was significantly greater in the clonidine group than in the placebo group (37 of 38 clonidine patients, or 97.4% vs. 38 of 47 placebo patients, or 80.8%; Fisher's two-tailed exact test $p=0.0208$). The incidence of adverse experiences affecting the cardiovascular system was significantly higher in the clonidine group (29 of 38 clonidine patients, or 76.3%, vs. 11 of 47 placebo patients, or 23.4%; $p<0.001$). This difference appears to have been caused largely by the higher incidence of hypotension (17 of 38 clonidine patients, or 44.7% vs. 5 of 47 placebo patients, or 10.6%; $p=0.001$) and postural hypotension (12 of 38 clonidine patients, or 31.6% vs. 0 of 47 placebo patients, or 0.0%; $p<0.001$). The frequency of patients reporting one or more serious adverse experiences was slightly higher in the clonidine group (14/38) then in the placebo group (14/47) but the difference was not statistically significant ($p=0.64$). Incidence of other reported adverse experiences did not differ significantly between the clonidine and placebo groups ($p>0.05$). There was no difference between the clonidine and placebo groups regarding the other adverse reactions commonly attributed to clonidine such as dry mouth, nausea or somnolence, There was only one patient on clonidine and none on placebo listed as having bradycardia. Table S-5 compares the incidences of frequent adverse events for patients on clonidine in study EC-001 with the incidences reported from the labeling for the most commonly used form of clonidine, Catapres tablets.

TABLE S-5 Incidence of Frequent Adverse Events

Percent Patients Reporting:	EC-001	Catapres Tablet Labeling
dry mouth	13%	40%
drowsiness/sedation	13%	33%
hypotension	45%	
postural hypotension/dizziness	32%	16%
constipation	3%	10%
asthenia/fatigue/weakness	10%	5%
nausea/vomiting	13%	5%
bradycardia	3%	5%
palpitations	0%	5%
tachycardia	3%	5%

4. VITAL SIGN CHANGES: Blood pressures, heart and respiration rates, and temperature were monitored daily. Mean blood presures and heart rate decreased upon initiation of clonidine. Respiration rates remained relatively constant in the clonidine group throughout the study period, while tending to increase in the placebo group during the second week. There was little difference in mean temperatures between the two treatment arms. Figures show the mean measurements for these vital signs. More detailed figures are available in Dr. Cerny's review of safety showing the hypotensive effects of clonidine.

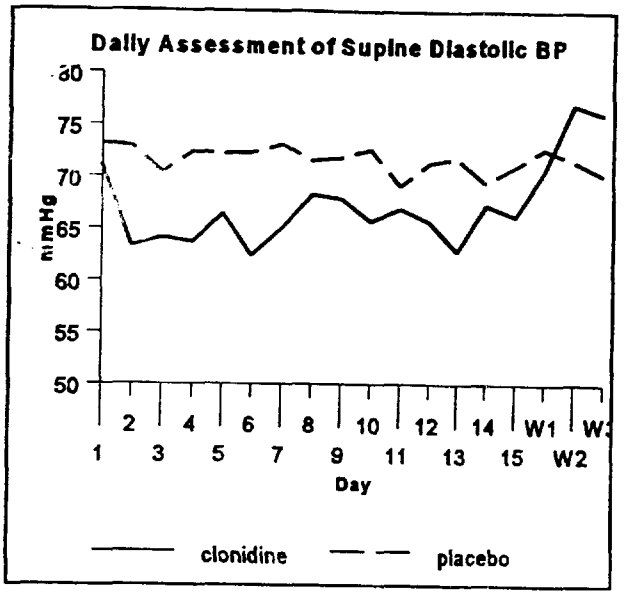


FIGURE S-1

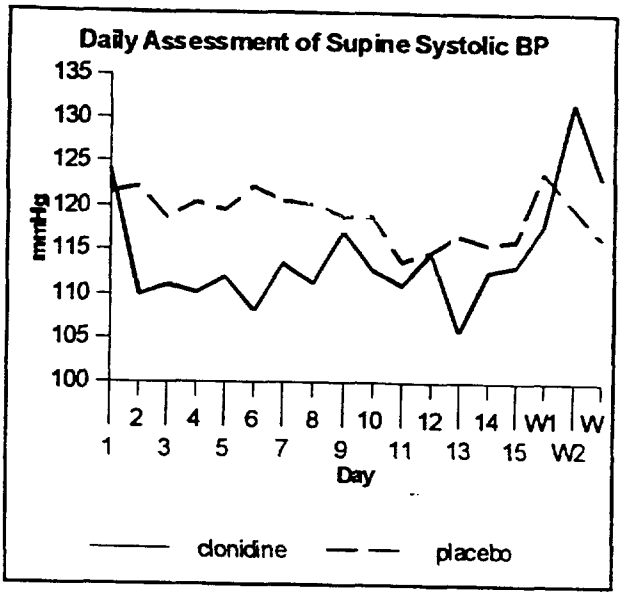


FIGURE S-2

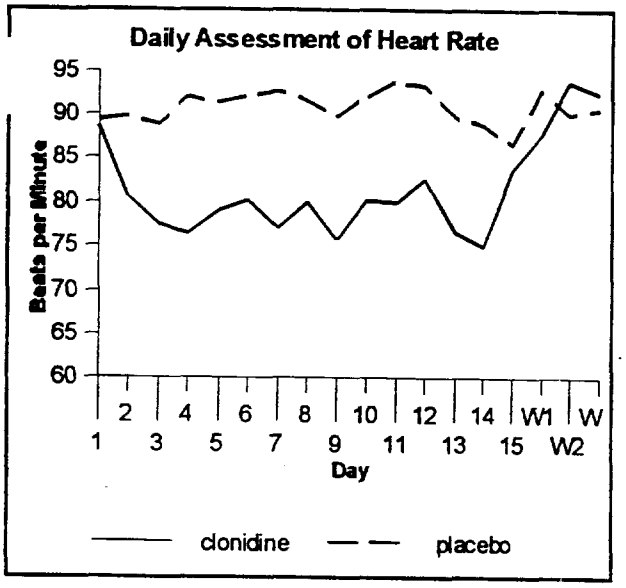


FIGURE S-3

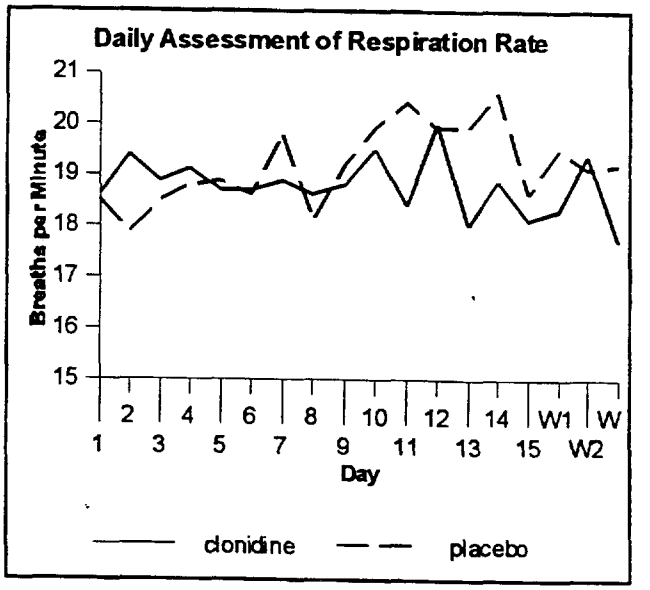


FIGURE S-4

a. Hypotension: There is the suggestion of attenuation of hypotensive effects as treatment with clonidine continues; however, formulations of clonidine used to treat hypertension are not known to lose effectiveness over the course of 14 days. Patients with hypotension in the study were given fluid and other support and two were discontinued for hypotension.

Table S-6 from Dr. Cerny's report reveals that patients who became hypotensive (according to the clinical judgment of the investigator) were generally lighter in body weight, more likely to be female, and had a higher Day 7 mean plasma clonidine level. Of the 33 hypotensive events in 24 subjects, 26 events occurred within the first four days. Duration of effects was only one day for 21 of these events; the others lasted two to 14 days. Nineteen hypotensive events were treated with fluid, nine with ephedrine, three by lowering clonidine dose.

Table S-6: Summary of Differences between subjects who did or did not become Hypotensive (including postural) on clonidine

GROUPS	N	Mean Age	Sex	Race	Mean % Success	Weight (kg) ± SEM	Day 7 clonidine level
HYPOTENSIVES	24	55	15 M 9 F	22 W 2 B	45.8	67.5 ± 3.5	2.37**
NON-HYPOTENSIVES	14	58	12 M 2 F	13 W 1 B	42.9	78.4 ± 4.0	1.89**

, were dropped from the study due to postural hypotension and thus did not have day 7 serum clonidine levels drawn

b. Rebound Hypertension: Rebound hypertension is a well-known problem associated with withdrawal of oral clonidine therapy. Dr. Cerny's review notes that upon cessation of clonidine administration, mean blood pressure levels in the clonidine group exceeded the original baseline values and also mean blood pressure levels for the placebo group, although this latter difference obtained statistical significance only on the third washout day and only for supine diastolic blood pressure ($p = 0.047$). Four of the five reports of "hypertension with clonidine occurred during this withdrawal phase. Three of these four subjects required treatment: one with a clonidine patch and one with oral clonidine; treatment was not reported for the third. Dr. Cerny points out that the latter patient (EC05-12-002), whose supine pressure rose from 106/48 on Day 14 to 156/74 on withdrawal Day 1, experienced a cerebrovascular accident two days later. This serious event seems likely to be related to the rebound hypertension resulting from sudden termination of epidural clonidine treatment.

c. Heart Rate: Mean heart rate at baseline was slightly, but not significantly lower in the clonidine group (See Figure S-3). Upon initiation of therapy, mean heart rate was consistently lower in the clonidine group than in the placebo group ($p<0.025$ for all study days except 14). Upon cessation of clonidine, heart rate in the clonidine group recovered to and surpassed baseline values. However, on Days 2 and 3 of the washout period, heart rate was faster in the clonidine group than in the placebo group, although these differences were not statistically significant. There was only one report of "bradycardia in the clonidine group (from a baseline of 76 bpm to 44 bpm) and none in the placebo group.

d. Nausea and Sedation: Figures S-5 and S-6 below show the severity of nausea and sedation over the study period. For both nausea and sedation, the baseline scores were lower in the clonidine group than in the placebo group. Both groups continued to have approximately the same scores compared to their respective baseline scores throughout the 15 day study period. However, on washout days, nausea severity increased substantially in the clonidine patients whereas it stayed about the same for the placebo patients. This increase in nausea severity in the clonidine patients was associated with the increase in both the morphine use and pain severity during the washout period. Morphine levels are discussed below.

e. Morphine Levels: At baseline, the mean plasma free morphine concentration for 23 clonidine subjects with processed samples was 109.7 ng/mL with a standard error of 31.00, while the mean concentration for 34 placebo subjects was 59.0 ng/mL with a standard error of 10.13. This difference was not statistically significant. Differences in plasma free morphine concentrations between treatment arms decreased during the post-treatment period, and variances became more homogeneous. On study day 7, the mean plasma free morphine concentration for 26 clonidine subjects was 64.1 ng/mL with a standard error of 17.73, while the mean concentration for 34 placebo subjects was 88.3 ng/mL with a standard error of 18.12. On day 14, the mean plasma free morphine concentration for 23 clonidine subjects was 93.1 ng/mL with a standard error of 27.35, while the mean concentration for 30 placebo subjects was 85.5 ng/mL with a standard error of 23.56. Independent t-tests for equal variances suggested differences in plasma free morphine concentrations between treatment arms were not significant for either post-treatment assessment period.

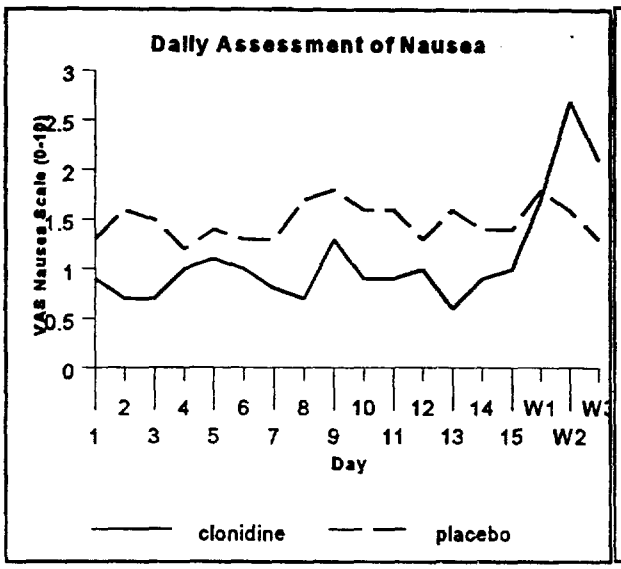


FIGURE S-5

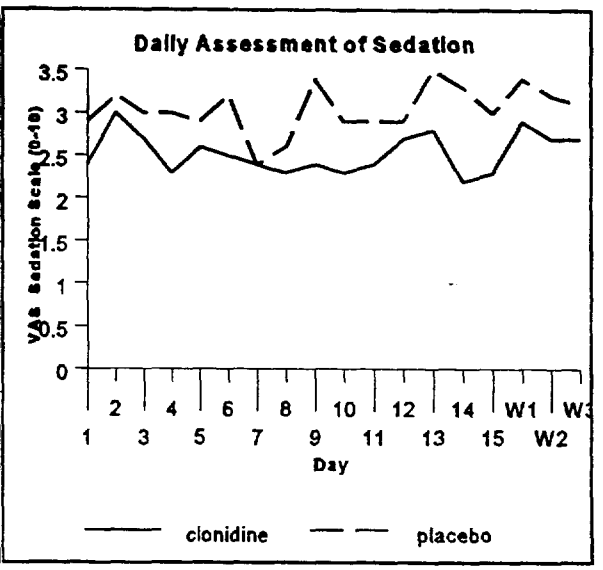


FIGURE S-6

B. OTHER SAFETY: There were no reports of serious EKG or laboratory abnormalities related to epidural clonidine in the study. The frequencies of emergent ECG abnormalities between clonidine and placebo groups were similar. Generally, adverse effects of these kinds were rarely reported with oral or topical clonidine usage.

C. CONCLUSIONS: Epidural clonidine caused hypotensive and sedative effects and lowered heart rate as might be expected from its known pharmacology. However, considering the terminal nature of the cancer patients studied, the treatment was generally safe and well tolerated. Rebound hypertension can occur on abrupt withdrawal of epidural clonidine, such as when the catheter becomes inadvertently dislodged. Caution is particularly in order for epidural clonidine treatment of patients with underlying hypertension and/or those with cardiovascular risk factors.

S-II. EC-001 EXTENSION STUDY

The safety aspects of this extension study are discussed in detail in Dr. Cerny's review (Appendix II). There were 35 patients who received infusions of epidural clonidine for periods up to 94 weeks (median duration 10 weeks). There were 21 patients (60%) who were maintained on treatment until their death. The most common adverse event was hypotension/postural hypotension in 47% of patients, then nausea (41%), anxiety/confusion (38%) and somnolence (25%). Bradycardia was not a problem in this part of the study. There were epidural catheter problems in 18% of clonidine patients. These included clogging, dislodging, inadvertent intrathecal administration and infection. One patient experienced meningitis possibly associated with catheter infection. These problems are not unanticipated with prolonged epidural catheterization. In conclusion, epidural clonidine infusion (30 mcg/h) appeared to be well tolerated in cancer pain treatment since most patients stayed with the treatment until death. A true assessment of safety is difficult since there were no clear baselines and there was no substantive placebo group for comparison. However, considering the terminal nature of the patients' conditions, the treatment appears to be sufficiently safe for their long-term use.

S-III. OTHER STUDIES

A. OTHER CANCER PATIENT STUDIES SPONSORED BY FUJISAWA

1. Study 87-3000

a. Design: This open-label, exploratory study involved bolus dose treatment with epidural clonidine of nine patients (mean age 55; five men and five women) with intractable metastatic cancer pain. Patients received three escalating bolus doses of epidural clonidine on consecutive days. The first three received 100, 200 and 300 mcg, the next three received 400, 500 and 600 mcg, and the last three were administered 700, 800 and 900 mcg epidural clonidine. Supplemental analgesia was provided through Patient Controlled Analgesia with intravenous morphine. Further details of the trial are found in Section E-III-A-2 and in the publication: Eisenach JC et al, Anesthesiology 1989:71:647-52.

b. Safety Results:

i. Blood Pressure: Mean time for maximum change in blood pressure was 83±14 min (range 0-240 min). Mean arterial blood pressures prior to injection were similar for low, medium and high dose groups (range 94 to 101 mm). All doses resulted in lowering of blood pressure: -18±4.2 mm for the 100-300 mcg group and -31±2.6 mm and -28±3.1 mm for the 400-600 mcg and 700-900 mcg groups respectively. The magnitude of blood pressure decrease was greater in two patients with hypertension.

ii. Heart rate: Mean time for maximum changes in heart rates 131 + 17 min (range 15-360 min). Mean heart rates prior to injection were similar (range 86 to 98 bpm). All doses resulted in lowering of heart rate: -15±2.0 bpm for the 100-300 mcg group and -25±2.5 mm and -24±2.0 mm for the 400-600 mcg and 700-900 mcg groups respectively.

iii. Sedation: There was a dose-related sedative effect of clonidine over the 6-hours of close measurement following epidural administration. Patients tended to be dozing or asleep at the high doses (700-900 mcg) and usually drowsy at the lower doses.

iv. Other: Mean serum glucose and cortisol were unchanged for all groups. Seven of the patients received epidural clonidine and morphine infusions on a compassionate basis for periods up to five months until their death.

c. Conclusions: There were hypotensive and bradycardiac effects of epidural clonidine that were significantly greater for the higher dose groups, but seem to have plateaued at the level of the middle dose group. There was also a dose related sedative effect.

B. PUBLISHED STUDIES OF TREATING INTRACTABLE CANCER PAIN WITH EPIDURAL CLONIDINE

1. Open-Label Publications: Five publications of open-label studies refer to 32 other cancer patients treated with boluses of epidural clonidine; these are also discussed in Section E-III.

Reference	Number of Patients	Dose/(Adverse Events)
Petros and Bowen Wright (Lancet 1987;(8540):1034)	1	150 μg q 12 hours + morphine (no adverse event reported)
Strum, et al. (Anaesthesia 1984;39:834-5)	1	300 to 900 μg + morphine (bradycardia, hypotension and sedation)
Lund et al (Eur J Anaesthesiology 1989;6:207-13)	12	150 μg (11 of 12 patients had decreased blood pressure. Mean arterial pressure fell by 19 mm)
Ferit et al (Regional Anesthesia 1992;17:173)	15	750 μg (sedation x 2 hours; heart rate reduced 24%; mean arterial pressure fell by 27%)
Germain H (Proceedings of the World Congress on Pain 1988;ch52:472-6)	3	4 to 10 μg/kg (sedation, xerostomia, hypotension).

2. Conclusions: These studies confirm the hypotensive, bradycardiac and sedative effects of epidural clonidine previously discussed.

C. OTHER PATIENT POPULATIONS EXPOSED TO EPIDURAL CLONIDINE

1. Post Caesarian Section Patients:

a. Fujisawa Supported Study: 60 of 63 patients completed a double-blind comparison of epidural boluses of clonidine 800 mcg and 400 mcg vs. saline, followed by infusions of 40 mcg/h clonidine or placebo (Huntoon M et al. Anesthesiology 1992; 76:187-93). Patients had received either bupivacaine or chloroprocaine anesthesia and could receive intravenous morphine as needed.
i. Efficacy: The study is poorly reported, but the authors claim significant analgesic effects detected for clonidine after bupivacaine, and only at the highest dose of clonidine, after chloroprocaine. The numbers of patients in each subgroup were not reported; but whether the total patient population showed significant pain reduction or morphine usage lowering effects relative to placebo with these relatively high bolus doses of clonidine is questionable.
ii. Safety: Clonidine did seem to prolong motor blockade in women receiving bupivicaine. There were decreases in blood pressure, particularly in the low-dose group and in heart rate. One patient required fluid for treatment of hypotension; one patient had bradycardia (48 beats/min) and one had hypoxemia with snoring associated with deep sedation.

b. Other C-Section Study: A published study of 60 women receiving epidural boluses of clonidine 800 mcg or 400 mcg or saline, followed by infusions of 10 or 20 mcg/h clonidine or placebo, used only bupivacaine for anesthesia and also allowed supplemental intravenous morphine use. The authors claimed some reduction in morphine use with clonidine, but admitted that part of the analgesia may have been attributable to the long action of bupivicaine. Again, blood pressure was lowest in the low-dose clonidine group. Both doses decreased heart rate relative to placebo. One patient had bradycardia (42 beats/min) along with premature atrial contractions and underwent treatment with atropine. There was dose-dependent sedation and high-dose prolongation of bupivacaine-induced motor blockade.

c. Conclusions: The analgesic efficacy of epidural clonidine in managing post-Caesarian Section pain is not proven by these trials. The possibility of prolongation of bupivacaine effects can be hypothesized from these trials, particularly since motor blockade was prolonged. Sedation was dose dependent. The hypotensive and bradycardiac effects have been clinically significant in a few patients. Labeling of epidural clonidine should specifically exclude usage for this indication, since safety is inadequately tested and efficacy is unproven.

2. Other Types of Patients with Pain: Dr. Lillian Burke's Medical Officer Review of the literature on epidural and other routes of administration of clonidine is attached as Appendix I. Also attached as Appendix II is Dr. Burke's brief summaries of the many publications describing clinical trials of epidural clonidine for postoperative pain, cancer pain, and chronic nonmalignant pain, such as refractory reflex sympathetic dystrophy or spinal cord injury pain. The efficacy data for these indications are skimpy and anecdotal or hypothetical in nature. The safety information gleaned from these trials is in accord with the expected effects of clonidine, namely blood pressure and heart rate reduction and sedation, but is inadequate to support its epidural usage in indications other than intractable cancer pain.

S-IV. OVERALL SAFETY CONCLUSIONS

The use of epidural clonidine is associated with significant reduction of blood pressure and heart rate and with dose-related sedative effects. Many patients became significantly hypotensive. There were also cases of rebound hypertension on abrupt withdrawal of treatment. Considering the terminal nature of the patient population, the treatment of intractable cancer pain by continuous infusion of epidural clonidine at 30 µg/hr appeared to be safe and well tolerated. The data associated with the treatment of other patient populations with various pain conditions is limited and does not justify safe usage of epidural clonidine for these conditions.

MEDICAL OFFICER REVIEW
DIVISION OF ANESTHETIC, CRITICAL CARE & ADDICTION DRUG PRODUCTS

NDA#: 20,615 Orphan Drug Designation No. 88-80-343-S
NAME: Epidural Clonidine HCl
APPLICANT: Fujisawa USA
SUBMISSION DATE: 7/95
INDICATION: Intractable Cancer Pain
REVIEWERS: Monte L. Scheinbaum, PhD., MD, Medical Officer, Lillian Burke, MD, Medical Officer, and Igor Cerny, Pharm D
PEER REVIEWER: Robert Bedford, MD CSO: Mildred Wright
DATE OF REVIEW: 6/6/96

REVIEW OF EPIDURAL CLONIDINE FOR THE TREATMENT OF PAIN ASSOCIATED WITH ADVANCED CANCER

INTRODUCTION

Clonidine is a well known α_2-adrenergic partial agonist approved by FDA in 1974 for the treatment of hypertension. It is available in both oral and transdermal forms in the USA and as a parenteral formulation in Europe. Clonidine is thought to reduce blood pressure by various mechanisms. It suppresses sympathetic outflow from the brain by activation of α_2-adrenergic receptors in the cardiovascular control centers. It inhibits preganglionic sympathetic nerve activity and suppresses epinephrine release from peripheral nerve endings activating presynaptic α_2-receptors. Clonidine can also activate postsynaptic α_2-receptors in vascular smooth muscles, resulting in increased blood pressure.

Animal and human studies have suggested analgesic properties for clonidine, particularly when given intraspinally. Eisenach et al found dose-dependent α-adrenergic-mediated analgesia of epidural clonidine in sheep, using chronic indwelling epidural cannulae. There were mild reductions in heart rate and cardiac output, but no neurotoxicity was observed, as evidenced by the absence of effects on neurobehavior, spinal cord histology and spinal cord blood flow.

Clonidine is postulated to produce analgesia by mimicking the actions of norepinephrine, normally released from the bulbo-spinal neurons that modulate pain transmission. It is thought to block transmission of pain signals in the spinal cord by activating both presynaptic α_2-receptors that inhibit substance P release and also postsynaptic α_2-adrenoceptors that inhibit dorsal horn firing. In contrast to opiates, its analgesic effects are not inhibited by naloxone.

Since clonidine may produce analgesia by a non-opiate mechanism, it could be useful in individuals tolerant to opiates and in pain states where opiates are less effective, such as neurogenic or deafferentation pain syndromes. Clonidine might be better tolerated than morphine by certain patients, since it has a different adverse event spectrum than the opiates. It would be unlikely to cause narcotic effects such as respiratory depression; the latter is frequently a limiting factor in the use of morphine for cancer pain. However, clonidine might be expected to cause hypotensive and other cardiovascular problems in many patients. Because clonidine is absorbed into the circulation more extensively following epidural than intrathecal injection, the sponsors reasoned that epidural clonidine would be preferred to intrathecal administration since peripheral, systemic hypertensive effects would tend to balance the central hypotensive activity.

This NDA includes a randomized, double-blind, placebo-controlled, multicenter, 2-week trial (EC-001) of continuously infused epidural clonidine in advanced cancer patients with intractable pain (38 of 85 patients received clonidine). This is designated as the pivotal efficacy study and is the basis for evaluating the efficacy of clonidine in this indication. There was also a long-term extension associated with this trial (35 patients receiving clonidine). Also included in the submission are brief summaries of a healthy volunteer study (92-3001) involving single bolus doses of epidural clonidine (19 subjects), an open-label pilot study (87-3000) in ten patients with cancer pain, and a double-blind, placebo-controlled study (89-3003) of C-section patients (83 of 123 received clonidine). These latter studies, along with published studies, provide data relevant to the safety of epidural clonidine administration.

There are a number of published studies describing results of continuous infusions of epidural clonidine included in the submission: There was an open-label study of seven healthy volunteers. There were four open-label studies of epidural clonidine in a total of 29 patients with intractable cancer pain. There were two published trials in chronic non-cancer pain, one in patients with reflex sympathetic dystrophy (19 of 26 received clonidine), another was in 12 patients with non-cancer pain treated up to 23 days. There were seven trials involving a total of 169 patients with postoperative pain receiving continuous infusions of epidural clonidine. There were also 37 publications of controlled trials involving bolus injections of epidural clonidine in a total of 787 patients with non-cancer pain.

Dr. Lillian Burke's Medical Officer review of the clonidine literature, attached as Appendix I, with summaries of individual published studies attached as Appendix II, discusses results of these trials.

MEDICAL OFFICER REVIEW
DIVISION OF ANESTHETIC, CRITICAL CARE & ADDICTION DRUG PRODUCTS

NDA#: 20,615 Orphan Drug Designation No. 88-80-343-6
NAME: Epidural Clonidine HCl
APPLICANT: Fujisawa USA
SUBMISSION DATE: 7/95
INDICATION: Intractable Cancer Pain 6/6/96
REVIEWERS: Monte L. Scheinbaum, PhD., MD, Medical Officer, Lillian Burke, MD, Medical Officer and Igor Cerny, Pharm D, Interdisciplinary Scientist
PEER REVIEWER: Robert Bedford, MD CSO: Mildred Wright
DATE OF REVIEW: 6/6/96

REVIEW OF EPIDURAL CLONIDINE FOR THE TREATMENT OF PAIN ASSOCIATED WITH ADVANCED CANCER

CONCLUSIONS

1. Epidural clonidine infusion at a rate of 30 mcg/h is recommended for approval for the treatment of cancer patients with intractable pain primarily of neuropathic nature inadequately responsive to morphine.

2. Epidural clonidine showed hypotensive and sedative effects and lowering of heart rate as might be expected from the known history of oral and topical use of clonidine, but was generally well tolerated by cancer patients. Long-term epidural catheterization did cause expected problems, such as infection, clogging and dislodging.

3. Epidural clonidine, like the traditional formulations of clonidine, can cause serious rebound hypertension on abrupt withdrawal. This can happen in association with inadvertent dislodging or clogging of the epidural catheter. Appropriate cautions, particularly for patients with underlying hypertension and/or cardiovascular risk factors, are in order for the labeling.

4. The analgesic efficacy was no different from placebo in cancer patients with intractable pain primarily of somatic or visceral nature. Epidural clonidine should not be recommended for the treatment of such patients, particularly if they have not otherwise undergone epidural catheterization.

Medical Officer Secondary Review

JUN 24 1996

NDA #: 20-615

PRODUCT TRADE NAME: Epidural Clonidine JUN 24 1996

SPONSOR: Fujisawa

LETTER/SUBMISSION DATE: Aug 9, 1996

CSO: Millie Wright

Primary Reviewers: Monte Scheinbaum, M.D., Ph.D.: Pivotal Efficacy Trial

Igor Cerny, Pharm.D.: Safety Review of Pivotal Trial

Lillian Burke, M.D.: Literature Review

Secondary Reviewer: Robert F. Bedford, M.D.

COMPLETION DATE: June 24, 1996

1. Background

Cancer pain has been identified as one of the scourges of the human condition and the World Health Organization has promoted relief of cancer pain as one of its major world-wide public health initiatives. Traditionally, cancer pain has been managed by opioids and non-steroidal analgesic agents, given either alone or in combination. These drugs are usually given orally, but may be given parenterally when subtherapeutic blood levels or GI toxicity become problematic during oral dosing.

Intraspinal administration of opioids, usually morphine, permits effective relief of cancer pain in patients suffering debilitating side-effects of parenteral or orally-adminstered medications. Because administration of intraspinal opioids results in high concentrations of drug at spinal cord opioid receptors, this route offers symptomatic pain relief with fewer systemic opiate side effects than either oral or parenteral administration. Usually, intraspinal opioids are given epidurally, although occasionally, the intrathecal route may be utilized. The primary hazards of intraspinal opioid administration at high levels are: respiratory depression due to mμ agonist effects on brainstem respiratory centers and thoracolumbar CNS excitability, characterized by epileptiform movements generated from spinal segments with maximal opioid concentration.

Among patients whose pain progresses to the point where intraspinal opioids are required, there is a minority in whom pain recurs despite progressive intraspinal opioid dose escalation or in whom opioid side-effects become intolerable. At this point in the disease progression, there is little additional analgesia that can be offered short of

neuroablative procedures such as intrathecal phenol injection or neurolytic surgery.

Clonidine, an alpha-2 adrenergic agonist, has long been recognized to have analgesic, sedative and hypotensive effects when administered either parenterally or intraspinally. Thought to stimulate release of norepinephrine from inhibitory intermedullary neurons impinging on the spinal cord sensory pathways in the dorsal columns, it has been found to be effective in producing segmental analgesia for intraoperative and postoperative pain relief when injected epidurally in single doses of approximately 150 μg. In addition, under treatment IND conditions, it has been found to relieve cancer pain in many patients who have become resistant to the effects of intraspinally administered opioids, particularly those with neuropathic pain, who are notoriously refractory to the analgesic effects of opioids. While analgesia induced by clonidine is not reversible with naloxone, it does appear to interact additively with intraspinally-administered opioids, thus reducing opioid-induced side-effects.

The sponsor seeks approval of this NDA under the Orphan Drug Statutes, since only a limited number of cancer patients are expected to become resistant to the effects of epidurally administered opioids. This application consists of one pivotal trial in cancer patients, plus approximately 100 reports from the world's literature on the subject of analgesic effects of epidurally administered clonidine in a variety of clinical contexts.

2. Clinical Study: EC-001. Reviewed by Drs. Scheinbaum and Cerny.

This trial was performed as a double-blind, placebo-controlled multicenter study in cancer patients with pain below the C-4 level who were requiring large doses of systemic or epidural opioids. They were stabilized for 1-7 days on epidurally-administered morphine via a PCA-pump (5 to 15 supplements/day) to a moderate-to-good level of analgesia. Prior to randomization, patients were stratified into those with evidence for neuropathic pain (referable to a peripheral nerve or dermatomal distribution) and those without neuropathic pain elements.

Efficacy was determined by titration of morphine self-administration and VAS scale recorded twice daily. In addition, patients were examined and their blood pressures were checked daily during the 2-week observation period. Patients received either clonidine, 30μg/hr, or placebo, via their epidural catheter, and were then allowed *ad lib* additional opioid PCA access. The epidural infusions were scheduled to last 14 days, with an additional 3 days of followup during a "washout" period. Initially there were 85 patients recruited: 38 received clonidine and 47 received placebo for at least 1 day. At day 8, there were 66 patients and a total of 50 patients received epidural clonidine or placebo for all 14 days. Treatment success was defined as a reduction in either VAS or morphine usage, without an increase in either variable.

While epidural clonidine infusion, 30 μg/hr, added to epidural morphine PCA, resulted in a statistically significant improvement in all patients, it was in patients with neuropathic pain, where there was a 56% incidence (10 of 18 patients) of treatment success, that the efficacy of this treatment modality was made evident. By contrast, in patients without neuropathic pain, epidural clonidine resulted in the same incidence of treatment success (7/20=35%) as was observed in those receiving placebo (9/20 = 31%). Prior use of epidural narcotics had no influence on the incidence of treatment success with epidural clonidine. Withdrawal of clonidine at the end of the 14-day infusion period resulted in a significant increase in epidural morphine usage and a decrease in theVAS scores. The efficacy data were reanalysed in a variety of ways, but the same conclusions hold: epidural clonidine infusion was effective from the beginning of its infusion until its termination, but only in patients who had neuropathic pain.

This finding creates a difficult conundrum with regard to labeling, since in many patients with refractory cancer pain, it is difficult to predict who has neuropathic elements in their pain syndrome. Given the desperate situation of these patients, it would be a shame not to offer this modality to all in the hope that some might benefit. For those who do not, it appears that the diagnosis will be made early-on and that nobody would be over-treated in hopes of developing a delayed response.

As expected, epidural clonidine infusion resulted in a significant reduction in blood pressure and, as expected, the major complications of active drug treatment were cardiovascular, with a 45% incidence of hypotension in clonidine patients, compared to 11% of placebo-treated patients. In addition, postural hypotension was noted in none of the placebo group, but in 32% of the clonidine-treated patients. Two patients (both in the clonidine group) dropped out of the study because of hypotension. The vast majority of hypotensive episodes occurred during the first 4 days of treatment. Women were more likely than men to develop hypotension (82% vs 56%), probably due to higher sympathectomy induced by a fixed-dose clonidine infusion in smaller people. There was no difference between the treatment groups with regard to the incidence of other typical clonidine reactions such as dry mouth, nausea, bradycardia or somnolence.

At the time of clonidine discontinuation there was also a significant increase in blood pressure. Five patients were reported as having hypertension during the washout phase and 2 of these required re-institution of clonidine treatment. An additional patient had rebound hypertension followed by a cerebrovascular accident, which was a direct cause of the patient's death. Clearly, the risks of rebound hypertension must be addressed adequately in the product labeling.

While bradycardia was not a clinical problem during the trial, it is noteworthy that patients treated with clonidine had significantly lower heart rates than those treated with

placebo. The combination of lower heart rate responsiveness and decreased blood pressure makes possible off-label use of epidural clonidine for perioperative pain relief a particularly worrisome modality, since hypovolemia is common after major surgery and compensatory cardiovascular mechanisms may be inhibited by clonidine treatment.

3. Literature Review: Dr. Burke

In addition to the clinical trial noted above, Dr. Lillian Burke reviewed the available literature on the use of epidural clonidine for a variety of painful conditions in addition to opioid-resistant cancer pain. Her review involves publications covering over 1600 patients, including 66 patients in the above study and an additional 29 patients in supportive studies.

The primary thrust of the studies performed in cancer patients is that epidural clonidine, administered in doses from 150 to 2300 μg/day, rapidly induces segmental analgesia in a dose-dependent fashion and interacts additively with opioids administered systemically or intraspinally. Tachyphylaxis appears to develop with time (days to weeks), although the increased dose-requirement may also be related to disease progression. Side-effects of epidurally administered clonidine can be frequently mitigated by decreasing dosage, although specific symptoms referrable to hypotension may require specific treatment with IV fluid replacement and/or vasopressors.

Reports on the impact of epidural clonidine administration on neuropathic pain have been uniformly favorable. Although rarely placebo-controlled, the overall incidence of success for these myriad indications (reflex sympathetic dystrophy, deafferentation, arachnoiditis, post-herpetic neuralgia, etc.) approaches 82%. In reviewing the available literature on this subject, it seems that these syndromes appear to be more sensitive to epidural clonidine, with nearly uniformly successful responses even when given in low, single doses.

Acute perioperative pain can also be treated successfully with epidural clonidine, albeit with higher doses than are required for neuropathic pain and with a higher incidence of side-effects, particularly hypotension. Indeed, as Dr. Burke points out in her review, there may be an anti-analgesic effect of low-dose epidural clonidine in the acute pain setting. As is the case with chronic pain syndromes, however, epidural clonidine interacts in an additive fashion with concurrently-administered opioids and appears to markedly increase the duration of analgesia obtained with both epidurally administered opioids and local anesthetics.

The primary concern regarding the use of epidural clonidine for perioperative pain relief is the relatively high incidence (20-30%) of arterial hypotension, which appears to be dose-dependent until higher doses (800 μg) result in increases in blood pressure

from peripheral α–2 agonist effects. Pre-treatment fluid loading appears to reliably reduce the incidence of hypotension in perioperative patients, but the success of this prophylactic therapy also suggests that routine postoperative use of epidural clonidine in patients who are at risk for hypovolemia from third-space fluid losses is likely to result in severe hypotension and possible serious cardiovascular complications. As expected, higher levels of α–2 agonist effects result in greater degrees of hypotension due to a greater degree of thoracolumbar sympathectomy.

Another side-effect of clonidine is sedation which, in turn, can augment the respiratory depressant effects of opioids. In the case of cancer patients who are refractory to the effects of opioids, the additional sedation caused by clonidine is unlikely to be problematic. By contrast, sedation in opioid-naive patients who are simultaneously receiving opioids has the potential to produce serious respiratory depression. Studies that have examined postoperative respiratory function following either epidural opioids or opioid/clonidine combinations have, in general, noted a lower incidence of decreased SpO_2 in the combination patients, apparently due to their lower opioid dose-requirement. Thus, it appears that postoperative respiratory depression is not more likely in clonidine-treated patients, as long as their dosage of opioid is reduced appropriately.

Rebound hypertension is well-described in the clonidine literature and has been noted in several instances following epidural administration, both in the above pivotal study and elsewhere. This is clearly an issue that needs to be adequately addressed in the labeling, since administration of clonidine via other routes can rapidly control this complication.

Interaction of epidural clonidine with concomitant local anesthetics also requires attention. While this combination potentiates the sensory effects of local anesthetics and increases the duration of analgesia, there is substantial evidence that it also increases the degree of sympathectomy, since both drugs reduce sympathetic outflow at the thoracolumbar level. Thus, the incidence of hypotension in the perioperative situation is likely to be increased when patients are treated with both local anesthetic and clonidine simultaneously for perioperative pain relief.

4. CONCLUSIONS:

It is this reviewer's opinion that the sponsor's NDA for epidural clonidine, as indicated for opioid-resistant cancer pain, should be approved. There is extensive documentation that the drug is an effective analgesic and the risks appear to be relatively minor for this patient population. Whether the indication should be further-refined to patients with neuropathic pain is debatable. While the application makes it appear that there is a bright-line distinction between somatic and neuropathic pain, that has not been my

clinical experience. Indeed, one of the clinical tip-off's that neuropathic pain is present is resistance to epidural opioids. Therefore, I would favor indicating epidural clonidine for all cancer pain refractory to intraspinally-administered opioids, since the risks of co-administration are relatively low and the benefits can be impressive.

The major concern with this approval is the possibility that epidural clonidine will be used off-label for routine postoperative pain control. In this setting, the risk of cardiovascular collapse in the face of modest postoperative hypovolemia is not inconsiderable.

5. RECOMMENDATIONS:

a. Approval, with a black-box label warning against use for perioperative analgesia.

b. Additional issues to be resolved with appropriate labeling:
Appropriate dosing regimen for chronic administration,
Arterial hypotension,
Respiratory depression,
Rebound hypertension,
Interaction with local anesthetics

Robert F. Bedford

Robert F. Bedford, MD 6/24/96

Orig NDA # 20-615
HFD-170/Div File
HFD-170/RBedford
HFD-170/ MWright
~~HFD-502~~
~~HFD-340~~
~~F/T by~~
HFD-170/ Scheinbaum, Burke.

Safety Review
of Pivotal Study EC-001 and EC-001 Extension

NDA#: 20-615 (Orphan Drug Designation #88-80-3434-6)

Drug: Clonidine hydrochloride 100 mcg/ml Injection for Epidural use

Sponsor: Fujisawa USA, Inc.

Indication: "...adjunctive therapy with intraspinal opiates for the treatment of pain in cancer patients tolerant to, or unresponsive to, intraspinal opiates alone."

Reviewer: Igor Cerny, Pharm.D. Igor Cerny, Pharm.D. 6/11/96

Submission Date: 8/4/95

Date to Reviewer: 5/2/96

Date of Review: 6/11/96

INDEX To Review:

1. Pivotal Study EC-001 (placebo-controlled):

2. Extension Study EC-001 (open-label):

1. Pivotal Study EC-001

A. Study Objective: To evaluate the analgesic efficacy and clinical safety of epidurally administered clonidine compared to epidurally administered placebo in the treatment of intractable cancer pain

B. Protocol Synopsis: This was a randomized, double-blind, placebo-controlled, parallel-group multi center phase III study of epidurally administered clonidine and placebo. Many of the study design issues are discussed in Dr. Scheinbaum's efficacy review but the essential elements will be re-stated here for convenience.

Subjects eligible for study participation included those:

- having cancer with a life expectancy beyond the 18 study days.
- with severe intractable pain located below the C4 dermatome, severe intractable pain being defined as severe pain not relieved by large doses of opiates (equivalent to 100 mg morphine/day systemically or 20 mg/day epidurally), or severe pain in individuals intolerant of opiates due to therapy-limiting adverse events.
- Eighteen years of age or older

Those hypersensitive to clonidine or with a serum creatinine > 3.5 mg/dl (clonidine being renally eliminated) were excluded. During the titration period, subjects were switched from alternative morphine dosing to epidural patient controlled (CADD-PCA® pump) morphine dosing over a 1-7 day period. Morphine was titrated to a dosage at which the patient requested medication between 5-15 times per day. For a minimum of 24 hours before randomization, the patient had to be on a single dose of morphine that was triggered by the patient approximately 5 to 15 times. This dosing schedule had to keep the patient in a pain category of moderate or less.
Subjects were then randomized to a continuous epidural infusion of clonidine hydrochloride at 30 mcg/hr or an equal volume of placebo for 14 days as an add on treatment to the titrated morphine dose. Randomization included stratification to one of four (4) strata based on previous use of epidural narcotics and type of pain. All subjects remained in the hospital for the first 24 hours following the onset of clonidine (or placebo) infusion. Thereafter, insubjects were seen daily during the two-week trial by one of the co-investigators or a research nurse. Outpatients were seen in the clinic by one of the co-investigators at weekly intervals and daily at home by a research nurse during the two-week trial.

On study day 14, the study medication was discontinued. Daily observations were continued for three days following end of drug administration. Subjects continued to have access to epidural morphine delivered only by an ambulatory PCA device.

The sponsor refers to the last baseline day as Day 1 of the study, and the 14th (last) day of dosing as Day 15. This reviewer will refer to the baseline Day as Day 0, and the 14th day of treatment as Day 14.

C. Adverse Event Monitoring:
Assessment and description of adverse events was done daily during the 14-day treatment period and the 3-day wash-out period.

At the end of the titration period, at Day 7 and 14, a blood sample was analyzed for cortisol levels, BUN, creatinine, sodium, potassium, chloride, bicarbonate, total bilirubin, AST, LDH, alkaline phosphatase, glucose, hemoglobin, white blood cell count, platelet count and differential blood

count. An ECG was performed at these times as well.

Blood pressure (supine and standing), heart rate, temperature and respiration rate as well as the degree of sedation and nausea (as measured with 10 cm visual analog scales), were recorded:

- Twice daily during the titration period
- Every four hours for the first 24 hours following the onset of clonidine (or placebo) infusion
- Daily during the 14-day treatment period and the 3-day wash-out period

Definition and Treatment of Hypotension: Symptomatic hypotension or decrease in mean arterial blood pressure greater than 40% had to be treated with intravenous fluid administration and, if necessary, incremental intravenous ephedrine (10 mg) followed by oral ephedrine (25 mg every 4-6 hours).

A >30% increase (above pre-study baseline) in mean arterial blood pressure or any symptomatic hypertension was treated with clonidine 300 µg, orally followed by transdermal clonidine for one week.

If nausea or pruritus occurred and the subject was not already being treated for these side effects, they could be treated with oral hydroxyzine or diphenhydramine, respectively.

Adverse clinical events or abnormal laboratory values were followed until resolved. Differences between treatment arms in the frequency of out of range laboratories at baseline and again at day 7 and day 14 were assessed using Fisher's exact test (two-tailed). The frequency of adverse reactions (both individually and by body system)were compared between treatment arms using Fisher's exact test (two-tailed). Differences between treatment arms in daily assessments of vital signs, as well as in the sedation and nausea visual analog scales, were assessed using independent t-tests on each treatment day.

D. RESULTS:

1. Baseline Demographics: Table S-1 below summarizes selected baseline demographic characteristics of the 85 randomized subjects.

Table S-1: Selected baseline Demographics of Randomized Subjects

CHARACTERISTIC		Clonidine (N=38) N	Placebo (N=47) N	Total (N=85) N
SEX	Male Female	27 11	24 23	51 34
RACE	White Black Other	35 3 0	37 7 3	72 10 3
AGE (years), MEAN(S.D.)		56.8 (11.6)	56.4 (11.8)	56.6 (11.6)
WEIGHT (kg), MEAN(S.D.)		71.5 (17.2)	68.4 (16.8)	69.8 (17.0)
DISTANT METASTASES		28	38	66
MONTHS from cancer diagnosis, MEAN(S.D.)		42	30	35

2. Extent of Exposure: Of the 38 subjects randomized to receive clonidine, all 38 (100%) completed the first 24 hours of therapy (0.72 mg total dose/patient), 30 (78.9%) completed one week of therapy (5.04 mg total), and 22 (57.9%) completed the 14 day study (10.8 mg total). The mean number of days on study for clonidine subjects was 10.6, with a standard deviation of 4.7 days.

3. Subject Accounting/Discontinuations: Of the 85 subjects randomized and treated, 50 completed the 14-day treatment period, 22 subjects randomized to clonidine, 28 to placebo. Reasons for discontinuing the 15 portion of the trial are presented in Table S-2 below:

Table S-2: Reasons for Discontinuation before Completion of the 14 Day Treatment Period

Reason for Discontinuation	Clonidine (N=38)		Placebo (N=47)		TOTAL (N=85)	
	(N)	(%)	(N)	(%)	(N)	(%)
All Discontinuations	16	42.1%	19	40.4%	35	41.1%
Disease Progression	4	10.5%	4	8.5%	8	9.4%
Death	0	0.0%	2	4.3%	2	2.4%
Adverse Experience	5	13.2%	3	6.4%	8	9.4%
Patient Refused to Continue	2	5.3%	4	8.6%	6	7.1%
Physician refused to let patient continue	1	2.6%	0	0.0%	1	1.2%
Other	2	5.3%	5	10.6%	7	8.2%
Protocol Violation	2	5.3%	2	4.3%	4	4.7%

Rates of withdrawal were generally similar for the clonidine and placebo groups. Based on a proportional hazards analysis, rates of withdrawal were not significantly different between the clonidine and placebo groups after control for primary pain mechanism and prior epidural narcotic use (p=0.772). Rates of withdrawal were also similar during the first and second weeks of the study, with 78.9% (30/38) of clonidine subjects and 76.6% (36/47) of placebo subjects completing the first week (Study Day 7) and 57.9% (22/38) of clonidine subjects and 59.6% (28/47) of placebo subjects completing the second week (Study Day 14).

4. Discontinuation of Therapy due to Adverse Experiences: Ten subjects (5 in the clonidine group and 5 in the placebo group) discontinued treatment prior to completion of the 15 day study due to adverse experiences or death. These are summarized in Table S-3 on the following page:

Table S-3: Summary of Discontinuations from the 15-day trial due to Adverse Reactions

Subject#	Age	Sex	Race	Group	Day	Adverse Event
EC01-12-001	35	M	W	clonidine	3	somnolence and postural hypotension
EC01-21-001	35	F	W	placebo	6	severe drowsiness, nausea and vomiting
EC05-11-001	64	F	W	clonidine	3	severe confusion and hallucinations
EC06-22-002	65	M	B	clonidine	3	severe hypotension, postural hypotension and dizziness.
EC08-22-001	48	M	W	placebo	3	severe respiratory depression and confusion
EC08-22-002	51	M	W	placebo	14	severe dehydration, hypercalcemia and sedation
EC11-21-001	78	M	W	placebo	12	Death due to complications of malignant disease including pneumonia, shortness of breath, decreasing consciousness and decreased oxygen saturation
EC12-21-001	57	F	B	placebo	5	Death due to disease progression evidenced by tachypnea that required an increase in supplemental oxygen.
EC14-21-003	46	M	W	clonidine	5	severe pain associated with catheter infections
EC25-11-001	46	M	W	clonidine	2	severe pain associated with catheter infections

5. Adverse Events - General Discussion: Adverse events encountered during the 14-day trial experienced by two or more subjects in either group are summarized in Table S-4. The frequency of patients reporting one or more adverse experiences was significantly greater in the clonidine group than in the placebo group (37 of 38 clonidine patients, or 97.4% vs. 38 of 47 placebo patients, or 80.8%; Fisher's two-tailed exact test $p=0.0208$). The incidence of adverse experiences affecting the Cardiovascular system was significantly higher in the clonidine group (29 of 38 clonidine patients, or 76.3%, vs. 11 of 47 placebo patients, or 23.4%; Fisher's two-tailed exact test $p<0.001$). The bulk of this difference appears to have been caused by the higher incidence of hypotension (17 of 38 clonidine patients, or 44.7% vs. 5 of 47 placebo patients, or 10.6%; Fisher's two-tailed exact test $p=0.001$) and postural hypotension (12 of 38 clonidine patients, or 31.6% vs. 0 of 47 placebo patients, or 0.0%; Fisher's two-tailed exact test $p<0.001$) in the clonidine group. Incidence of other reported adverse experiences did not differ significantly between the clonidine and placebo groups (Fisher's two-tailed exact test $p>0.05$). There was no significant difference between the clonidine and placebo groups with regards to the other adverse reactions commonly attributed to clonidine such as dry mouth, nausea, somnolence, or bradycardia.

Table S-4: Summary of Adverse Reactions from the 14-day trial occurring in ≥2 subjects

Body System	Event	Clonidine (N)	Clonidine (%)	Placebo (N)	Placebo (%)	P-Value
EVENTS	ANY	37	**97.4%**	38	**80.9%**	**P = 0.021**
Cardiovascular	ANY	29	**76.3%**	11	**23.4%**	**P < 0.001**
	Hypotension	17	**44.7%**	5	**10.6%**	**P = 0.001**
	Postural Hypotension	12	**31.6%**	0	**0.0%**	**P < 0.001**
	Hypertension	5	13.2%	2	4.3%	P = 0.234
	Tachycardia	1	2.6%	2	4.3%	P = 1.000
Whole Body	ANY	17	44.7%	12	25.5%	P = 0.071
	Asthenia	2	5.3%	2	4.3%	P = 1.000
	Fever	5	13.2%	6	12.8%	P = 1.000
	Headache	2	5.3%	3	6.4%	P = 1.000
	Chest pain	2	5.3%	0	0.0%	P = 0.197
	Pain @ Injection Site	2	5.3%	1	2.1%	P = 0.584
Nervous	ANY	21	55.3%	19	40.4%	P = 0.196
	Anxiety	4	10.5%	1	2.1%	P = 0.168
	Confusion	5	13.2%	5	10.6%	P = 0.747
	Dizziness	5	13.2%	2	4.3%	P = 0.234
	Hallucinations	2	5.3%	1	2.1%	P = 0.584
	Somnolence	5	13.2%	10	21.3%	P = 0.399
Digestive	ANY	14	36.8%	19	40.4%	P = 0.824
	Constipation	1	2.6%	2	4.3%	P = 1.000
	Dry Mouth	5	13.2%	4	8.5%	P = 0.505
	GI Hemorrhage	0	0.0%	2	4.3%	P = 0.500
	Ileus	0	0.0%	2	4.3%	P = 1.000
	Nausea	5	13.2%	10	21.3%	P = 0.399
	Nausea & Vomiting	3	7.9%	1	2.1%	P = 0.320
	Vomiting	4	10.5%	7	14.9%	P = 0.747
Respiratory	ANY	7	18.4%	7	14.9%	P = 0.772
	Dyspnea	3	7.9%	4	8.5%	P = 1.000
	Hypoventilation	1	2.6%	2	4.3%	P = 1.000
Miscellaneous	Peripheral edema	1	2.6%	2	4.3%	P = 1.000
	Sweating	2	5.3%	0	0.0%	P = 0.197
	Tinnitus	2	5.3%	0	0.0%	P = 0.197
	Urinary Tract Infect	2	5.3%	0	0.0%	P = 0.197

Table S-5 on the next page summarizes those adverse events that occurred during the 14-day trial in ≤1 subject.

Table S-5: Summary of Adverse Reactions from the 14-day trial occurring in ≤1 subject

Body System	Event	Clonidine (N)	Clonidine (%)	Placebo (N)	Placebo (%)	P-Value
Cardiovascular	Arrhythmia	0	0.0%	1	2.1%	P = 1.000
	Atrial Arrhythmia	0	0.0%	1	2.1%	P = 1.000
	Bradycardia	1	2.6%	0	0.0%	P = 0.447
	Ventricular Extrasystoles	0	0.0%	1	2.1%	P = 1.000
	Atrial Fibrillation	1	2.6%	0	0.0%	P = 0.447
	Heart Failure	1	2.6%	0	0.0%	P = 0.447
	Syncope	1	2.6%	0	0.0%	P = 0.447
	Cerebrovascular Accident	1	2.6%	0	0.0%	P = 0.447
Whole Body	Chills	1	2.6%	0	0.0%	P = 0.447
	Infection	0	0.0%	1	2.1%	P = 1.000
	Injection Site Reaction	1	2.6%	0	0.0%	P = 0.447
	Pain	1	2.6%	0	0.0%	P = 0.447
	Back Pain	1	2.6%	0	0.0%	P = 0.447
Nervous	Agitation	1	2.6%	0	0.0%	P = 0.447
	Amnesia	1	2.6%	0	0.0%	P = 0.447
	Convulsion	1	2.6%	0	0.0%	P = 0.447
	Diplopia	0	0.0%	1	2.1%	P = 1.000
	Dry Mouth	1	2.6%	0	0.0%	P = 0.447
	Dysarthria	0	0.0%	0	0.0%	P = 1.000
	Hyperkinesia	0	0.0%	0	0.0%	P = 1.000
	Myoclonus	0	0.0%	1	2.1%	P = 1.000
	Nervousness	1	2.6%	0	0.0%	P = 0.447
	Neuropathy	1	2.6%	1	2.1%	P = 1.000
	Stupor	1	2.6%	0	0.0%	P = 0.447
	Tremor	1	2.6%	0	0.0%	P = 0.447
	Vertigo	1	2.6%	0	0.0%	P = 0.447
Digestive	Diarrhea	0	0.0%	1	2.1%	P = 1.000
	Dyspepsia	1	2.6%	0	0.0%	P = 0.447
	Dysphagia	0	0.0%	1	2.1%	P = 1.000
	Rectal Hemorrhage	0	0.0%	1	2.1%	P = 1.000
	Hematemesis	0	0.0%	1	2.1%	P = 0.447
	Oral Monilia	1	2.6%	0	0.0%	P = 0.399
Respiratory	Apnea	1	2.6%	0	0.0%	P = 0.447
	Asthma	0	0.0%	1	2.1%	P = 1.000
	Epistaxis	1	2.6%	0	0.0%	P = 0.447
	Pharyngitis	1	2.6%	0	0.0%	P = 0.447
	Pneumonia	0	0.0%	0	0.0%	P = 1.000
	Rhinitis	0	0.0%	0	0.0%	P = 1.000
Heme/Lymph	Anemia	1	2.6%	1	2.1%	P = 1.000
	Anemia (hypochromic)	1	2.6%	0	0.0%	P = 0.447
	Leukopenia	1	2.6%	0	0.0%	P = 0.447
Metabolic	Dehydration	0	0.0%	1	2.1%	P = 1.000
	Edema	0	0.0%	1	2.1%	P = 1.000
	Hypercalcemia	0	0.0%	1	2.1%	P = 1.000
Musculoskeletal	Myasthenia	0	0.0%	1	2.1%	P = 1.000
	Bone pain	1	2.6%	0	0.0%	P = 0.447
Skin	Herpes Zoster	1	2.6%	0	0.0%	P = 0.447
	Pruritus	0	0.0%	1	2.1%	P = 1.000
	Skin Ulcer	1	2.6%	0	0.0%	P = 0.447
Senses	Amblyopia	1	2.6%	0	0.0%	P = 0.447
	Taste perversion	1	2.6%	0	0.0%	P = 0.447
Urogenital	Urinary incontinence	0	0.0%	1	2.1%	P = 1.000
	Impaired urination	0	0.0%	1	2.1%	P = 1.000
	Urinary retention	0	0.0%	1	2.1%	P = 1.000

6. Specific Adverse Events

a. **Hypotension:** As noted above, hypotension and postural hypotension occurred much more frequently in the clonidine group than in the placebo group ($p \leq 0.001$). Figures S-1 through S-4 on the following pages summarize the mean supine diastolic, supine systolic, standing diastolic, and standing systolic blood pressures.

FIGURE S-1: Daily Mean Supine Diastolic Blood Pressure (mmHg) compared (* = P<0.05)

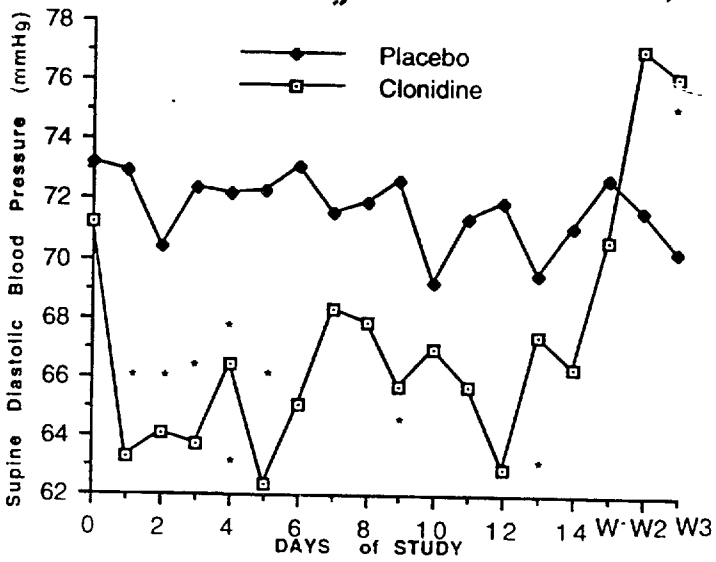
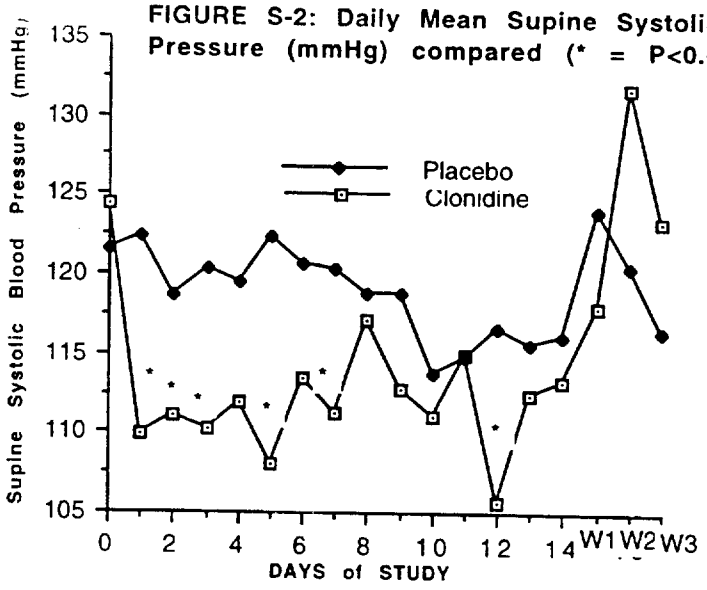
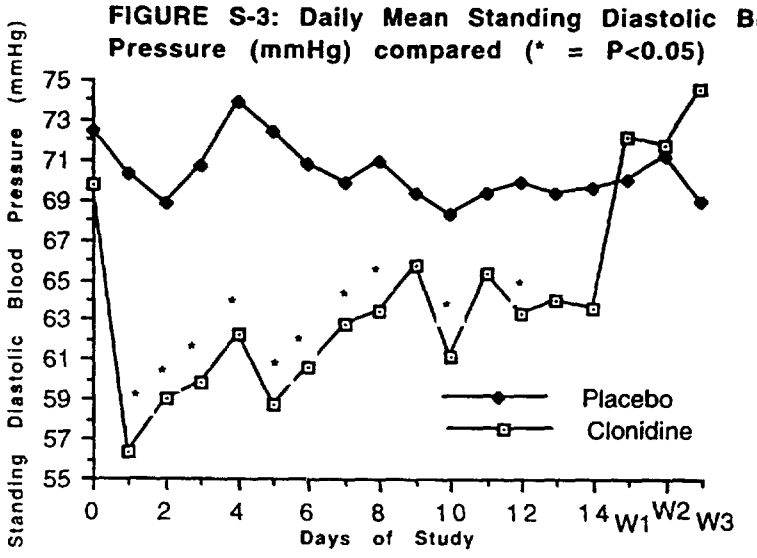
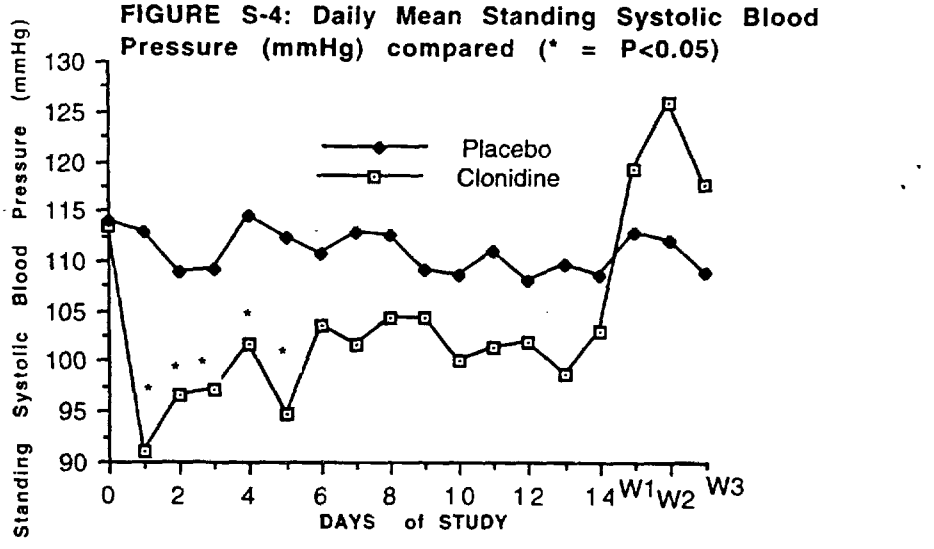


FIGURE S-2: Daily Mean Supine Systolic Blood Pressure (mmHg) compared (* = P<0.05)







There are a few problems in the assessment of the hypotension data presented by the sponsor. First of all, the sponsor has rather vaguely defined hypotension as *"Symptomatic hypotension or decrease in mean arterial blood pressure greater than 40% ..."*. It is not clear what symptoms were considered indicative of hypotension or how much of a decrease in either systolic or diastolic blood pressure accompanied by these symptoms would be sufficient to label the event "hypotension." Also it is not clear if supine or standing readings were to be used. And, this reviewer is *assuming* that the 40% decrease is measured from a baseline reading.

Second, "Mean arterial pressure" is typically defined as Diastolic BP+ 1/3(Systolic BP - Diastolic BP). Again, it is unclear if supine or standing readings were to be used in this calculation, or even if the investigator actually did this calculation and compared it to the baseline reading before treating a subject (none of the sponsor's submitted data discuss mean arterial pressure).

Third, there are no criteria described for defining "postural hypotension" so it is unclear how an event would fall into this category.

Fourth, since after the first study day subjects were seen only once a day, it is unclear how hypotensive events were caught. Were these events diagnosed and treated only at the time of the co-investigator or research nurse's visit or could hypotension be diagnosed and treated at other times by other personnel?

Thus, these questions appear to compromise the reliability of the sponsor's hypotension data. It appears perhaps that the labeling of an event as either "hypotension" or "postural hypotension" was left to the individual co-investigator or research nurse.

That said, this reviewer attempted to determine if there were any differences between those subjects on clonidine who were judged to have had a hypotensive event versus those on clonidine who did not have such an event. Table S-6 below summarizes these findings.

Table S-6: Summary of Differences between subjects who did or did not become Hypotensive (including postural) on clonidine

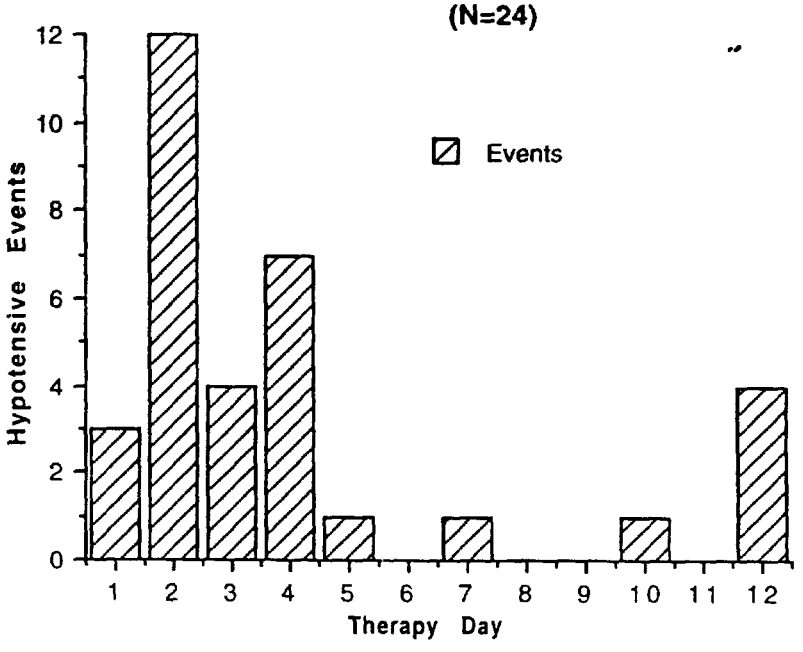
GROUPS	N	Mean Age	Sex	Race	Mean % Success	Weight (kg) ± SEM	Day 7 clonidine level
HYPOTENSIVES	24	55	15 M 9 F	22 W 2 B	45.8	67.5 ± 3.5	2.37**
NON-HYPOTENSIVES	14	58	12 M 2 F	13 W 1 B	42.9	78.4 ± 4.0	1.89**

** = two subjects (EC1-12-001 and EC6-22-002) were dropped from the study due to postural hypotension and thus did not have day 7 serum clonidine levels drawn

Given that the data from Table S-6 are generated from a retrospective analysis and with a rather small number of subjects, this reviewer would urge caution before broadly extrapolating these findings. That said, sex, weight, and Day 7 clonidine level stand out as differences between those subjects who experienced a hypotensive event versus those who didn't. Of the 11 women who received clonidine, 9 (82%) experienced a hypotensive episode versus 15 of 27 (56%) of the men. However, both of the subjects who discontinued the study due to hypotension were men. Also, those experiencing a hypotensive episode were 11 kg lighter than those that did not. Lastly, those subjects experiencing hypotension tended to have a slightly higher Day 7 serum clonidine level. However, it is important to note that the majority of subjects' hypotensive episodes occurred in the first 4 days (see Figure S-5, on the following pages), and that two subjects dropped out due to hypotension *prior* to Day 7. Also, one of the subjects who experienced hypotension, EC11-12-007, was receiving oral clonidine for the treatment of hypertension at the time of randomization and throughout the study period. Thus the relationship between the serum clonidine levels as drawn in this study and hypotension is difficult to discern.

Figure S-5 on the following page displays when hypotensive/postural hypotensive events took place in this study.

FIGURE S-5: Number of Hypotensive Events in Clonidine Subjects per Therapy Day (N=24)



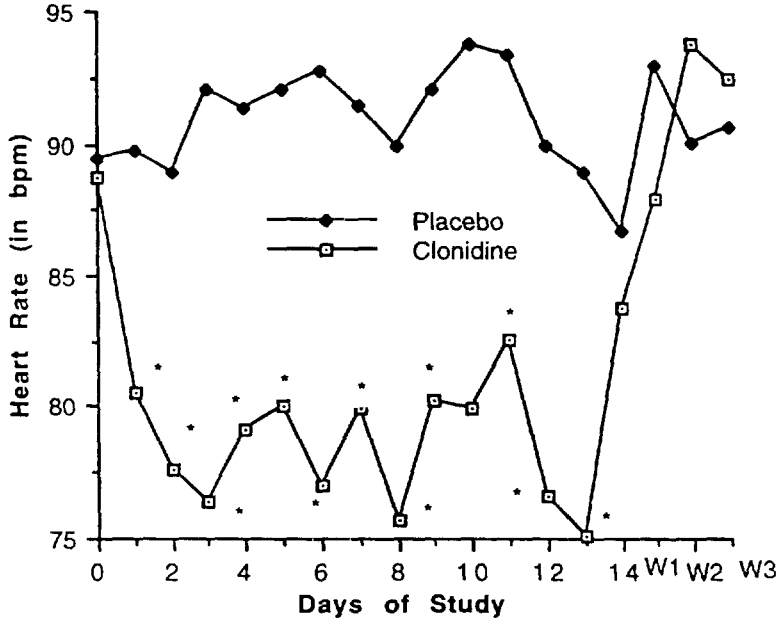
There were a total of 33 hypotensive/postural hypotensive events in 24 subjects (some subjects had more than one event). Of these 33 events, 21 lasted for a day or less whereas the remaining 12 lasted anywhere from 2 to 14 days. Nineteen of these events were treated with fluids, 9 with either oral or IV ephedrine, 3 subjects had their clonidine dose temporarily lowered, 2 subjects discontinued, 4 resolved without treatment, and 5 episodes were undescribed (total is >33 since more than one modality may have been used).

Based on Figures S-1 through S-5, a possible conclusion is that there is somewhat of an attenuation of epidural clonidine's effects on blood pressure over 14 days. This indeed may be true. However, neither oral nor transdermal clonidine's effects are known to attenuate over the course of 14 days. Also, many subjects were assisted in maintaining their blood pressure, and two subjects for whom no blood pressure sustaining treatment worked were dropped. Thus, these data are not a "clean" presentation of clonidine's effects on blood pressure.

b. Rebound Hypertension/ Hypertension: Upon cessation of clonidine administration, mean blood pressure levels in the clonidine group exceeded the original baseline values as well as mean levels for the placebo group, although this latter difference obtained statistical significance only on the third washout day and only for supine diastolic blood pressure ($p=0.047$). Four of the five reports of "hypertension" with clonidine occurred during this withdrawal phase. Three of these four subjects required treatment: one with a clonidine patch, one with oral clonidine, and the third the treatment was not reported. However, it is this third (EC05-12-002) case that is potentially the most distressing. This subject's supine pressures went from 106/48 on Day 14 to 156/74 on withdrawal Day 1. Two days later this patient experienced a cerebrovascular accident. Rebound hypertension appears to be a potential complication of sudden termination of epidural clonidine treatment.

c. **Heart Rate:** Mean heart rate at baseline was slightly, but not significantly lower in the clonidine group (See Figure S-6). Upon initiation of therapy, mean heart rate was consistently lower in the clonidine group than in the placebo group ($p<0.025$ for all study days except 14). Upon cessation of clonidine, heart rate in the clonidine group recovered to and surpassed baseline values. In fact, on Days 2 and 3 of the washout period, heart rate was faster in the clonidine group than in the placebo group, although these differences were not statistically significant. There was only one report of "bradycardia" in the clonidine group (from a baseline of 76 bpm to 44 bpm) and none in the placebo group.

FIGURE S-6: Daily Mean Heart Rate (bpm) Compared (* = p<0.05)



d. **Respiration:** Mean respiration rates at baseline were slightly, but not significantly higher in the clonidine group. Respiration rates remained relatively consistent in the clonidine group throughout the study, but tended to increase in the placebo group. Mean respiration rates were significantly higher for placebo than for clonidine on study days 10 and 12 ($p \leq 0.0225$ on both days). There appeared to be no difference in respiratory adverse events between the clonidine and placebo groups.

e. **Morphine Levels:** At baseline, the mean plasma free morphine concentration for 23 clonidine subjects with processed samples was 109.7 ng/mL with a standard error of 31.00, while the mean concentration for 34 placebo subjects was 59.0 ng/mL with a standard error of 10.13. This difference was not statistically significant. Differences in plasma free morphine concentrations between treatment arms decreased during the post-treatment period, and variances became more homogeneous. On study day 7, the mean plasma free morphine concentration for 26 clonidine subjects was 64.1 ng/mL with a standard error of 17.73, while the mean concentration for 34 placebo subjects was 88.3 ng/mL with a standard error of 18.12. On day 14, the mean plasma free morphine concentration for 23 clonidine subjects was 93.1 ng/mL with a standard error of 27.35, while the mean concentration for 30 placebo subjects was 85.5 ng/mL with a standard error of 23.56. Independent t-tests for equal variances suggested differences in plasma

free morphine concentrations between treatment arms were not significant for either Day 7 or Day 14 assessment period. Morphine levels were not measured during the washout period.

As seen from Dr. Scheinbaum's figure E-2, daily morphine use (in mg.) was comparable between groups until the washout period where the clonidine group used much more morphine than the placebo group (numbers approached statistical significance but did not attain).

f. **Nausea:** Nausea was slightly, but not significantly lower in the clonidine group at baseline). Nausea scores continued to be lower in the clonidine group versus placebo over all 14 days of the study, this difference reaching statistical significance on Study Days 1, 2, 7 and 12. During the washout period, nausea levels in the clonidine group increased substantially, to levels as high or higher (although not significantly so) than those observed for the placebo group. This difference during the washout period may be in part due to the greater amount of morphine used by the clonidine subjects during this period.

g. **Sedation:** Sedation scores were slightly, but not significantly lower in the clonidine group at baseline (indicating less sedation). Sedation scores continued to be slightly lower in the clonidine group throughout the 14 day study period and all three days of washout, with the exception of Study Day 5. This reviewer speculated that the increase in nausea in the clonidine group during washout may have been as a result of the increased use of morphine in that group. However, this increased use of morphine did not appear to result in any difference in sedation scores between the clonidine and placebo groups during washout.

h. **ECG Data:** A total of 44 subjects (51.8%) exhibited ECG abnormalities at baseline. Of subjects demonstrating ECG abnormalities at baseline, 20 were randomized to the clonidine arm and 24 to the placebo arm. Of the remaining 18 clonidine subjects with normal ECG studies at baseline, 4 (22.2%) demonstrated post-treatment ECG abnormalities. Of the remaining 23 placebo subjects with normal ECG results at baseline, 3 (13.0%) demonstrated post-treatment ECG abnormalities. The difference in frequency of emergent ECG abnormalities between clonidine and placebo groups was not statistically significant.

i. **Laboratory Data:** Many variations in clinical laboratory values were observed during the course of the study (as might be expected in terminal cancer subjects). However, few of these variations differed significantly in frequency of occurrence between the clonidine and placebo groups. At baseline, out of range creatinine values (predominately below the normal limits) were significantly more frequent in placebo subjects at baseline ($p=0.002$) and out of range bilirubin values (predominately above the normal limits) were significantly more frequent in clonidine subjects ($p=0.012$). On Study Day 7, out of range neutrophil values (predominately above the normal limits) were significantly more frequent in placebo subjects ($p=0.033$). None of the variations observed on Study Day 14 differed significantly in frequency of occurrence between the clonidine and placebo groups.

7. DEATHS:

Fourteen subjects (5 in the clonidine group and 9 in the placebo group) died during the course of the study or within a 30-day period following the last administration of the study drug. None of the deaths was considered related to the study drug. All of the deaths were attributed to malignant disease with the exception of a single death (placebo patient) attributed to stroke. Information relating to deceased subjects is summarized in Table S-7 on the following page:

Table S-7: Summary of Deaths occurring either during the course of the study or within a 30-day period following last administration

Subject#	Age	Sex	Race	Group	Days on Drug	Cause of Death
EC01-12-001	35	M	W	clonidine	3	died 24 hrs after last dose due to malignant disease.
EC02-12-001	45	M	W	clonidine	5	withdrew from the study after 5 days after dislodging the catheter and died the following day from cardiovascular failure related to malignant disease
EC03-11-004	73	F	W	placebo	14-complete	completed the study and died 3 days later related to malignant disease.
EC03-12-002	66	F	W	placebo	14-complete	completed the study and died 29 days later related to malignant disease
EC05-11-004	37	M	W	placebo	14-complete	completed the study and died 6 days later related to malignant disease.
EC06-22-001	49	M	W	placebo	14-complete	completed the study and died 14 days later related to malignant disease
EC07-11-001	44	F	A	placebo	14-complete	completed the study and died 14 days later due to septic shock and metabolic acidosis
EC07-22-005	79	F	W	placebo	14-complete	completed the study and died 21 days later from a stroke
EC08-22-002	51	M	W	placebo	13	withdrew from the study after 13 days due to severe dehydration, hypercalcemia and sedation. Death the following day was reported as related to malignant disease
EC10-12-003	63	M	W	clonidine	14-complete	completed the study and died 8 days later related to malignant disease
EC11-12-007	54	F	W	clonidine	13	withdrawn from the study after 13 days based on a misinterpretation of the study protocol. Death 13 days later was reported related to malignant disease
EC11-21-001	78	M	W	placebo	11	died on the 11th day of the study due to complications of malignant disease including pneumonia, shortness of breath, decreasing consciousness and decreased oxygen saturation
EC12-21-001	57	F	B	placebo	4	died on the 4th day of the study secondary to disease progression evidenced by tachypnea that required an increase in supplemental oxygen
EC14-21-002	70	M	W	clonidine	7	withdrew from the study after 7 days because of disease progression. Death 24 days later was reported related to malignant disease.

8. Miscellaneous:

a. Quality of Life Scores: Quality of life scores did not differ significantly between treatments at baseline, or at either post-treatment assessment.

E. COMMENTS

1. Overall Safety: There were no unexpected or unusual adverse events in this study as clonidine exhibited the types of adverse reactions seen in previous trials of oral and transdermal clonidine. Of note in this study are hypotension, decreased heart rate, and rebound hypertension. There was no difference between clonidine and placebo with regards to dry mouth, sedation, or nausea. There was one report of bradycardia in a clonidine-treated subject.

2. Hypotension: The sponsor's assessment of this important adverse reaction is hampered by either poor or absent explicit criteria defining either "hypotension" or "postural hypotension." It appears therefore that the decision to label someone as having experienced a hypotensive event was

left mostly to the co-investigator or research nurse's clinical opinion, rather than pre-stated explicit criteria.

Given that caveat, as expected, epidural clonidine produces both hypotension and postural hypotension. These two adverse reactions represented the bulk of the difference in adverse reaction incidence between clonidine and placebo. Forty-five percent of clonidine subjects reported hypotension versus 11% for placebo, and 32% of clonidine subjects reported postural hypotension versus none for placebo, both findings being highly significant ($P \leq 0.001$).

A preliminary retrospective analysis performed by this reviewer revealed that individuals who suffered a hypotensive reaction to clonidine weighed 11 kg less than those that did not. Those suffering a hypotensive reaction also had slightly higher clonidine levels although this metric may not be as reliable: most of the hypotensive events occurred in the first 4 days whereas the first clonidine level measured was on Day 7. Also, of the 11 women who received clonidine, 9 (82%) experienced a hypotensive episode versus 15 of 27 (56%) of the men. However, both of the subjects who discontinued the study due to hypotension were men. Due to the retrospective nature of this analysis and the small number of subjects involved, this reviewer would urge caution before broadly applying these observations.

Lastly, although the data suggest some attenuation of epidural clonidine's effects on blood pressure over 14 days, neither oral nor transdermal clonidine's effects are known to attenuate over the course of 14 days. Also, subjects were often provided assistance in maintaining blood pressure, with either fluids or ephedrine. Some subjects had their infusion rates temporarily decreased, and two subjects, for whom no blood pressure sustaining treatment worked, were dropped. Thus, it is difficult to determine whether or not an attenuation of blood pressure lowering actually occurred.

3. **Rebound Hypertension/Hypertension:** Upon cessation of clonidine administration, mean blood pressure levels in the clonidine group exceeded the original baseline values as well as mean blood pressure levels for the placebo group. Four of the five reports of "hypertension" with clonidine occurred during this withdrawal phase. Three of these four subjects required treatment; one of these subjects suffered a cerebrovascular accident two days after this blood pressure rebound. Thus, rebound hypertension can be a complication of sudden termination of epidural clonidine treatment, especially in those subjects with underlying cardiovascular conditions.

4. **Heart Rate:** During clonidine therapy, mean heart rate was consistently lower in the clonidine group than in the placebo group ($p<0.025$ for all study days except 14). Upon cessation of clonidine, heart rate in the clonidine group recovered to and surpassed baseline values. There was one report of "bradycardia" in the clonidine group and none in the placebo group.

2. Pivotal Study EC-001 Extension Study

A. Study Objective: This was an open-label extension of Study EC-001 to describe the safety profile of the long-term use of epidural clonidine as an analgesic in terminally-ill cancer patients with intractable pain.

B. Protocol Synopsis: Any subject who completed EC-001 was eligible to participate in this extension study. Following discontinuation of study medication and the 3 day wash out period, subjects were offered the opportunity to receive epidural clonidine on an open label basis. Subjects were maintained on epidural morphine as previously described. As in the first treatment day of the double blind treatment period, subjects were rehospitalized and monitored every 4 hours for vital signs and adverse events. The dose of the clonidine remained 30 mcg/hr. Following the first day of hospitalization, subjects able to return home were monitored on a twice a week basis for the first two weeks, then weekly thereafter.

C. Adverse Event Monitoring:
Blood pressure (supine and standing), heart rate, temperature and respiration rate were monitored twice a week for the first two weeks and then weekly for blood pressure and heart rate only. Assessment and description of adverse events was done twice a week for the first two weeks and then weekly.

D. RESULTS:

1. Baseline Demographics: Of the 39 subjects, 35 received epidural clonidine, while 4 subjects received epidural placebo. Table S-8 below summarizes selected baseline demographic characteristics of the 35 enrolled subjects receiving clonidine.

Table S-8: Selected baseline Demographics of Enrolled Subjects

CHARACTERISTIC		Clonidine (N=35) N (%)
SEX	Male	20 (57)
	Female	15 (43)
RACE	White	30 (86)
	Black	3 (9)
	Asian	1 (3)
	Hispanic	1 (3)
AGE (years)	25-35	1 (3)
	36-45	4 (11)
	46-55	9 (26)
	56-64	12 (34)
	≥65	9 (26)
Those in EC-001, who took:	Clonidine	17
	Placebo	18

2. Extent of Exposure: The sponsor presents data for only 32 of the 35 subjects due to administrative errors with subjects 01-008, 01-009, and 17-003. Epidural clonidine dosing ranged

from 1 to 94 weeks with a median dosing duration of 10 weeks .

Tables S-9 and S-10 below assess the extent of exposure to clonidine in the open-label period.

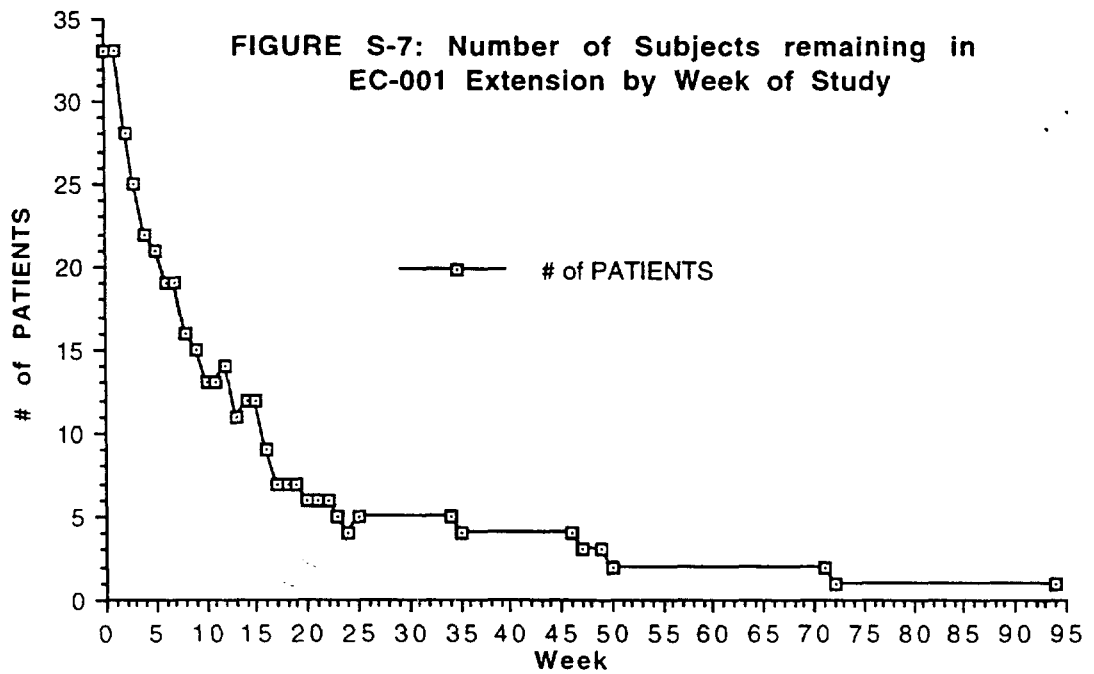
Table S-9: Number of Subjects exposed to various total clonidine doses (N=32)

Total Dose (in mg)	0-10	10-20	20-40	40-100	100-300	300+
N	32	28	22	16	8	2

Table S-10: Number of Subjects exposed to clonidine grouped by days of exposure doses (N=32)

DAYS	0-14	14-30	30-90	90-180	180+
N	32	28	21	13	5

3. Subject Accounting/Discontinuations: As seen in Table S-10 and from Figure S-7 below, although the study continued for 94 weeks, the bulk of subjects discontinued in the early part of the study. By the 6 month point (26 weeks), 84% of subjects had already discontinued.



Reasons for discontinuing the extension trial are presented in Table S-11 below:

Table S-11: Reasons for Discontinuation from the Extension Trial

Reason for Discontinuation	Clonidine (N=35) (N)	(%)
Death	21	(60%)
Disease Progression	4	(11)
Catheter Dislodged/Removed	3	(9)
Catheter Infection	3	(9)
Patient Refused to Continue	1	(3)
Morphine Pump Implanted	1	(3)
Drug Ineffective	1	(3)

Given that this population was composed of subjects with advanced cancer, it is not surprising that 60% of the subjects in the trial discontinued as a result of death. No subject discontinued as a result of an adverse event directly related to clonidine.

Of the 4 placebo patients, one discontinued as a result of orthostatic hypotension, two subjects died, and one subject discontinued due to an epidural catheter problem, then subsequently died of cardio-pulmonary arrest.

4. DEATHS:

Information relating to the 21 deceased subjects on clonidine is summarized in Table S-12 on the following page:

Table S-12: Summary of the 21 Deaths in Clonidine Subjects occurring during EC-001 Extension Study (N=35)

Subject#	Age	Sex	Race	Days on Drug**	Cause of Death
S01-009	56	M	W	23	Malignant disease
S03-025	56	M	W	72	Malignant disease
S04-005	50	M	W	47	Malignant disease
S05-001	64	F	W	510	Malignant disease
S05-015	51	M	W	145	Malignant disease
S07-003	58	M	W	55	Cardiac arrest
S07-006	83	M	W	56	Cardiopulmonary arrest
S10-003	63	M	W	22	Malignant disease
S10-011	50	M	W	58	Pulmonary bleed
S14-003	70	M	W	31	Malignant disease
S23-002	54	M	W	75	Respiratory Failure secondary to metastatic renal carcinoma
S03-030	66	F	W	43	Malignant disease
S03-035	74	M	W	381	Pneumonia
S04-006	46	F	W	193	Malignant disease
S04-008	62	M	W	110	Malignant disease
S05-008	37	M	W	20	Malignant disease
S05-012	62	M	W	372	Malignant disease
S07-004	44	F	Asian	28	Septic shock/metabolic acidoses
S07-005	70	F	W	35	Stroke
S11-002	38	F	W	161	Malignant disease
S11-004	56	M	W	103	Malignant disease

** = dosing duration during controlled and extension phase

Of the 3 subjects on placebo who died, 1 did so due to malignant disease and 2 due to cardiopulmonary arrest. All three subjects were white males.

5. Adverse Events - General Discussion: Adverse events encountered by those receiving clonidine during the extension trial are summarized in Tables S-13 and S-14 on the following page. As a reminder, the sponsor was only able to provide data for 32 of the 35 clonidine-treated subjects due to administrative errors. The sponsor provided sparse raw adverse event data for 3 of the 4 placebo subjects. One of the 3 subjects reported nausea and vomiting (33%) while another reported orthostatic hypotension (33%). However, due to the small number of placebo subjects, making definitive comparisons to the clonidine group is probably unwise.

What does appear fairly consistent with (placebo-controlled) EC-001 is the high (47%) incidence of hypotension/postural hypotension seen in the extension study. Hypotension will be additionally discussed on the following pages.

Table S-13: Summary of Adverse Reactions from the Extension Trial occurring in ≥2 subjects (N=32)

EVENT	N	EVENT	N
Any Event	32 (100)	General Edema	3 (9)
Hypotension/Postural Hypotension	15 (47)	Hypertension	3 (9)
Nausea	13 (41)	Intestinal Obstruction	3 (9)
Anxiety/Confusion	12 (38)	Sweating	3 (9)
Somnolence	8 (25)	Anemia	2 (6)
Urinary Tract Infection	7 (22)	Anorexia	2 (6)
Constipation	6 (19)	Cellulitis	2 (6)
Dyspnea	6 (19)	Depression	2 (6)
Fever	6 (19)	Diarrhea	2 (6)
Infection	6 (19)	Peripheral Edema	2 (6)
Asthenia	5 (16)	Hypercalcemia	2 (6)
Hyperaesthesia	5 (16)	Urinary Incontinence	2 (6)
Pain	5 (16)	Accidental Injury	2 (6)
Skin Ulcer	5 (16)	Jaundice	2 (6)
Vomiting	5 (16)	Nervousness	2 (6)
Dizziness	4 (13)	Paresthesia	2 (6)
Hypertonia	4 (13)	Rash	2 (6)
Injection Site Reaction	4 (13)	Rhinitis	2 (6)
Dry Mouth	3 (9)	Tremor	2 (6)

Table S-14: Summary of Adverse Reactions from the Extension Trial occurring in 1 subject (N=32)

EVENT	N	EVENT	N	EVENT	N
Agitation	1 (3)	Headache	1 (3)	Myasthenia	1 (3)
Amblyopia	1 (3)	GI Hemorrhage	1 (3)	Neoplasm	1 (3)
Apnea	1 (3)	Hematuria	1 (3)	Pharyngitis	1 (3)
Ascites	1 (3)	Hydronephrosis	1 (3)	Prostate Disease	1 (3)
Bronchitis	1 (3)	Hypokalemia	1 (3)	Pruritus	1 (3)
Cardiovascular Disease	1 (3)	Hyponatremia	1 (3)	Skin Disease	1 (3)
Dysphagia	1 (3)	Hypothermia	1 (3)	Speech Disorder	1 (3)
Dysuria	1 (3)	Hypotonia	1 (3)	Stomatitis	1 (3)
Edema	1 (3)	Insomnia	1 (3)	Stupor	1 (3)
Pleural Effusion	1 (3)	Intestinal Perforation	1 (3)	Tachycardia	1 (3)
Pulmonary Edema	1 (3)	Melena	1 (3)	Taste Perversion	1 (3)
Hallucinations	1 (3)	Meningitis	1 (3)	Impaired Urination	1 (3)

6. Specific Adverse Events

a. **Hypotension:** As noted above, hypotension and postural hypotension (combined) was the most commonly occurring adverse reaction. The sponsor has provided summary blood pressure data for each week of the study, but has not included baseline data as a comparitor. The sponsor does state that "*No clinically meaningful deviations were noted in the weekly readings of ...blood pressure, though, overall, a trend toward decreases in blood pressure relative to baseline was seen.*"

The problems with the assessment of hypotension noted in the review of (placebo-controlled) EC-001 exist here as well. Namely, the lack of precise definitions of hypotension/postural hypotension, whether mean arterial pressure was truly used, and how hypotensive events were caught when subjects were to be monitored only once daily for purposes of the study.

As was done in with EC-001, this reviewer attempted to determine if there were any differences between those subjects on clonidine who had a hypotensive event versus those on clonidine who did not. In the extension data, there was no difference with regards to gender and weight as was previously seen in EC-001. However, this reviewer could find data for only 13 of the 15 subjects experiencing either hypotension or postural hypotension.

Six (40%) of the 15 hypotensive events occurred during the first day of clonidine treatment. Nine (60%) of the events occurred within the first 6 days of therapy. These findings are similar to those seen in (placebo-controlled) EC-001.

b. **Heart Rate:** There were no reports of bradycardia in the extension subjects. As mentioned previously, since the sponsor did not provide baseline data, it is not possible to estimate the effects of the clonidine infusion upon heart rate. However, the sponsor does state that "*No clinically meaningful deviations were noted in the weekly readings of heart rate ....*"

c. **Hypertension:** The sponsor did not provide follow-up blood pressure data in subjects whose clonidine infusion was discontinued. Thus it is not possible to assess if rebound hypertension occurred in these subjects. All three reports of "Hypertension" appeared to occur during an epidural clonidine infusion.

d. **Miscellaneous clonidine reactions:** Nausea was the second most frequent adverse reaction, occurring in 41% of subjects, followed by Anxiety/Confusion in 38%, somnolence in 25% , and Dry mouth in 9%. Again, without a placebo group, it is difficult to assess the meaning of these incidences. Also, 9% of subjects experienced intestinal obstruction. The sponsor did not provide laboratory or ECG data.

e. **Epidural Catheter Problems:** Eighteen percent of clonidine subjects experienced some form of catheter-related problems, either catheter clogging, dislodging, or infection. There were a few reports of inadvertent intrathecal administration of clonidine. There was also a disturbing case of meningitis in subject S05-009. One and a half months prior to the meningitis, the subject experienced a fever of 100.6 °C and it was noted that the epidural catheter site was pink. The subject was started on Ceftin and topical Neosporin. Additionally, three weeks after the meningitis resolved, the subject spiked a fever and the epidural catheter was pulled due to infection. This reviewer can not directly attribute this subject's meningitis to the epidural catheter problems experienced, nor is he attributing the meningitis to some disturbing property of clonidine. However, this case does point out the real and potential difficulties of long-term epidural drug administration.

f. Concomitant drugs: In those subjects receiving epidural clonidine, there were a number of agents administered concomitantly that were potentially confounding of some of the observations. Fourteen of the 32 subjects (44%) received either oral or topical clonidine. Fifteen subjects (47%) received diuretics (8 loop, 7 thiazide-type). Also, 6 subjects (19%) received either pseudoephedrine or ephedrine. Even if baseline blood pressure data had been provided, this data would have been difficult to interpret given the aforementioned concomitant therapies.

Half of the 32 subjects were taking some form of antidepressant drug, most commonly a tricyclic. The labeling for both oral and topical clonidine states "*If a patient receiving clonidine is also taking tricyclic antidepressants, the effect of clonidine may be reduced, thus necessitating an increase in dosage.*" Clonidine is believed to act as an antihypertensive by stimulating brain stem alpha$_2$ receptors thus resulting in reduced sympathetic outflow from the CNS. How tricyclics interfere with clonidine's antihypertensive effects is unclear. Tricyclics increase transmission of catecholamines and serotonin either through interfering with neurotransmitter uptake or by influencing the postsynaptic receptor. Clonidine is believed to block transmission of pain signals by activating both pre- and postsynaptic alpha$_2$ receptors in the spinal cord, which inhibits substance P release, and dorsal horn neuron firing, respectively. It is unclear whether tricyclics could actually diminish clonidine's effects as an analgesic.

E. COMMENTS

1. Overall Safety: In this extension study of a group of very ill cancer patients, there were many deaths and serious events. However, attribution of these events to clonidine without a placebo group is difficult. As in the placebo-controlled EC-001, clonidine exhibited the types of adverse reactions seen in previous trials of oral and transdermal clonidine. Of note in this study are hypotension, nausea, and somnolence.

However, there was a fair amount of data that was either unavailable or not collected. It was not possible to compare baseline heart rate and blood pressure readings to those on treatment since the baseline reading were unavailable. Subjects took numerous concomitant medications that could have interfered with the interpretation of these results anyway, such as tricyclics, clonidine, diuretics, and ephedrine/pseudoephedrine. Data to assess the possibility of rebound hypertension was not collected. Also, ECG and clinical laboratory test results were not available. Thus, full assessment of epidural clonidine's safety in this extension study is hampered by these absences.

2. Hypotension: As in placebo-controlled EC-001, the sponsor's assessment of this important adverse reaction is hampered by either poor or absent explicit criteria defining either "hypotension" or "postural hypotension." However, as expected, epidural clonidine produces both hypotension and postural hypotension, with 47% of subjects reporting this reaction. A retrospective analysis to determine differences between subjects who did or did not suffer a hypotensive reaction found no difference between the two groups with regards to either weight or sex. However, that this data is from an open-label study, and the fact this reviewer could find data for only 13 of the 15 subjects experiencing hypotension makes definitive conclusions from this type of analysis even more risky than the same analysis with placebo-controlled EC-001.

3. Epidural Catheter problems: Eighteen percent of clonidine subjects experienced some form of catheter-related problems, either catheter clogging, dislodging, or infection. There was also a disturbing case of meningitis in one subject. Although one can not directly attribute this subject's meningitis to the epidural catheter or some property of clonidine, this case does point out the real and potential difficulties of long-term epidural drug administration.

SEP – 5 1996

Department of Health and Human Services Public Health Service

Division of Anesthetic, Critical Care and Addiction Drugs

Review of Pediatric Experience with Clonidine

NDA	~~20,076~~ 21,515 & 4/4/96
REVIEW DATE:	September 3, 1996
CSO:	M. Wright
REVIEWER:	Lillian Burke, M.D.
SECONDARY REVIEWER:	Curtis Wright, M.D.

Use of Clonidine in Children

This review summarizes the available information relating to clonidine and the use of clonidine in children[1]. Oral and transdermal clonidine have been used in children for various conditions including hypertension and attention deficit disorder[1]. The literature on the use of clonidine is limited. Based on these limited reports, the side effect profile and efficacy of clonidine in general, and of epidural clonidine in particular, appear to be similar in children and in adults.

Use of Epidural Clonidine in Pediatric Patients

Pediatric subjects were not included in the pivotal trial for the use of clonidine in patients with refractory cancer pain. The only reported use of epidural clonidine in children is the short-term use for analgesia during and after surgery. As in adults, analgesia is prolonged by the addition of clonidine to bupivacaine. Decreases in blood pressure and heart rates were noted, and mild respiratory depression was also seen. These surgical studies are summarized below.

Clonidine, 2 μg/kg, added to bupivacaine for intraoperative anesthesia, prolonged analgesia and decreased the use of other medications in 23 patients who were undergoing orthopedic surgery[2]. No further decreases in blood pressure or heart rates were seen as compared to bupivacaine

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[1] It is based on the manufacturer's articles submitted for the NDA, and searches of Medline and Sedbase. Comprehensive searches have not been rechecked due to the unavailability of the searching facilities on this date (September 3, 1996)

alone. Sedation was prolonged from 5.8±1.5 hours to 8.4±5.8 hours. Similarly, 2 μg of clonidine added to bupivacaine, provided adequate analgesia following hernia surgery in eight patients[3]. Clonidine 5 μg, added to bupivacaine, produced analgesia and was well tolerated in thirty patients who received it for postoperative analgesia[4].

In another study, 45 patients, 1 to 7 years old, received bupivacaine via caudal block with light general anesthesia for surgical anesthesia during hernia repair or urological surgery[5]. In these patients, pain scores and the number of patients requiring additional analgesia was reduced and the duration of analgesia was increased with clonidine. Clonidine did not increase sedation or cause respiratory depression.

Use of Epidural Clonidine in Pediatric Patients[2]

Sponsor #	First Author; yr	type study	dose/route	Total subjects	Clonidine subjects	Ages	Outcome
#58	Lee; 94	randomized; active control	2 μg/kg with bupivacaine	46	23	1 to 10 yrs	Blood pressure and respiratory effects were similar to those seen in adults.
#59	Jamali; 94	randomized, active control; caudal block during orthopedic surgery	1 μg/kg with bupivacaine	45	15	1 to 7 years	Clonidine decreased the number of subjects requiring additional analgesia and increased the duration of analgesia from 460±439 minutes to 987±573 minutes ($p<0.001$). Mild sedation, respiratory depression and sedation were seen.
#60	Klimscha	randomized, active control	2 μg/kg with bupivacaine	24	8	*	Hemodynamic parameters were reported to be less than those seen in adults at the equivalent doses. Pain relief was prolonged.
#61	Motsch; 93	randomized, active control	5 μg/kg with bupivacaine	45	30	4 to 8 yrs	Heart rate and blood pressure were lower in the clonidine group, but this effect did not occur until after emergence from anesthesia
	Totals			160	76		

Fetal Exposure

Several published studies document the use of clonidine during labor and delivery with intra partum exposure of at least 222 infants (see below). The condition of the infant is not always specifically documented. However, there is an absence of reports of a negative effect in infants for this short-term use. Given the extent of the exposure this indicates that if there are side

[2] Only short-term use during surgery has been reported.

effects peculiar to infants, they are uncommon or rare. Hypotension and mild respiratory depression may be seen in the mothers and these effects may potentially affect the fetus.

One case-controlled study looked at the effects of intrauterine long-term clonidine exposure on behavior. Restless sleep appeared to be more common in children who had been exposed to clonidine before birth (N=22) than in those not so exposed (N=21). Ten of 10 children whose mothers received more than 300 μg clonidine per day had sleep disorders as compared to approximately one third of those whose mothers received lower doses.

Effect on Infant When Clonidine Used for Obstetrical Anesthesia

Sponsor Ref#	First Author;yr	type study	dose/route (if not epidural)	Total subjects	Clonidine subjects	Outcome
#9	Mendez; 90	randomized, placebo-control	400 to 800 μg ep +10 to 20 μg/hr	60	40	No mention of infant outcomes
#10	Huntoon; 92	rnadomized, active control	400 or 800 with bupivacaine or chloroprocaine	63	40	No mention of infant outcomes
#35	Cigarini; 92	randomized, active control	75 μg with bupivacaine	48	12	Fetal heart rate ("Krebs" score), "Apgar" score were the same. No changes were noted in infant glucose levels.
#36	Brichant; 94	randomized, active control	37.5, 75 or 150 μg with bupivacaine	60	45	Fetal heart rates were monitored and no ill effects were reported.
#37	O'Meara; 93	randomized, active control	120 μg	42	20	No specific mention of infant outcomes
#38	Le Polain; 93	randomized, active control	30 μg with bup + epi+sufen	50	25	No specific mention of infant outcomes
#45	Capogna; 95	randomized, placebo-controlled	75 or 150 μg; repeated prn (75 to 450 μg)	60	40	No specific mention of an infant outcome
	Totals			383	222	

Adverse Events Reported in Children

A comprehensive review of the literature of clonidine poisoning[6] in 146 children reported only the expected side effects including: depressed consciousness (86%), bradycardia (29%), hypotension (23%), respiratory depression (20%), miosis (19%), and hypertension (4%). Fifty-

five per cent of 11 subjects in whom temperature was reported were noted to be mildly hypothermic.

Bradycardia is consistently seen with therapeutic doses of epidural clonidine[7]. Clonidine slows conduction in the sinoatrial node and this effect responds to treatment with atropine. Cardiac arrhythmias including sinoatrial block and PVCs have been reported in both children and adults[8]. These conduction abnormalities resolve spontaneously with treatment.

Sudden death was reported in three children taking clonidine[9]. In each of these cases, there was no clear relationship to clonidine use. An eight-year-old child taking methylphenidate and clonidine vomited and died, but neither clonidine nor methylphenidate was detected in his blood therefore the relationship between clonidine and this death seems unlikely. A 7-year-old boy on these same medications died unexpectedly and an autopsy revealed extensive myocardial fibrotic scarring. This death was most probably due to an underlying congenital abnormality or was the sequelae of a previous, undiagnosed myocarditis. Another child taking clonidine died with seizures and had evidence for an intentional overdose of fluoxetine.

Respiratory depression requiring ventilatory support has been reported[10]. Other effects reported in children include seizures[11], hypoglycemia with seizures in a child with hypopituitarism[12], and exacerbation of self-injurious behavior[13] or tics[14] in children with La Tourette's disorder.

Pharmacokinetics

No specific information on pharmacokinetics in children is available in the literature submitted, nor is this information available in the pharmacokinetics review written by John Hunt, Ph.D. The pharmacokinetics of clonidine in children do not appear to have been studied.

Chemistry

Extremely small amounts of 2-,6- dichloroaniline are present in the final product and result from the production of clonidine. This compound is related to aniline, a known carcinogen. The mutagenic capability of 2-,6-dichloroaniline has not been well studied. Its 2-chloro structure tends to pull electrons from the phenyl ring and makes this compound less likely to be mutagenic than is aniline. The highest possible daily dose is many orders of magnitude less than that shown to cause mutagenesis. Based on these considerations, this contaminant is not likely to be of concern in patients in the target population, namely patients with refractory cancer pain. Nor is it likely to be a risk for patients who occasionally receive it off-label during surgery or for another short-term use. Long-term epidural high-dose use in a child could be of concern but such use would rarely, if ever, occur.

Summary

The use of epidural clonidine has been reported in 76 pediatric patients. These subjects exhibited approximately the same efficacy and side effects as those reported for adults. Hypotension, bradycardia and sedation are the most common side effects. One report suggested that the side effects in children were less than those seen in adults at equivalent doses[3]. The published literature documents that at least 222 infants were exposed to clonidine during labor and delivery. No adverse effects were reported in these infants although the status of the infants was not always systematically studied. In children there is evidence for prolongation of postoperative analgesia when epidural clonidine is used in conjunction with bupivacaine similar to that seen in adults. Cardiac arrhythmias have been reported in both children and adults. Although there have been reports of sudden death in children taking clonidine, the relationship of clonidine to these deaths is unclear and other possible etiologies for these deaths appear more likely. There is one report, a case-control study, suggesting that children who are exposed to long-term clonidine therapy *in utero* may be more likely to develop sleep disorders. This reviewer is unaware of any data on the pharmacokinetics of clonidine in children.

Conclusion

Review of the available literature suggests that epidural clonidine should not pose an unwarranted risk in children, especially for those with refractory cancer pain.

Addendum

Summary of References submitted with the NDA related to the use of epidural clonidine in children.

Ref #;Citation

#58; Lee JJ, Rubin AP. Comparison of a bupvacaine-clonidine mixture with plain bupivacaine for caudal analgesia in children. Br J of Anaesthesia (1994) 72:258-262.

Design:

Randomized, double-blind study of 46 children who received intraoperative caudal anesthesia during orthopedic surgery.
B: Bupivacaine 0.5% 1 ml/kg
BC: Same + clonidine 2 µg/kg

Efficacy Results:

Pain relief:

Pain score based on criteria of Hannallah et al. (Crying, arterial pressure, movement, agitation and localization of pain. Given medication when pain score >4 on scale of 10.

Reduction in use of other medications:

Number of administrations of additional medication:

	4 hours	12 hours	24 hours
B:	4	34	66
BC:	0	13	35

Safety Results:

Blood pressure effects and fluid management:

	Pre-op	Decrease	Time
B:	81±4	19.2±6.3	44±5
BC:	82±3	19.6±8.2	70±9

Bradycardia:

	Pre-op	Decrease	Time
B:	103±10	22±2	71±10
BC:	106±13	19±3	83±9

Respiratory Depression:

No respiratory rates of <16 or S_pO_2<95% were noted.

Sedation:

Duration of sedation:
B: 5.8 hours±1.5 BC: 8.4 hours±5.8

Other adverse events:

	Vomiting	Urinary retention
B:	13/23	1/13
BC:	11/23	0/13

Conclusions:

The addition of clonidine 2 µg/kg to bupivacaine prolonged analgesia in pediatric patients following orthopedic surgery. Side effects were not increased.

Ref #;Citation

#59; Jamali SM, Monin S, Begon C, Dubousset A, Ecoffey C. Clonidine in pediatric caudal anesthesia. Anaesth Analg (1994) 78:663-6.

Design:	45 patients , 1 to 7 years old, received bupivacaine via caudal block with light general anesthesia for surgical anesthesia during hernia repair or urological surgery. **B: Bupivacaine 0.25%, 1 ml/kg** **BC: Same + clonidine 1 µg/kg** **BE: bupivacaine + epinephrine 1/200,000**
Efficacy Results: Pain relief:	Maximum objective pain scores: B: 3.4±1.8 BC: 2.3±1.6 ($p<0.05$) BE: 3.4±1.4
Reduction in use of other medications:	Patients requiring no additional analgesia: B: 2/15 BC: 8/15 ($p<0.05$) BE: 1/15
Prolongation of analgesia:	Duration of Analgesia (min): B: 460±439 BC: 987±573 ($p<0.01$) BE: 377±341
Safety Results: Blood pressure effects and fluid management:	Systolic arterial pressure was lower in the BC group than in the B group, but did not differ from the BE group.
Bradycardia:	HR decreased by equivalent amounts in all groups.
Respiratory Depression:	B: Resp Rate 23(19-37) Low S_pO_2 97(94-100) Oxygen required 3/15 BC: 23(17-36) 97(94-99) 2/15 BE: 27(19-36) 97(95-99) 2/15
Sedation:	Duration of Sleep in Recovery Room B: 31±44 min BC: 36±47 min BE: 19±28 min
Nausea/ vomiting:	1/15 in BC and 1/15 in B groups.
Conclusions:	1. Clonidine, 1 µg/kg, added to bupivacaine, decreased the pain scores and prolonged analgesia. 2. Side effects were not significantly increased.

Ref #;Citation	**#60; Klimscha W, Sauberer A, Lerche A, Langenecker S, Semsroth M. Caudal block with clonidine provides prolonged analgesia after ambulatory hernia repair in children.**
Design:	24 children, (N=8 in each group) were given the study medications following inguinal hernia repair: **B: Bupivaine 0.25%, 0.75 mg/kg** **BC: Bupivaine + clonidine 2 µg/kg** **BE: Bupivaine + epinephrine 3.75 µg/kg**
Efficacy Results: Pain relief:	Parameters recorded every 15 minutes for 5 hours Pain relief better in BC group than in B or BE Analgesia "prolonged"

Safety Results:	
Blood pressure effects and fluid management:	Hemodynamic parameters "stable"
Sedation:	Increased sedation in BC group, compared to the others.
Conclusions:	1. The addition of clonidine to bupivacaine improved and prolonged analgesia. 2. Hemodynamic effects were less pronounced than that reported in adults at equivalent doses.

#61;

Ref #;Citation	**#61; Motsch J, Schreckenberger R, Skoberne Th, Böttiger, Bach A, Böhrer, Martin E. Effects of clonidine added to bupivacaine for combined caudal and general anesthesia in children. Regional Anesthesia (1993) 18:31 (Abstract)**
Design:	45 children, aged 4-8 years old, were given study medications following induction of general anesthesia:**N=15 in each group** **B0.1C: 0.1% Bupivacaine 1 ml/kg + clonidine 5 µg/kg** **B0.175C: 0.175% Bupivacaine 1 ml/kg + clonidine 5 µg/kg** **B: 0.175% Bupivacaine 1 ml/kg**
Efficacy Results:	
Pain relief:	Pain relief (as measured by Tramadol by patient-controlled analgesia (PCA)) and duration of analgesia were significantly better in B0.175C than in B or B0.1C groups.
Safety Results:	During the postoperative period, blood pressure and HR were significantly lower in the subjects who received clonidine. However, there were no differences noted during anesthesia.
Conclusions:	1. Addition of clonidine 5 µg/kg to bupivacaine enhanced analgesia and prolonged its duration in children aged 4-8 years old. 2. BP and HR were decreased by the addition of clonidine, but this effect did not occur until the emergence from anesthesia.

Bibliography

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2. #58; Lee JJ et al. Br J of Anaesthesia (1994) 72:258-262

3.#60; Klimscha W et al.

4. #61; Motsch J et al. (1993) Regional Anesthesia 18:31 (abstract)

5.#59; Jamali SM et al. Anaesth Analg (1994) 78:663-6

6. Artman et al. Am J Dis Child 137: 171

7. See complete medical review of literature for further details.

8.DICP (1980) 23:465; Schwartz (1988) Clin Cardiol 11:53, Byrd (1988) Arch Intern Med 148(3):729; Nakagawa (1985) Br Heart J 53:654; Peters (1983) Clin Pharmacol Ther 34:435; Thormann (1981) Chest 80:210; Abuius (1978) JAMA 240:108; Roden (1988) Clin Pharmacol Ther 43:648; Scheinman (1978) Am J Med 64: 1013

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12. Sridhar GR. Clin Pediatr Phila (1993) 32(11):688-9

13.Dillon JE. (199) J Child Neurol 5(4):308-310

14. Huk SG (1989) J Am Acad Child Adolesc Psychiatry 28(4):583-6

JUL 10 1996

PHARMACOLOGY REVIEW OF NDA #20-615

NDA 20-615

Sponsor:
Fugisawa USA, Inc.

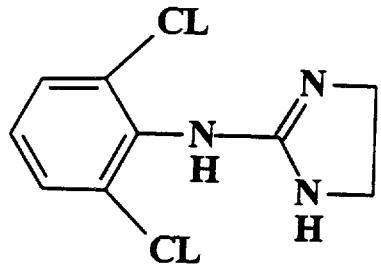
Type of Submission: Original

Date of Submission: 7/95
Date of Receipt:
CDER: August 8, 1995
Reviewer: August 16, 1995

Date of Review: July 10, 1996

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

Drug:
Trade name: unknown
Generic name: clonidine for epidural infusion
Structure:



CLONIDINE

CATEGORY: analgesic

INDICATIONS: Pain treatment in opiate resistant cancer patients

DOSAGE FORM: solution

NDA #20-615

COMPOSITIONS:	Clonidine HCl, USP	100 µg/ml
	Sodium Chloride, USP	9 mg/ml
	HCl, NF	to adjust pH
	Sodium Hydroxide, NF	to adjust pH
	Water for injection, USP	q.s. to volume

RELATED DRUG/INDs/NDAs/DMFs:
IND #31,243 Fujisawa USA, Inc.

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PRECLINICAL STUDIES

DOSE-RANGING STUDY OF EPIDURALLY INFUSED CLONIDINE.HCl IN DOGS

STUDY/REPORT NUMBER: TYA1-90

STUDY SITE: Department of Anesthesiology
University of California at San Diego
La Jolla, California 92121

SPECIES/NUMBER OF SUBJECTS/SEX: Five male Beagle dogs were surgically prepared with epidural catheters, between 7th lumbar and 1st sacral vertebra. Each dog was fitted with an infusion pump in a vest to deliver a dose of 4 ml/day through the spinal catheter.

DOSES/ROUTE OF ADMINISTRATION: The dose of clonidine was incrementally increased every four days from 0, 10, 20, 40, 80, 160 and 320 µg/hr in four dogs. The fifth dog was infused with 320 µg/hr for 3.5 days and then 640 µg/hr for 2 days to examine tolerance to high doses without prior exposure to the lower doses.

PROCEDURE: Each dog was surgically implanted with epidural

catheters which were attached to portable battery-operated infusion pumps and contained in vests worn by the dogs. The correct placement of the catheters was demonstrated post-surgery by a bolus of 2ml of 1% lidocaine and the resulting hindlimb paralysis. This was confirmed post-mortem.

Dogs were evaluated daily for general motor function; coordination (6 point scale) and muscle strength (6 point scale), somnolence (5 point scale), lethargy (2 point scale), placing and stepping reflexes and pain response to thermal stimuli inducing a skin-twitch, bilaterally on shaven areas of the back, both thoracic and lumbar. The heart and respiration rates were also recorded daily.

Clinical Hematology screens evaluated the following parameters pre-infusion, Day 14 and Day 28: Red blood cell count, Hemoglobin, Hematocrit, Mean corpuscular volume, Mean corpuscular hemoglobin, Mean corpuscular hemoglobin concentration, Platelet count, Prothrombin time, Activated partial thromboplastin time, White blood cell count, Differential leucocyte count and fibrinogen.

Clinical Chemistry parameters measured pre-infusion, Day 14 and Day 28 were: Glucose, Urea nitrogen, Creatinine, Total protein, Albumin, Globulin, Total bilirubin, Cholesterol, Triglycerides, Creatine kinase, Lactate dehydrogenase, Total CO_2, Aspartate aminotransferase, Alanine aminotransferase, Alkaline phosphatase, Calcium, Inorganic phosphorus, Sodium, Potassium, Chloride, Na/K ratio, BUN/Creatinine ratio and Albumin/Globulin ratio.

CSF and Spinal Cord Parameters: Appearance, Specific gravity, protein, glucose, Cell count (RBC and WBC) and cytology of the cervical, thoracic and lumbar portions of the spinal cord. These values were only obtained after the 28 day study. There were no baseline values.

RESULTS: The four dogs with patent epidural catheters tolerated the incremental infusion of clonidine.HCl throughout the 28 day study with no impairment of motor function. The skin-twitch response latency (analgesia) increased moderately in a dose-rate

dependent manner. At the higher doses of 160 and 320 μg/hr, the incidence of bradycardia, sedation and a decreased respiratory rate increased. No tables were found for either the somnolence or the lethargy measurements and only the somnolence was mentioned in the discussion and summary.

The single dog which received 3.5 days of 320 μg/hr and 2 days of 640 μg/hr showed significant sedation and lowered respiratory rate at the lower dose and after high dose iniation, the respiratory rate fell from 30 breaths/minute to 16 and the infusion was terminated. The dog had fully recovered 24 hours after infusion was stopped.

There were no pathological deviations observed in the Hematology or Clinical Chemistry screens. The CSF values were within normal ranges for control animals in the laboratory. Microscopic examination of the CSF did not reveal any notable pathology.

Dye injections just prior to sacrifice revealed correct placement and lack of leakage of all catheters. No signs of clots or gross morphological lesions were observed and the upper cervical cord and lower brainstem were without signs of bleed or meningeal adhesions.

All animals exhibited signs of acute or chronic inflammation around the catheter tip and one animal had gram-positive bacteria in a tissue section. Thickening of the dura was present in all dogs and three of the four had inflammatory cell infiltration of the dura. No inflammation was found in the subarachnoid space and the nerve roots were not remarkable.

Assays of plasma clonidine concentrations on Days 1, 2 and 4 of the 10 μg/hr infusions indicated a steady state was obtained the first day. The plasma concentrations were essentially linear from the 10 to 320 μg/hr rates. The Cisternal CSF concentrations of clonidine (mean = 4.42 ng/ml) were slightly below the concomitant plasma levels (mean = 5.62 ng/ml).

DISCUSSION: No indications of organ or system toxicity was noted after clonidine infusion in the blood, serum, urine or CSF and no microscopic changes were seen in the spinal cord or nerve roots.

Vehicle controls were not used and therefore the attribution of the inflammatory responses in the spinal cord could have been due to either the clonidine infusion or the presence of foreign material in spinal space.

The dose of 320 μg/hr was found to cause transient somnolence and bradycardia while at twice this dose, the somnolence was considered excessive for chronic treatment. The latter test and finding was only done in one dog.

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DETERMINATION OF THE MAXIMUM TOLERATED DOSE OF 28-DAY EPIDURALLY INFUSED CLONIDINE.HCl IN DOGS

STUDY/REPORT NUMBER: TYA2-91

STUDY SITE:

SPECIES/SEX - NUMBER OF SUBJECTS/GROUP: Male beagle dogs were used in four treatment groups of six dogs each.

DOSES: Dose for lumbar epidural infusion at 4 ml/day were 0 (saline), 80, 200 and 320 μg/hour for 28 days. The clonidine concentrations were up to 1920 μg/ml.

PROCEDURE: Each dog was surgically implanted with epidural catheters which were attached to portable battery-operated infusion pumps and contained in vests worn by the dogs. The correct placement of the catheters was demonstrated post-surgery by a bolus of 2ml of 1% lidocaine and the resulting hindlimb paralysis. This was confirmed post-mortem.

Dogs were evaluated daily for general motor function; coordination (6 point scale) and muscle strength (6 point scale), somnolence (5 point scale), lethargy (2 point scale), placing and stepping reflexes and pain response to 1) mechanical paw pinch

and 2) thermal stimuli inducing a skin-twitch, bilaterally on shaven areas of the back, both thoracic and lumbar. The heart and respiration rates were also recorded daily.

Blood samples were taken on Days 1, 3, 6, 12, 24 and 28 for determination of clonidine concentrations and compared to CSF concentrations on Day 28.

Clinical Hematology screens evaluated the following parameters: Red blood cell count, Hemoglobin, Hematocrit, Mean corpuscular volume, Mean corpuscular hemoglobin, Mean corpuscular hemoglobin concentration, Platelet count, Prothrombin time, Activated partial thromboplastin time, White blood cell count, Differential leucocyte count and fibrinogen.

Clinical Chemistry parameters measured were:
Glucose, Urea nitrogen, Creatinine, Total protein, Albumin, Globulin, Total bilirubin, Cholesterol, Triglycerides, Creatine kinase, Lactate dehydrogenase, Total CO_2, Aspartate aminotransferase, Alanine aminotransferase, Alkaline phosphatase, Calcium, Inorganic phosphorus, Sodium, Potassium, Chloride, Na/K ratio, BUN/Creatinine ratio and Albumin/Globulin ratio.

CSF and Spinal Cord Parameters: Appearance, Specific gravity, protein, glucose, Cell count (RBC and WBC) and cytology of the cervical, thoracic and lumbar portions of the spinal cord. These values were only obtained after the 28 day study. There were no baseline values.

RESULTS: No deaths or lost catheters occurred and the disconnection of the pumps (13X) or loss of pump action (3X) lasted a maximum of 12 hours among the 24 dogs and was not considered a compromise of the experimental integrity. There was no significant difference between treatment groups in terms of body weight gains.

The occurrence of lethargy and somnolence increased with dose but was not observed in any dog during the last two weeks of the experiment. The motor coordination was unimpaired at all doses. The latencies of the skin-twitch response to thermal stimuli was increased in all clonidine treatment groups in both lumbar and

thoracic areas. The increased latency was dose related in both magnitude and duration. The latency of the control group decreased below baseline by the second day in both lumbar and thoracic areas. The treatment group with clonidine at 80 μg/hr had increased latencies for the first week of treatment and by the last week of treatment the latencies were significantly below baseline in both lumbar and thoracic regions. In the 200μg/hr group the latencies were increased for nearly the first two weeks in the lumbar region and slightly more than one week in thoracic area. In the 320 μg/hr group the latency was above baseline for the initial two weeks in the lumbar area and at baseline for the remaining two weeks. In the thoracic area, the latency was above baseline for three weeks and at baseline on final week. This development of tolerance to the analgesic effects are of interest. The analgesic effects were significantly different from control at all doses on day 1 in both lumbar and thoracic areas. On day 28, only the high dose at the thoracic site was significantly different from control latencies.

At the 80 μg/hr dose, the heart rate (HR) was depressed for only the initial two days of treatment. At the higher doses of 200 and 320 μg/hr the heart-rate was depressed for about two weeks. At 28 days, no significant depression of HR was observed in any dose group. The respiratory rate was suppressed in the low dose group for only about 4 days and longer at the higher doses. The difference was significant at all doses on day 2 but insignificant by day 28.

Clonidine concentration in blood and CSF: The plasma concentrations were about the same within each treatment group from Day 1 to Day 28. The values were 0.3 ng/ml in the saline group, 2.5 ng/ml in the 80 μg/hr group, 5.3 in the 200 μg/hr group and 8.9 in the 320 μg/hr group and this dose-response relationship was statistically significant. On day 28, the respective CSF concentrations were 0.3, 1.3, 2.8 and 5.1 ng/ml. The plasma/CSF ratios were 1.9, 1.89 and 1.75 for the low, mid and high doses, respectively. The correlation between epidural infusion rate and plasma levels was statistically significant ($r=0.705$).

Hematology: No clinically significant changes were observed in

any treatment group at 14 or 28 days when compared to the presurgical baseline values and the normal reference range.

Clinical Chemistry: No clinically significant changes were observed in any treatment group at 14 or 28 days when compared to the presurgical baseline values and the normal reference range. Some subjects had liver enzymes or reticulocyte values slightly beyond reference ranges, but these values were about the same pretreatment as post treatment and as pronounced in controls as in any other treatment group.

CSF Parameters: There was no significant difference between the treatment groups in CSF protein content, glucose concentrations, specific gravity or WBC count. There were elevated RBC levels seen in several animals in the 200 μg/hr group and this was considered to be contamination of the CSF with blood during the percutaneous sampling. The protein and WBC levels were normal in the same samples. Microscopic examination of the CSF samples did not reveal any notable cellular pathology in any group. There were no CSF parameters to distinguish clonidine treated animals from controls.

Spinal Cord Pathology/Histology: There were a few animals with chronic leptomeningeal inflammation and perineural calcification in the cervical spinal cord sections that the investigator considered incidental. This is true of the calcification as it appears as prevalent in the saline controls as in any other treatment group in the lumbar region, although none was seen in the controls at the level of the catheter tip but in 2, 1 and 3 of six dogs in the low, medium and high dose groups. The incidences of leptomeningeal inflammations were not found in this report. At the catheter tips, the severity of chronic and acute inflammation appears greater in the clonidine treated dogs than in the control, but without any dose relationship. The same appears to be true for peri-catheter fibrosis in the lumber spinal cord. This was also noticed by the investigator but due to the small number of animals and lack of a dose-response relationship a causal hypothesis was not presented.

DISCUSSION:

No treatment related toxicity was observed at any of the doses of clonidine, 80, 200 and 320 μg/hr. The plasma levels of clonidine were about one-half the CSF levels and the effects of lethargy, somnolence, bradycardia, decreased respiratory rate and analgesia were all expected pharmacological consequences on clonidine.

There were no significant changes in the CSF parameters or histopathology of the spinal cord, although the severity of inflammatory responses and peri-catheter fibrosis were slightly increased in animals treated with clonidine.

XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX

A 28-DAY TOXICITY STUDY ON CONTINUOUSLY INFUSED EPIDURAL CLONIDINE.HCl AT THE MAXIMUM TOLERABLE DOSE IN BEAGLE DOGS

(V5/1500)

STUDY/REPORT NUMBER: TYA3-92

STUDY SITE:

GLP/QA SPECIFICATIONS: In compliance (NDA 5/1506)

SPECIES/NUMBER OF SUBJECTS/SEX: Beagle dogs, male, 4/saline control and 6/clonidine infusion at 320μg/hr (4ml/24 hr)

DOSES/ROUTE OF ADMINISTRATION: epidural infusion into lumbar space through implanted chronic catheter.

PROCEDURE: The ten dogs were implanted with epidural catheters in the lumbar space which traveled subcutaneously to the upper back where the catheter exited and was secured in a fitted nylon vest which also housed the continuous infusion pump. After recovery from surgery, the placement was tested by the administration of 2 ml of 1% lidocaine and the expected rear-limb paralysis was observed. For the following three days, the dogs received

continuous infusion of normal saline and then, either infusion was continued with saline (controls) or were started on clonidine.HCl (320μg/hr) for the following 28 days.

All dogs were observed at least twice daily for general behavior, food consumption and presence of stools and urine.

Clinical Hematology screens evaluated the following parameters: Red blood cell count, Hemoglobin, Hematocrit, Mean corpuscular volume, Mean corpuscular hemoglobin, Mean corpuscular hemoglobin concentration, Platelet count, Prothrombin time, Activated partial thromboplastin time, White blood cell count, Differential leucocyte count and fibrinogen.

Clinical Chemistry parameters measured were:
Glucose, Urea nitrogen, Creatinine, Total protein, Albumin, Globulin, Total bilirubin, Cholesterol, Triglycerides, Creatine kinase, Lactate dehydrogenase, Total CO_2, Aspartate aminotransferase, Alanine aminotransferase, Alkaline phosphatase, Calcium, Inorganic phosphorus, Sodium, Potassium, Chloride, Na/K ratio, BUN/Creatinine ratio and Albumin/Globulin ratio.

CSF and Spinal Cord Parameters: Appearance, Specific gravity, protein, glucose, Cell count (RBC and WBC) and cytology of the cervical, thoracic and lumbar portions of the spinal cord. These values were only obtained after the 28 day study. There were no baseline values.

RESULTS:

No dogs died prior to scheduled sacrifice at 28 days after initiation of saline or clonidine HCl infusion. The infusion pumps ceased to operate in two saline dogs for about three hours in one case and 24 in another, however this was not considered to have compromised the experiment by either the investigator or this reviewer. There was no significant change in body weight in either the saline or clonidine treated dogs. Although the clonidine dogs were larger than the saline treated animals and significantly by the end of the experiment. The clonidine treated dogs also ate significantly more food but this probably reflected the size difference and was not a treatment effect.

Mild depression, somnolence, was observed in all clonidine treated dogs for 2 to 5 days starting from Day 0 to Day 3. In the saline treated dogs, one was observed to be mildly depressed on days 2, 3 and 8. The motor function was not affected in any dogs in either treatment group.

Heart-rate was significantly reduced in the clonidine treated animals throughout the study. Although the difference was less in the second two weeks than in the initial two weeks. The systolic blood pressures (BP) was reduced in the clonidine treated dogs only in the initial three days. Only on day 3 of infusion, the mean arterial pressure (87 vs. 70 mmHg) and the diastolic BP (76 vs. 57 mmHg) were significantly reduced in the clonidine treated animals.

Hematology and serum chemistry values were compared at 28 days with baseline values in both saline and clonidine treated animals. There was no significant change with either treatment and no significant difference between treatment groups.

At the end of 28 days, the cisternal CSF values of protein content, specific gravity and RBC and WBC cell counts were not significantly different between treatment groups. However, there was a significant elevation of glucose in the CSF of the clonidine treated group, 67.8±4.3 vs 82±7.8 mg/dL. These values were from the four saline controls and five of the six clonidine treated dogs because the cisternal tap was bloody in the sixth dog.

The gross inspection of the catheters and the results of dye injection indicated that all catheters were intact, operational and correctly placed with insertion at L6-S1 interspace and termination at or around lower thoracic/upper lumbar level. The epidural fat accumulation around the catheters was similar in both treatment groups.

Microscopic Pathology: The cervical sections were normal except for one saline dog which exhibited dural thickening was observed. The mid- to upper thoracic sections were also normal except another saline dog which had mild chronic epidural inflammation and two dogs (one in saline group and one in clonidine group)

which had focal palor in the dorsal central gray matter. These changes were limited to these sections and no gliosis or evidence of spinal injury was evident. At the catheter tips, all animals showed chronic inflammatory reactions, varying from mild to severe. A rank-sum test did not reveal any significant difference between treatment groups. In the lumbar region of the epidural space the same chronic inflammation was seen in all dogs and in eight there was evidence of acute inflammation in the epidural space. In one clonidine treated dog, dura infiltration by inflammatory cells was observed. The arachnoid and sub arachnoid spaces were without significant pathology in the lumbar sections of all dogs and a rank-sum analysis of the degree of irritation in the lumbar section did not reveal a treatment related effect.

DISCUSSION:

The results indicated that the clonidine.HCl dose of 320 μg/hr produced expected pharmacological effects such as bradycardia, decreased respiratory rate, decreased systolic and diastolic blood pressure and somnolence. Motor function was not affected. The desired pharmacological effect of antinocioception was shown by an increased latency of the skin-twitch response to thermal stimuli. Over the 28 days of testing, tolerance developed to all the pharmacological effects except the decreased heart rate and respiratory rate.

The Hematology and Clinical Chemistry values did not indicate that any significant changes were induced by clonidine treatment and there was also no treatment induced change in CSF protein content, specific gravity or RBC and WBC counts.

The accumulation of epidural fat around the spinal catheters was similar in clonidine and saline treated animals. Although there were chronic and acute inflammatory reactions in the lumbar region to the thoracic section in the region of the catheter tip, there was no distinct relationship between treatment and the severity of inflammation. No gliosis or evidence of neuronal toxicity was observed.

SUMMARY:
Clonidine.HCl was administered chronically, for 28 day, by epidural catheter to a total of 28 dogs in three separate experiments. The clonidine infusion rates in the initial four dogs was incrementally increased from 10 to 320 μg/hr and in the second experiment, 6 dogs per treatment group were chronically infused with 80, 200 or 320 μg/hr. In the third experiment 6 dogs were infused with 320 μg/hr.

The expected pharmacological effects of clonidine; decreased heart rate, respiratory rate and systolic and diastolic blood pressure and increased somnolence were observed without affecting motor function. The treatment with clonidine increased the skin-twitch latencies to thermal stimuli on both thoracic and lumbar areas of the shaved back. Tolerance developed to this antinocioceptive effect and to the somnolence and blood pressure effects, but less extensively to the decreased heart rate and respiratory rate.

The hematology and plasma chemistry screens did not indicate any significant pathological consequences of clonidine treatment and neither did the CSF parameters. The conditions of the spinal cord and membranes were changed by catheter insertion but the resulting inflammatory reactions, peri-catheter fibrosis and epidural fat accumulation were not significantly different between the saline controls and the clonidine treated animals. No gliosis or neuronal damage was observed.

For the **label**, carcinogenicity, mutagenicity, fertility and reproductive effects of clonidine were obtained from PDR reports of reviewed data and this reviewer has requested and submitted recalculations of safety ratios on the basis body surface area instead of body weight.

NDA #20-615

CONCLUSION AND RECOMMENDATIONS:

The review of the effects of clonidine.HCl in animal studies has provided no pharmacology/toxicology basis to prohibit its use in humans and with requested changes in the label for ratio values to be expressed in terms of body surface area, it is recommended for approval.

Harry M. Geyer, III Ph.D.

In concurrence: MaGoheer 7/15/96
Acting Team Leader: Anwar Goheer, Ph.D. date

cc
Original NDA #20-615
HFD-007/Div. File
HFD-007/HMGeyer
HFD-007/MWright
HFD-345
F/T by HMGeyer
WP#NDA20615.tdo

APR 3 1996

REVIEW FOR HFD-170
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGIST'S REVIEW #1 OF SUPPLEMENT
3 April 1996

A. 1. NDA 20-615
APPLICANT: Fujisawa USA, Inc.
Parkway North Center
Three Parkway North
Deerfield, IL 60015-2548

2. PRODUCT NAMES: Clonidine Hydrochloride Injection

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
Sterile solution for epidural administration, supplied 0.1 mg/mL in 10 mL vials.

4. METHODS OF STERILIZATION:

5. PHARMACOLOGICAL CATEGORY and/or PRINCIPLE INDICATION:
The product is indicated for continuous epidural administration as adjunctive therapy with intraspinal opiates for the treatment of pain in cancer patients tolerant to, or unresponsive to, intraspinal opiates alone.

B. 1. DATE OF INITIAL SUBMISSION: 4 August 1995

2. DATE OF AMENDMENT: (none)

3. RELATED DOCUMENTS:

4. ASSIGNED FOR REVIEW: 2 February 1996

C. REMARKS: The product is manufactured by:
Fujisawa USA, Inc. (FUSA)
3159 Staley Road
Grand Island, NY 14072

D. CONCLUSIONS: The application is approvable pending resolution of microbiology issues.

3 April 1996

Paul Stinavage, Ph.D.

4/3/96

cc: Original NDA 20-615
HFD-170/M. Wright/Maturu
HFD-805/Consult File/Stinavage

Drafted by: P. Stinavage, 3 April 1996
R/D initialed by P. Cooney, 3 April 1996

JUN 13 1996

REVIEW FOR HFD-170
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGIST'S REVIEW #2 OF SUPPLEMENT
11 June 1996

A. 1. NDA 20-615
APPLICANT: Fujisawa USA, Inc.
Parkway North Center
Three Parkway North
Deerfield, IL 60015-2548

2. PRODUCT NAMES: Clonidine Hydrochloride Injection

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
Sterile solution for epidural administration, supplied 0.1 mg/mL in 10 mL vials.

4. METHODS OF STERILIZATION:

5. PHARMACOLOGICAL CATEGORY and/or PRINCIPLE INDICATION:
The product is indicated for continuous epidural administration as adjunctive therapy with intraspinal opiates for the treatment of pain in cancer patients tolerant to, or unresponsive to, intraspinal opiates alone.

B. 1. DATE OF INITIAL SUBMISSION: 4 August 1995

2. DATE OF AMENDMENT: 10 May 1996 (Subject of this Review)

3. RELATED DOCUMENTS:

4. ASSIGNED FOR REVIEW: 20 May 1996

C. REMARKS: The product is manufactured by:
Fujisawa USA, Inc. (FUSA)
3159 Staley Road
Grand Island, NY 14072

D. CONCLUSIONS: The application is recommended for approval on the basis of the information provided.

13 June 1996
Paul Stinavage, Ph.D.

cc: Original NDA 20-615
HFD-170/M. Wright/Maturu
HFD-805/Consult File/Stinavage

Drafted by: P. Stinavage, 13 June 1996
R/D initialed by P. Cooney D. Hussain for PH Cooney 6-13-96

COPY

PILOT DRUG EVALUATION STAFF HFD-170
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-615 with user fees due date 8th August 1996 (orphan drug file WR 95-036)

REVIEW #1 DATE REVIEWED: 1 REVIEW COMPLETION DATE: 2.6.96

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
SUBMISSION	8-5-95	8-8-95	11-15-95.

This file was reassigned from Ms. Juanita Ross on 15th November 1995. 3rd copy of this NDA was sent to FDA Buffalo District.

NAME & ADDRESS OF APPLICANT: Fujisawa USA Inc, 3 Parkway North, 3rd floor, Deerfield, Illinois 60015-2548, Jerry D. Johnson, 708-317-8898.

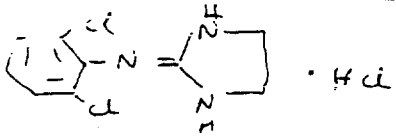
DRUG PRODUCT NAME

Proprietary: Epidural clonidine hydrochloride injection
Established:
Code Name/#: CAS# 4205-91-8
Chem.Type/Ther.Class: 3S

PHARMACOL. CATEGORY: Adjunct therapy with intraspinal opiates for the treatment of pain in cancer patients.

DOSAGE FORM: Epidural injection (SVT profile).
STRENGTHS: 1,000 ug/10 ml supplied in flint glass vial.
ROUTE OF ADMINISTRATION: Epidural.
DISPENSED: X Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:
Clonidine hydrochloride USP is 2-(2-6-dichlorophenyl)imino)imidazolidine monohydrochloride with mol wt 266.6. It is soluble in water (1 in 6) but insoluble in chloroform (1 in 5,000).



SUPPORTING DOCUMENTS: IND submitted by Fujisawa USA

RELATED DOCUMENTS:

CONSULTS: (1) Micro consult was sent to Dr. Peter Cooney (1.30.96), (2) EER consult was sent to Mr. Mark Lynch (11.21.95), (3) MV consult was sent to Mr. Smith, Buffalo District Director (1.24.96), (4) EA consult to Ms. Sanger is in progress (2.1.96 ?).

REMARKS: Adequate CMC information was submitted to support

Fujisawa has claimed no patent infringement and requested marketing exclusivity for 7 years post-NDA approval

CONCLUSIONS & RECOMMENDATIONS: Adequate CMC information was submitted for the approval of epidural clonidine injection. However, the following clarifications are initiated for the missing pieces of information.

cc:
Orig. NDA 20-615
HFD-170/Division File
HFD-170/PMaturu, JRoss, MTheodorakis
HFD-007/MWright, RBedford

filename: N20615.296
APPROVED/ INFORMATION REQUEST

P. Maturu 12.6.96
P.Maturu, PhD, Primary Review Chemist

M Theodorakis 2/6/96
M.Theodorakis, PhD, Chemistry Team Leader
Acting

MAY 21 1996

PILOT DRUG EVALUATION STAFF HFD-007
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-615 (orphan drug file WR 95-036)

REVIEW # 2 **DATE REVIEWED:** **5.15.96 (PDUFA date 8.8.96)**

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
AMENDMENT	5-10-96	5-12-96	5-14-96.

This amendment is in response to 2 deficiency letters, 3-19-96 letter for CMC and 4-25-96 letter for micro.

NAME & ADDRESS OF APPLICANT: Fujisawa US, 3 Parkway North, 3rd floor, Deerfield, Illinois 60015-2548, Jerry D. Johnson, tel 708-317-8898.

DRUG PRODUCT NAME

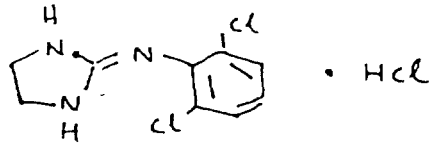
Proprietary: Epidural clonidine hydrochloride injection
Established:
Code Name/#: CAS# 4205-91-8
Chem.Type/Ther.Class: 3 S

PHARMACOL. CATEGORY: Adjunct therapy with intraspinal opiates for the treatment of pain in cancer patients.

DOSAGE FORM: Epidural injection (SVT profile).
STRENGTHS: 1,000 ug/ 10 ml supplied in flint glass vial.

ROUTE OF ADMINISTRATION: Epidural.
DISPENSED: X Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:
Clonidine hydrochloride USP is 2-(2-6-dichlorophenyl)imino)imidazolidine monohydrochloride with mol wt 266.6. It is soluble in water (1 in 6) but insoluble in chloroform (1 in 5,000).



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Response is ADEQUATE.

CONCLUSIONS & RECOMMENDATIONS:

Response is ADEQUATE, and CMC excluding micro is SATISFACTORY.

Response to 4.25.96 letter for micro was sent to micro on 5.14.96 for review. Statement on CMC status from prior review, EER is pending for a request dated 11.21.95, MV is pending for a request dated 12.26.95, there is no trademark proposal for clonidine injection, and EA is in the process of resubmission to Ms. Nancy Sager with FOI copy.

P. Maturu
P.Maturu, PhD, Primary Review Chemist

A.D'Sa, PhD, Acting Chemistry Team Leader

cc:
Orig. NDA 20-615
HFD-170/Division File
HFD-170/PMaturu, JRoss, AD'Sa, MWright, RBedford

filename:
SATISFACTORY

PILOT DRUG EVALUATION STAFF HFD-007
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-615 (orphan drug file WR 95-036)

REVIEW # 3 **DATE REVIEWED:** **7.24.96 (PDUFA date 8.8.96)**

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
AMENDMENT	7-23-96	7-23-96	7-23-96 (label)
AMENDMENT to teleconference dated 7.17.96).	7-18-96	7-18-96	7-19-96 (fax response
AMENDMENT and carton label).	7-17-96	7-18-96	7-19-96 (vial label
AMENDMENT	7-3-96	7-8-96	7-9-96
AMENDMENT teleconference dated 6.11.96).	6-24-96	6-25-96	6-27-96 (response to

NAME & ADDRESS OF APPLICANT: Fujisawa US, 3 Parkway North, 3rd floor, Deerfield, Illinois 60015-2548, Jerry D. Johnson, tel 708-317-8898.

DRUG PRODUCT NAME

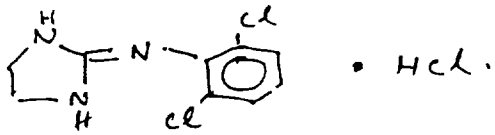
Proprietary: Epidural clonidine hydrochloride injection (DURACLON™)
Established:
Code Name/#: CAS# 4205-91-8
Chem.Type/Ther.Class: 1 S

PHARMACOL. CATEGORY: Adjunct therapy with intraspinal opiates for the treatment of pain in cancer patients.

DOSAGE FORM: Epidural injection (SVT profile).
STRENGTHS: 1,000 ug/ 10 ml supplied in flint glass vial.

ROUTE OF ADMINISTRATION: Epidural.
DISPENSED: __X__ Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:
Clonidine hydrochloride USP is 2-(2-6-dichlorophenyl)imino)imidazolidine monohydrochloride with mol wt 266.6. It is soluble in water (1 in 6) but insoluble in chloroform (1 in 5,000).



REMARKS:

1. Amendment dated 7-23-96 for the label is ADEQUATE for the following sections, description, how supplied, and dosage administration.

2. Amendment dated 7-18-96 provided as fax response to teleconference dated 7.17.96 is ADEQUATE based on the justification between stability program storage condition (25 to 27 C) for 8 stability lots and recommended CRT storage condition (15 to 30 C). Stability lots were listed as, R039108, R030025, R030054, C030002, C031008, R035001, R035002, 350059A.

3. Amendment dated 7-17-96 for vial label and carton label is INADEQUATE for prominence of the established name (21 CFR 201.15). Suggested a revision of the label with increased prominence for established name.

CONCLUSIONS & RECOMMENDATIONS:

Suggested a revision of the vial label and carton label with increased prominence of the established name (21 CFR 201.15).

EER is still pending. Buffalo District has recommended withhold approval recommendation, and this recommendation is under review by compliance headquarters.

P. Maturu

P.Maturu, PhD, Primary Review Chemist

A.D'Sa 7/29/96

A.D'Sa, PhD, Chemistry Team Leader

cc:
Orig. NDA 20-615
HFD-170/Division File
HFD-170/PMaturu, JRoss, AD'Sa, MWright

filename: N206153.967
ADEQUATE/SUGGESTION

PILOT DRUG EVALUATION STAFF HFD-007
Review of Chemistry, Manu[illegible]nd Controls

NDA #: 20-615 (orphan drug fi[illegible] Need Stamp dated copy

REVIEW # 4 **DATE REVIEWED:** 11.8.96)

SUBMISSION TYPE	DOCUMENT DATE	[illegible]GNED DATE
AMENDMENT	8-7-96	8-8-96 -96 (response to request for authentic stability data for clonidine injection, as suggested by compliance).

NAME & ADDRESS OF APPLICANT:

Fujisawa US, 3 Parkway North, 3rd floor, Deerfield, Illinois 60015-2548, Jerry D. Johnson, tel 708-317-8898.

DRUG PRODUCT NAME
Proprietary: Epidural clonidine hydrochloride injection
Established:
Code Name/#: CAS# 4205-91-8
Chem.Type/Ther.Class: 3 S

PHARMACOL. CATEGORY:

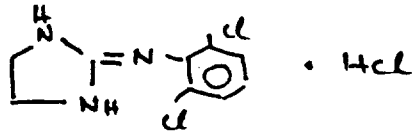
Adjunct therapy with intraspinal opiates for the treatment of pain in cancer patients.

DOSAGE FORM: Epidural injection (SVT profile).
STRENGTHS: 1,000 ug/ 10 ml supplied in flint glass vial.

ROUTE OF ADMINISTRATION: Epidural.
DISPENSED: __X__ Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:

Clonidine hydrochloride USP is 2-(2-6-dichlorophenyl)imino)imidazolidine monohydrochloride with mol wt 266.6. It is soluble in water (1 in 6) but insoluble in chloroform (1 in 5,000).



REMARKS:

CONCLUSIONS & RECOMMENDATIONS:

One year RT stability data was presented to support two years shelf life request for clonidine injection, and it is ADEQUATE.

FPL, container label, is being revised to comply with half the prominence requirement for the established name.

EER is supposedly satisfactory, but still pending in writing, with a revision from unacceptable to acceptable for Grand Island mfg. site.

P. Maturu / 8.12.96
P.Maturu, PhD, Primary Review Chemist

mrc; 8/12/96
A.D'Sa, PhD, Chemistry Team Leader

cc:
Orig. NDA 20-615
HFD-170/Division File
HFD-170/PMaturu, JRoss, AD'Sa, MWright

filename: N206154.968
ADEQUATE

COPY

650

REQUEST FOR TRADEMARK REVIEW

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

From: Division of Anesthetic, Critical Care, & Addiction Drug Products HFD-170	
Attention: Millie Wright, Project Manager	Phone: 443-4250
Date: 6/27/96	
Subject: Request for Assessment of a Trademark for a Proposed New Drug Product	
Proposed Trademark: Duraclon; Duraclon	NDA XXXXXX #20-615

Established name, including dosage form:

clonidine hydrochloride injection (epidural); 0.1mg/mL

Other trademarks by the same firm for companion products:

None

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

Indicated for continuous epidural administration as adjuctive therapy with intraspinal opiates for the treatment of pain in cancer patients tolerant to, or unresponsive to, intraspinal opiates alone.

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

The Division thinks Duraclon is acceptable. We do not approve of Duraclon. It would lend itself to errors when prescriptions are being written.
**Please note that our user fee date for this application is August 8, 1996. If it is possible for you to give us your feedback, we would greatly appreciate it.

MAY 28 1996

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

Epidural clonidine injection, 1,000 ug/10 ml

NDA 20-615

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION HFD-170

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-615

Epidural clonidine injection, 1,000 ug/10 ml

The Food and Drug Administration (FDA) recognizes the National Environmental Policy Act of 1969 (NEPA) as the national charter for protection, restoration, and enhancement of the environment. NEPA establishes policy, sets goals (section 101), and provides procedures (section 102) for carrying out the policy.

Environmental information is to be available to the public and the decision maker before decisions are made about actions that may significantly affect the quality of the human environment; FDA actions are to be supported by accurate scientific analyses; and environmental documents are to concentrate on timely and significant issues, not to amass needless detail.

The Food and Drug Administration Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

Fujisawa US has prepared an abbreviated environmental assessment 21 CFR 25.31a(b)(3) in support of their new drug application for Epidural clonidine injection, 1,000 ug/10 ml, intended as an adjunct therapy with intraspinal opiates for the treatment of pain. The EA has evaluated the potential environmental impacts of the manufacture, use and disposal of the drug product.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured and used without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release.

5·15·96 P. Maturu
DATE PREPARED BY
[P.Maturu]
[Review Chemist]
[HFD-170 DIVISION]

5/20/96
DATE CONCURRENCE
[A. D'Sa] Acting
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5/21/96
DATE CONCURRENCE
Nancy B. Sager
Environmental Scientist
Center for Drug Evaluation and Research

Attachment: Environmental Assessment
Material Safety Data Sheet (drug substance)

FREEDOM OF INFORMATION (FOI)
NON-CONFIDENTIAL
ABBREVIATED ENVIRONMENTAL ASSESSMENT

FOR
NDA 20-615

Epidural clonidine injection, 1000 ug/ 10 ml
For cancer pain as adjunct therapy with intraspinal opiates

SECTION 1 DATE

April 16, 1996

SECTION 2 NAME OF APPLICANT/PETITIONER

Fujisawa USA, Inc.

SECTION 3 · ADDRESS

Fujisawa USA, Inc.
Parkway North Center
Three Parkway North
Deerfield, IL 60015-2548

SECTION 4 DESCRIPTION OF THE PROPOSED ACTION

INTRODUCTION

The proposed drug product, Epidural Clonidine Hydrochloride (HCl), is intended for use as an analgesic delivered by continuous infusion into the epidural space. Clonidine hydrochloride was granted designation as an orphan drug on January 24, 1989 for administration by the epidural route (either bolus injection or intermittent or continuous infusion), for treatment of pain in cancer patients tolerant to, or unresponsive to, intraspinal opiates. The revised proposed indication is for continuous epidural administration as adjunctive therapy with intraspinal opiates for the treatment of pain in cancer patients tolerant to, or unresponsive to, intraspinal opiates alone.

For the proposed action, Epidural Clonidine-HCl will be used with a limited patient population, and production volumes of the drug substance and drug product will be low, resulting in a minimal impact to the environment. Based on the proposed use of Epidural Clonidine-HCl for infrequent use in the treatment of a rare condition and as allowed under 21 CFR 25.31 a(b), the Environmental Assessment for this drug will follow the abbreviated format in Sections 6, 7, 8, 9, 10, 11, and 15.

4.1 The proposed requested approval:

Fujisawa USA, Inc. is requesting approval to manufacture, package, distribute, and market Epidural Clonidine-HCl, a drug product for human use as an epidurally delivered analgesic. Epidural Clonidine-HCl will be supplied as a sterile, preservative-free, pyrogen-free, 0.1 mg/mL normal saline (100 µg/mL) solution in a clear, single-dose, 10-mL vial. The inactive ingredients are Sodium Chloride, USP and Sterile Water for Injection, USP. Clinical data suggest that a dose of 20 to 40 µg/hr by continuous epidural infusion produces analgesia with a good safety profile. The marketed drug product will be distributed to a limited number of medical providers for use in hospitals, clinics, and homes in the United States. It will be dispensed only on the order of a licensed physician.

4.2 Statement of need for the action

Clonidine hydrochloride is an α_2-adrenergic partial agonist currently formulated for oral or transdermal administration and available as a parenteral formulation in Europe for the treatment of hypertension (Appendix A-1, Reference 1). Currently, clonidine hydrochloride formulations also are marketed in the United States for oral and transdermal delivery for the treatment of hypertension. Applied near the spinal cord, clonidine hydrochloride produces powerful dose-dependent analgesia.

4.2.1 Indication for which the application is made

Epidural Clonidine-HCl is indicated for continuous epidural administration as adjunctive therapy with intraspinal opiates for the treatment of pain in cancer patients tolerant to, or unresponsive to, intraspinal opiates alone.

Seventy percent (70%) of cancer patients with advanced disease experience severe pain. Cancer pain may be managed with oral analgesics in 85% of patients, whereas 15% will require invasive procedures for pain management. Epidurally administered clonidine, acting by non-opiate mechanisms in the spinal cord, produces effective analgesia in these patients without serious side effects and without cross tolerance with opiates. Epidural Clonidine-HCl may represent the first alternative to destructive neurolytic procedures in cancer patients with intractable pain not relieved by opiates.

4.2.2 Mode of Action

Clonidine hydrochloride is an α_2-adrenergic partial agonist postulated to produce analgesia by mimicking the actions of norepinephrine, normally released from the bulbo-spinal neurons which modulate pain transmission (Appendix A-1, Reference 2). Specifically, clonidine hydrochloride is thought to block transmission of pain signals in the spinal cord by activating both presynaptic and postsynaptic α_2-adrenoceptors, which inhibit substance P release (Appendix A-1, Reference 3) and dorsal horn neuron firing (Appendix A-1, Reference 4), respectively.

4.2.3 Estimated patient population

Epidural Clonidine-HCl is expected to be indicated for administration as adjunctive therapy with intraspinal opiates for the treatment of pain in a small subpopulation of cancer patients tolerant to, or unresponsive to, intraspinal opiates alone. The total patient population expected to receive the proposed therapy in the fifth year after approval for this indication is estimated at 25,200. Information on the projected patient population and market volume for Epidural Clonidine-HCl subsequent to approval of the proposed action is provided in Confidential Appendix B-1.

4.3 Production locations

The bulk drug substance, clonidine hydrochloride, will be manufactured at:

Leiras
Huhtamaki Oy
SF-20101 Turku, Finland

The finished drug product, Epidural Clonidine-HCl, supplied as a 0.1 mg/mL normal saline solution in a clear, single dose, 10-mL vial, will be manufactured at:

Fujisawa USA, Inc.
3159 Staley Road
Grand Island, NY 14072

4.4 Locations where the products will be used and disposed of

This proposed drug product is intended for sale and distribution in the United States. Usage of this product will primarily occur in hospitals and clinical settings, administered by, or under direct supervision of, trained physicians. The product packaging and administration equipment would be disposed of by the hospital and clinics using their normal disposal procedures.

4.4.1 Disposal of excreted products from clinical use

Epidural Clonidine-HCl is proposed for limited distribution. Patient populations are estimated to be small and consistent with the rare disease definition. The drug product introduced into patients and its metabolites will primarily be excreted through the urine and feces into sanitary sewer systems, with ultimate distribution to wastewater treatment systems throughout the United States.

4.4.2 Medical provider actions for returned goods

Returned goods goods will be sent by the medical provider to the following location:

Fujisawa Distribution Warehouse
600 Supreme Drive
Bensenville, IL 60106

The medical provider will be instructed to package and ship the returned goods consistent with the US Department of Transportation (DOT) regulations using appropriate packaging to prevent possible breakage and leakage.

4.4.3 Handling and disposal of returned/rejected goods

Rejected drug substance manufactured at the Leiras Oy facility in Finland will be disposed of through the local municipal wastewater treatment facility. Prior to discharge to the local treatment facility, wastes are processed through a preliminary treatment unit located at the Leiras site. Dilution and neutralization are carried out in this on-site facility as required by Finnish laws. Waste handling, treatment, and disposal associated with manufacturing operations at the Leiras facility are carried out in accordance with the environmental laws and regulations of Finland, subject to the jurisdiction of the Environmental Department of the Provincial Government of Turku and Pori.

Rejected drug product manufactured at the Fujisawa USA Grand Island facility will be disposed of by one of two methods. In either case, general solid waste paper cartoning material currently is designated for disposal at

the following municipal solid waste landfill operated by Browning-Ferris Industries:

Niagara Recycling
56th and Pine Avenue
Niagara Falls, NY

The Niagara Recycling facility does not handle hazardous wastes and, thus, does not have an Environmental Protection Agency (EPA) Facility Identification Number.

The Epidural Clonidine-HCl vials and the drug product are considered non-hazardous materials. The first alternative method of disposal will use a crusher to shred the vials and separate the solid material from the liquid drug product. The solid material will be landfilled at the Niagara Recycling facility identified above. The liquid will be consolidated and sent to the following wastewater treatment contractor:

Laidlaw Environmental Services, Inc.
North Andover, MA

Laidlaw Environmental Services will arrange for disposal of the waste material at an appropriate waste disposal facility operating in compliance with applicable federal, state, and local laws and regulations. Several alternative facilities are utilized by Laidlaw Environmental Services for disposal of these non-hazardous wastes.

It is anticipated that the Fujisawa USA Grand Island facility will begin to treat bulk pharmaceutical liquid waste from its crusher program in an on-site wastewater treatment facility currently under construction at the site. This treatment option is currently being reviewed by the New York State Department of Environmental Conservation.

The second alternative method for disposal of the rejected Epidural Clonidine-HCl vials and liquid drug product will be high temperature incineration. The vials will be consolidated for shipment and sent to a waste-to-energy facility. The designated facility for this disposal is:

Ogden Martin Systems
100 Recovery Way
Haverhill, MA 01835
Facility State ID #: RR0128.008

More detailed information on this facility, as well as solid waste, water discharge, and air emissions permit numbers are provided in Confidential Appendix B-2.

Drug product returned by medical providers will be inspected upon receipt at the Fujisawa Distribution Warehouse in Bensenville, Illinois. If disposal is required, the material will be shipped to a designated disposal facility operated by Ogden Martin Systems. The current designated facility is the Ogden Martin Systems facility in Haverhill, Massachusetts, identified above.

4.5 Types of environments present at and adjacent to production facilities and disposal facilities for excreted drug product and returned/rejected goods

4.5.1 Production facilities

The bulk drug substance, clonidine hydrochloride, will be manufactured at Leiras Oy in Turku, Finland. Turku is a city of approximately 150,000 people on the southwest coast of Finland. Topography of the region is flat and land use in the vicinity of the facility is rural. The climate in southern Finland is temperate. Further details can be found in DMF #4778.

The production facility for the finished drug product, Epidural Clonidine-HCl, is the Fujisawa USA facility in Grand Island, New York. The facility is located in the southwest quadrant of Grand Island, an island in the Niagara River. The island is approximately 26 square miles, is flat with a relief of about 50 feet, and has soil that is clay and silt with moderate to poor drainage. The island waters border Ontario, Canada to the north, Buffalo, New York to the south, and the city of Niagara Falls, New York to the northeast. The population of Grand Island is approximately 18,500. The area has a cool, temperate climate, with temperature and precipitation somewhat influenced by the Great Lakes. Properties nearby include another pharmaceutical company with a permitted water treatment facility, residential properties, and conservation land with federally protected wetlands.

4.5.2 Disposal locations for returned and rejected goods

General solid waste from the Fujisawa USA, Grand Island facility will be disposed of at Niagara Recycling, a municipal solid waste landfill in Niagara Falls, NY. Niagara Falls is a city of approximately 85,000 people in western New York. The area has a cool, temperate climate, with temperature and precipitation influenced by the Great Lakes.

Rejected drug product will be disposed of at one of two facilities. Bulk liquid pharmaceutical product may be disposed of through Laidlaw Environmental Services, Inc., a waste management firm in North Andover, MA. A number of alternative facilities are utilized by Laidlaw Environmental Services for disposal of these types of wastes.

Drug product vials and liquid drug product also may be disposed of at Ogden Martin Systems, a high temperature waste-to-energy facility in Haverhill, MA. Haverhill is a city of approximately 46,000 in northeast Massachusetts. The

Ogden Martin Systems facility is located on a peninsula bordered on three sides by the Merrimack River. The local topography is rolling terrain. Surrounding land uses are residential to the north and west, light industrial to the east, and farmland to the south. The area has a cool, temperate climate. A copy of general facility information, site description, and the relevant environmental permit for the Ogden Martin Systems facility in Haverhill, MA is included in Confidential Appendix B-2.

4.5.3 Disposal of excreted products from clinical use

Epidural Clonidine-HCl is proposed for limited distribution. The drug product and its metabolites will primarily be excreted through the urine and feces, resulting in distribution to wastewater treatment systems throughout the United States.

SECTION 5 IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE THE SUBJECT OF THE PROPOSED ACTION

The substances that are the subject of the proposed action can be divided into five categories: (1) drug substance, (2) drug substance impurities and degradants, (3) drug product additives, (4) drug substance and drug product manufacturing waste products, and (5) packaging materials and package disposal waste products.

5.1 Drug Substance:

Nomenclature: 2-[(2,6-dichlorophenyl) amino]-2-imidazoline hydrochloride

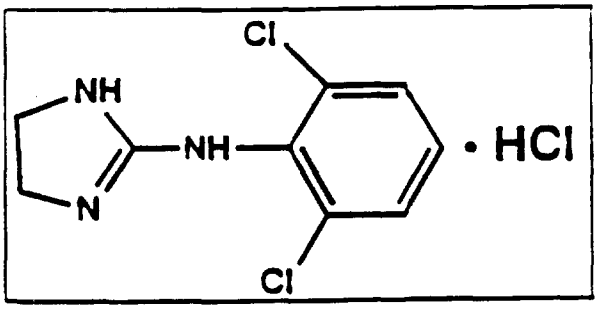
Common Name: clonidine hydrochloride

CAS Registration Number: 4205-91-8

Molecular weight: 266.56

Melting Temperature: 305°C

Structural formula:



$C_9H_9Cl_2N_3 \cdot HCl$ Mol. Wt. 266.56

Physical description: Clonidine hydrochloride is an odorless, bitter, white crystalline substance.

5.2 Drug Substance Impurities and Degradants

Additives: The drug substance, clonidine hydrochloride, contains no additives.

Impurities (USP/NF): USP-grade drug specifications are 98.5 to 101.0 percent of $C_9H_9Cl_2N_3 \cdot HCl$ calculated on a dried basis. Purity is evaluated using thin layer

chromatography. The R_f value of the principal spot from the test solution corresponds to that of the Standard solution. Any other spot obtained from the test solution does not exceed, in size or intensity, the principal spot obtained from a 0.1% diluted Standard solution, and the total of any spots does not exceed 0.2%.

5.3 Drug Product Additives

The proposed drug product, Epidural Clonidine-HCl, is a sterile, colorless liquid. It contains the following inactive ingredients:

Sodium Chloride, USP
Sterile Water for Injection, USP

5.4 Manufacturing Waste Products

Drug substance manufacturing wastes are materials that can potentially be released during the manufacture of clonidine hydrochloride, and the materials used in cleaning and maintaining the production facilities. These substances include the drug substance, and a number of substances typically found in a pharmaceutical manufacturing facility, such as organic solvents, alcohols, reagents and chemical intermediates, purified water, commercial surfactants, cleaning agents, and detergents. Confidential Appendix B-3 lists the chemicals used during the manufacture of clonidine hydrochloride at the Leiras facility in Turku, Finland.

Drug product manufacturing wastes are substances that can potentially be released during the drug product manufacturing process. These substances include components of the drug product, as well as commercial cleaning agents, surfactants, and detergents. Confidential Appendix B-3, Table 1, lists the ingredients used in the manufacture of Epidural Clonidine HCl at the Fujisawa USA, Inc. facility in Grand Island, New York.

5.5 Packaging Materials

The drug substance, clonidine hydrochloride, will be packaged in double polyethylene bags, within an outer fiber drum container. These packaging materials will enter the waste stream subsequent to manufacture of the drug product.

The drug product will be packaged in glass vials, with stoppers and seals. Paper and cardboard also will be used in packaging the drug product.

These packaging materials will enter the waste stream as a result of product use, and when rejected or expired materials are returned. These are widely available and used pharmaceutical packaging materials.

SECTION 6 INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

ABBREVIATED, AS ALLOWED UNDER 21 CFR 25.31 a(b), FOR HUMAN DRUGS INTENDED FOR TREATMENT OF A RARE DISEASE OR FOR A SIMILARLY INFREQUENT USE.

Epidural Clonidine-HCl and the substances associated with its manufacture can potentially enter the environment from four major sources: (1) the site of manufacture of the drug substance, clonidine hydrochloride; (2) the site of manufacture and packaging of the drug product, Epidural Clonidine-HCl; (3) the sites of use by patients; and (4) waste disposal sites for rejected, discarded, or returned product and packaging materials.

The manufacture of the drug substance, clonidine hydrochloride, will take place at Leiras Oy in Turku, Finland. A description of the Leiras manufacturing site is provided in Section 4.5.1 of this Environmental Assessment and, in more detail, in DMF #4778. The final drug product, Epidural Clonidine-HCl will be manufactured and packaged at Fujisawa USA in Grand Island, New York. The drug product will be distributed to hospitals, physicians, and pharmacies for limited use throughout the United States. Returned products will be collected for disposal at the Fujisawa Distribution Warehouse in Bensenville, Illinois.

The expected emissions, emissions controls, and compliance with relevant environmental and occupational laws for each source of emissions associated with the proposed action are discussed below.

6.1 Site for production of drug substance

Manufacture of the drug substance, clonidine hydrochloride, will take place at Leiras Oy, in Turku, Finland. Leiras attempts to minimize emissions of manufacturing wastes to the environment by maintaining highly controlled production systems; collecting wastes for recovery, recycling, or destruction where this is technically and economically feasible; and maintaining a high standard of general housekeeping through standard operating procedures and good manufacturing practices. The substances expected to be emitted in the production of clonidine hydrochloride at the Leiras facility in Turku are listed in Confidential Appendix B-3, Tabe II.

The principal routes of emissions will be to established air and wastewater handling systems at the facility. Only small amounts of solid wastes are generated by the clonidine hydrochloride manufacturing process.

6.1.1 Control of environmental emissions

Air emissions associated with production of clonidine hydrochloride and with storage and transfer of raw materials will be controlled by using appropriate control technologies and standard operating procedures. The primary releases to air are diffusion emissions through condensers used to control process emissions.

Sources of process-related wastewater include the clonidine hydrochloride manufacturing process, liquid collected from condensers, and liquid used in cleaning process equipment. These liquid process-related wastes will be diluted and neutralized in a preliminary treatment unit at the Leiras plant and then released to the local municipal treatment facility. Sanitary wastes from the Leiras facility are also released to the local municipal treatment facility.

Small amounts of solid waste materials are generated from the clonidine hydrochloride manufacturing process. These solid wastes consist of filter cakes containing insoluble process related wastes. These materials are disposed of at the following facility:

Ekokem Oy Ab
Riihimäki, Finland

This facility disposes of problem wastes under licenses No. 281/A231/29.9.1987 and No. 230/A231/3.10.1990, issued by the Provincial Government of Häme. Since March 1995, the Häme Regional Environment Centre has replaced the Provincial Government of Häme as a public supervisory authority. These licenses grant permission to treat hazardous wastes by incineration and physical-chemical treatment, and to operate a special landfill for final disposal of residues generated by the treatment processes. There are no expiration dates for these licenses. The Ekokem facility is located in a flat, rural area a few kilometers from Riihimäki in the southern part of Finland. The climate in this area is temperate.

6.1.2 Compliance with emissions requirements

This section describes the regulations to which operations at the Leiras facility are subject and the corresponding regulatory authorities responsible for issuing permits, monitoring compliance, and enforcing the regulations.

The primary Finnish regulations pertaining to safety, health, and environmental issues are the Chemical Act, the Occupational Health Act, and the Explosive Chemicals Act. Provincial government authorities typically are

responsible for enforcing these regulations. The Leiras chemical synthesis plant possesses (1) a Certificate of Manufacturers of Bulk Pharmaceutical Chemicals, issued by the National Agency for Welfare and Health, and (2) Operating Licenses No. 3331/320/89 and No. 1583/365/91, issued by the National Technical Inspection Agency under the Chemical Act (744/89).

Pursuant to 21 CFR §25.50 and Executive Order 12114, the manufacturer of the bulk drug substance, Leiras Oy, has provided in Appendix A-2 a letter certifying that the operations at their manufacturing facility, including manufacture of clonidine hydrochloride, are in full compliance with applicable environmental regulations concerning emissions at the site. The compliance letter was issued by the Environmental Department of the Provincial Government of Turku and Pori. This regulatory authority has responsibility for enforcing compliance of the Leiras pharmaceutical chemical manufacturing facility with Finnish environmental laws and regulations. The letter supplied by the Provincial Government of Turku and Pori is written confirmation of Leiras' compliance with the legal requirements of environmental laws and regulations in Finland. Monitoring, inspection, and reporting requirements are determined, as needed, by the Provincial authority; there are no specific numeric limits for environmental emissions associated with the Leiras facility's operating licenses.

Air emissions from the Leiras facility, including those associated with existing clonidine hydrochloride manufacturing operations, are in compliance with existing environmental regulations. Approval of the requested action is not expected to affect the facility's ability to comply with these regulations because adequate environmental controls are currently in place and increased emissions associated with the incremental clonidine hydrochloride production will be very small.

The discharge of wastewater from the Leiras facility, including liquid wastes associated with existing clonidine hydrochloride manufacturing operations, is in compliance with existing environmental regulations. No wastewater emissions associated with the clonidine hydrochloride manufacturing process are considered hazardous and, therefore, special hazardous waste handling and disposal procedures are not required. Process related wastewater is diluted and neutralized in an on-site wastewater pretreatment unit prior to discharge to the local municipal treatment facility. Approval of the requested action is not expected to affect the facility's ability to comply with wastewater handling requirements because adequate controls are currently in place and the increased emissions associated with the incremental clonidine hydrochloride production will be very small.

Disposal of solid waste from the Leiras facility, including wastes associated with existing clonidine hydrochloride manufacturing operations, is in compliance with existing environmental regulations. Only small amounts of solid wastes are generated from the clonidine hydrochloride manufacturing process. General wastes, such as office supplies and packing materials, are

disposed of in landfills operated by local municipalities. Filter cakes containing insoluble impurities will be disposed of at a special off-site waste handling facility, Ekokem, in Riihimäki, Finland. This facility is licensed to treat hazardous wastes, or other problem wastes, by the Provincial Government of Häme, Häme Regional Environmental Centre. Approval of the requested action is not expected to affect the Leiras facility's ability to comply with existing environmental regulations.

6.1.3 Compliance with occupational health and safety requirements

The Leiras facility operates in compliance with applicable occupational health and safety laws. In Finland, Occupational health and safety is regulated primarily under provisions of the Occupational Health Act. It should be noted, however, that the Good Manufacturing Practices applied in the pharmaceutical industry tend to result in more stringent protection of worker health and safety than typical occupational health requirements. In general, at the Leiras facility worker health and safety is protected by appropriate engineering controls that eliminate or reduce worker exposure to potentially hazardous chemicals or situations. Personal protective devices or clothing are used as necessary. A copy of the Material Safety Data Sheet for clonidine hydrochloride is provided in Appendix A-3.

6.1.4 Effects of approval on compliance

Approval of the proposed action is expected to have no effect on the ability of the Leiras facility in Turku, Finland to comply with any environmental or occupational safety and health laws or regulations currently in effect. The incremental increase in emissions to the environment associated with approval of the proposed action will be very small. The facility has adequate controls in place to allow for compliance with applicable air emissions regulations. Solid and liquid wastes generated as a result of clonidine hydrochloride production will be treated and disposed of in compliance with existing regulations.

6.2 Site for production of drug product

Manufacture of the finished drug product, Epidural Clonidine-HCl, will take place at Fujisawa USA in Grand Island, New York. Fujisawa USA minimizes emissions to the environment by maintaining highly controlled production systems; collecting wastes for recovery, recycling, or destruction where this is technically and economically feasible; maintaining a high standard of general housekeeping through standard operating procedures and good manufacturing practices; and committing its resources to complying with applicable federal, state, and local environmental and occupational statutes and regulations. Appropriate controls are in place to minimize emissions associated with the Epidural Clonidine-HCl manufacturing process. Substances expected to be emitted in the production of Epidural Clonidine-HCl at the Fujisawa USA, Inc. facility in Grand Island, N.Y. are listed in Confidential Appendix B-3. Table III.

The principal routes of emissions will be through established liquid and solid waste disposal mechanisms.

6.2.1 Control of environmental emissions

Air emissions

The air handling procedures required for the sterile drug facility in which Epidural Clonidine-HCl will be manufactured make atmospheric releases unlikely. Drug product solutions are manufactured in a clean, controlled environment supplied with HEPA filtered air. Any dust generated during the manufacturing process is controlled by HEPA-filtered air handling systems before the air is vented to the environment. The operating efficiency of the HEPA system is a minimum of 99.97%, as specified by standard operating procedures. Filters no longer meeting control specifications enter the solid waste stream from the facility. No hazardous materials will be used or generated in the Epidural Clonidine-HCl production process.

Wastewater generation and disposal

Liquid waste from the Epidural Clonidine-HCl production process will consist of process wastes and water used in cleaning operations. Wastewater from the process is discharged to a privately operated wastewater treatment facility prior to its permitted release to a stream that ultimately discharges to the Niagara River. Release of the treated water is allowed under a State Pollutant Discharge Elimination System Permit, under the jurisdiction of the New York State Department of Environmental Conservation. Currently, the wastewater treatment facility utilized by the Fujisawa USA Grand Island plant is a shared waste water treatment facility. This treatment facility is shared with the owner of the facility, Life Technologies, and is located on property adjacent to the Fujisawa USA plant. This facility employs a lagoon system to accomplish secondary wastewater treatment. Wastewater from the Epidural Clonidine-HCl production process can be discharged directly to the wastewater treatment facility with no pretreatment required.

The Fujisawa USA Grand Island plant is currently building its own on-site wastewater treatment facility. It is anticipated that Fujisawa USA will begin treating wastewater from the Epidural Clonidine-HCl process when the new on-site treatment facility is completed and the necessary operating permits are obtained from the New York State Department of Environmental Conservation. This facility will use an activated sludge system to accomplish secondary wastewater treatment. Sanitary sewage from the Fujisawa USA facility also enters the shared private wastewater treatment facility and ultimately will be treated in Fujisawa USA's anticipated on-site treatment facility.

Solid waste generation and disposal

Only small amounts of solid waste will be generated from the manufacturing process. These wastes will consist primarily of rejected (off-specification) drug substance or drug product. Solid wastes, such as packing materials, general supplies, and spent filters will be collected in dumpsters for off-site disposal by pre-approved disposal vendors. This material is currently designated for disposal at Niagara Recycling, in Niagara Falls, a municipal solid waste landfill operated by Browning Ferris Industries.

Rejected Epidural Clonidine-HCl vials and the drug product will be handled for disposal by one of two methods. The first method of disposal will use a crusher to shred the vials and separate the solid material from the liquid drug product. The solid material will be landfilled at the Niagara Recycling facility identified above. The liquid will be consolidated and disposed of at an appropriate waste disposal facility through Laidlaw Environmental Services, Inc. in North Andover, Massachusetts. It is anticipated that the Fujisawa USA Grand Island facility will begin treating the bulk liquid waste material on site when the on-site wastewater treatment facility, currently under construction, is completed. This treatment option is currently being reviewed by the New York State Department of Environmental Conservation.

The second option for disposal of Epidural Clonidine-HCl vials and liquid drug product will be high temperature incineration. The vials would be consolidated for shipment and sent to a massburn waste-to-energy facility. The designated facility for this disposal is Ogden Martin Systems, in Haverhill, Massachusetts (Facility ID #: RR0128.008).

Ogden Martin Systems of Haverhill is a massburn waste-to-energy facility accepting municipal solid waste and approved special waste (it is not a hazardous waste facility). Waste from the Fujisawa USA plant is transported to the Ogden Martin Systems facility and is mixed with household refuse. The waste is incinerated at a temperature of at least 1800°F. This waste is accepted as an approved special material, and an Ogden Martin representative must witness the burn to verify that the material is destroyed. If necessary, certificates of destruction can be provided to verify the disposal of a specified tonnage of material. The resulting inert ash residue is approximately 10% of the original volume. Combustion gases are utilized to heat water for the production of electricity. The ash is deposited into a water quench trough, and collected for disposal in covered leak proof trucks for disposal in a landfill designed to protect against groundwater contamination. The cooled combustion gases are passed through a lime slurry to neutralize any acid forming gases such as sulfur oxides and hydrogen chloride. Particulates are collected via a high efficiency electrostatic precipitator which removes 99% of contaminants. These particulates are collected and mixed with the ash previously collected. A brief description of the Ogden Martin Systems processing/ treatment operations, along with solid waste, water discharge, and air emissions permit numbers are provided in Confidential

Appendix B-2.

6.2.2 Compliance with emissions requirements

This section discusses Fujisawa USA's compliance with applicable environmental regulations and requirements.

Air emissions

The New York State Department of Environmental Conservation has regulatory jurisdiction for air emissions from the Fujisawa USA Grand Island facility. The Department of Environmental Conservation has evaluated the manufacturing operations and potential emissions at the Grand Island facility and has concluded that no air emission permits are required for the Fujisawa USA facility due to the nature or low volume of emissions.

Wastewater generation and disposal

Process wastewater is treated in a privately operated wastewater treatment facility shared with Life Technologies, owner of the treatment facility. The treatment facility is located on Life Technologies property, adjacent to the Fujisawa USA site. Treated water from the treatment facility is released to a stream and ultimately discharges to the Niagara River in compliance with State Pollutant Discharge Elimination System (SPDES) ID Number NY 0000400; there is no expiration date for this permit. The permit for this discharge is administered by the New York State Department of Environmental Conservation, which monitors operation of the wastewater treatment facility.

The wastewater treatment facility is in compliance with all applicable state and federal standards. A number of water quality parameters, including temperature, system flow rate, chemical oxygen demand, pH, dissolved oxygen, settleable solids, nitrogen, copper, toluene, bis(2-ethylhexyl phthalate, phenols, total dissolved solids, mercury, surfactants, oil and grease, and sulfite are monitored. The required monitoring frequencies range from once per day to once per month. Discharge monitoring reports are submitted to the New York State Department of Environmental Conservation each month.

The shared wastewater treatment facility is designed to treat a volume of 120,000 gallons/day. Approval of the proposed action would result in 15 production runs per year, each producing no more than 1,000 gallons of discharged water. This represents a small fraction of the total treatment plant discharge capacity. Thus, the proposed action is expected to have a negligible effect on Fujisawa USA's ability to adequately treat process-related wastewater. Fujisawa USA anticipates treatment of process wastewater generated at the Grand Island plant to ultimately take place at its own on-site treatment facility, currently under construction. This treatment option is

currently being reviewed by the New York State Department of Environmental Conservation.

Solid waste and rejected product generation and disposal

Solid waste generated from the Epidural Clonidine-HCl manufacturing process will consist primarily of rejected (off-specification) drug substance or drug product. These materials are handled as non-hazardous wastes. Intact vials containing the drug product or bulk drug substance will be disposed of at Ogden Martin Systems in Haverhill, Massachusetts. The Ogden Martin Systems facility is a state-licensed disposal facility; it holds Facility State ID # RR0128.008 and is under the regulatory jurisdiction of the Massachusetts Department of Environmental Protection. This facility has sufficient capacity to accept the additional waste expected to be generated as a result of approval of the proposed action. Transport of non-hazardous materials from the Grand Island site to the Ogden Martin facility typically is coordinated with hazardous waste transport; thus, transport of this waste is carried out by one of the licensed hazardous waste transport firms used by Fujisawa USA.

Bulk liquid pharmaceutical product will be disposed of through Laidlaw Environmental Services of Andover, Massachusetts. Laidlaw Environmental Services utilizes a number of different disposal facilities, as appropriate. The facilities used comply with federal, state, and local laws and regulations, as applicable for the types of wastes being handled. The available capacity for treatment of liquid wastes is sufficient to handle the small amounts of additional waste expected to be generated as a result of the proposed action.

Other solid wastes such as packaging materials, general supplies, and spent air filters will be disposed of at a local municipal solid waste landfill, Niagara Recycling in Niagara Falls, NY, under a local contract with Browning-Ferris Industries. These vendors operate in compliance with applicable local and state requirements, and have sufficient capacity to accept the small amounts of additional waste expected to be generated as a result of the proposed action.

6.2.3 Compliance with occupational health and safety requirements

Fujisawa USA takes all the necessary steps to comply with the Occupational Safety and Health Act (OSHA 1970), the OSHA Hazard Communication Standard (1983, 1987), and Title 29, Code of Federal Regulations, Part 1910.

In general, worker health and safety are protected by appropriate administrative and engineering controls that eliminate or reduce worker exposure to potentially hazardous chemicals or situations. Material Safety Data Sheets (MSDS) are available on-site for all chemicals used in the production process. The MSDS for the drug substance, clonidine

hydrochloride, is provided in Appendix A-3. Appropriate personal protective equipment, including protective clothing, gloves, safety glasses, hard hats, and respirators, are available, as necessary. All personnel directly sampling the drug substance will wear a fully sealing dust mask or respirator equipped with HEPA cartridges. Workplace monitoring is carried out as necessary and appropriate, e.g., to investigate suspected releases from existing operations or to characterize potential changes in the workplace environment associated with process changes.

A high emphasis is placed upon the training of proper health and safety techniques at the Grand Island facility. All temporary and permanent personnel working within the facility are required to attend a health and safety orientation program prior to starting work. This program varies in length and content depending upon the previous knowledge and experience of the individual, and the scope of work to be performed at the facility. All personnel also receive training in worker right-to-know issues, use of health and safety equipment and educational materials, safe work practices, and site-specific emergency response plans and procedures. In addition, several other types of specialized training are carried out for selected worker categories, as necessary; these include lock out/tag out training, laboratory practices and chemical hygiene programs, and forklift training. Training sessions are conducted throughout the year and are periodically conducted as refresher courses.

6.2.4 Effects of approval on compliance

Fujisawa USA, Inc. is in full compliance with all emissions requirements set forth in its operating permits and licenses, as well as with requirements set forth in federal, state, and local statutes and regulations, as applicable in the operation of the Grand Island facility.

Production of Epidural Clonidine-HCl involves a manufacturing process and packaging system similar to other products currently manufactured at the Grand Island site, and adequate controls are in place to minimize emissions to air, wastewater, and solid waste. A limited amount of Epidural Clonidine-HCl, will be produced during the fifth production year as a result of approval of the proposed action. Estimated maximum patient populations and production volumes for production years one through five are shown in Confidential Appendix B-1. Projected energy consumption associated with the production of Epidural Clonidine-HCl is shown in Confidential Appendix B-4. Fifth year production is expected to result in no more than a 4 percent incremental increase in total plant discharges to air, water, or waste disposal. Approval to manufacture Epidural Clonidine-HCl will have no significant effect on the ability of Fujisawa USA to comply with any environmental or occupational safety and health laws or regulations currently in effect for its Grand Island facility.

6.3 Introduction of substances from product use and disposal

This section discusses introduction of substances into the environment as a result of product use, and disposal practices for returned product.

6.3.1 Introduction from product use

A limited amount of Epidural Clonidine-HCl will be marketed to a small patient population subsequent to approval of the proposed action. Information on the maximum estimated patient population and production volume is provided in Confidential Appendix B-1. The drug product and its metabolites will be excreted primarily through the urine and feces subsequent to its clinical use, resulting in the distribution of very small amounts of these substances primarily to wastewater treatment systems throughout the United States. Packaging for the drug product also may enter either the general office waste stream or the medical waste stream. The packaging components consist of materials used in a wide variety of products and none are specifically regulated by federal, state, or local authorities.

6.3.2 Disposal of returned product

Returned goods (e.g., damaged or out-of-date) will be sent by the medical provider to the Fujisawa Distribution Warehouse in Bensenville, Illinois. The medical provider will be instructed to package and ship the returned products consistent with U.S. Department of Transportation (DOT) regulations using appropriate packaging to prevent possible breakage and leakage. Damaged or used vials will be placed in a tight-sealing plastic bag within an outer carton to prevent spills during shipment.

Upon receipt at the Fujisawa Distribution Warehouse, the returned product will be inspected. If disposal is required, the material will be labeled and placed in a designated staging area. The product will be packaged according to disposal vendor requirements and will be shipped to an approved disposal facility in the United States for destruction. The Ogden Martin Systems facility in Haverhill, Massachusetts is the facility currently designated for disposal of returned product. Safe handling practices for returned goods have been established to prevent employee respiratory, eye, and skin exposure through the use of engineering controls, administrative controls, and protective equipment. Spill prevention and clean-up procedures have also been established.

6.4 Statement of compliance

By signing this Environmental Assessment, Fujisawa USA, Inc. states that it is in compliance with all environmental laws and regulations applicable to the production of Epidural Clonidine-HCl at its facility in Grand Island, New York. Appendix A-4 contains a letter certifying compliance of the Grand Island facility.

SECTIONS 7 THROUGH 11 NOT REQUIRED FOR ABBREVIATED ENVIRONMENTAL ASSESSMENT

EPIDURAL CLONIDINE HYDROCHLORIDE IS INTENDED FOR THE TREATMENT OF A RARE DISEASE; THEREFORE, AS ALLOWED UNDER 21 CFR 25.31 a(b), THE ENVIRONMENTAL ASSESSMENT FOLLOWS THE ABBREVIATED FORMAT IN SECTIONS 6, 7, 8, 9, 10, 11 AND 15.

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SECTION 13 CERTIFICATION

The undersigned official certifies that the information presented is true, accurate, and complete to the best of the knowledge of Fujisawa USA, Inc.

Signature of responsible official: Jerry D. Johnson

Name of responsible official: Jerry Johnson, Ph.D., Fujisawa USA, Inc.

Title: Vice President, Regulatory Affairs

Date: 4/19/96

SECTION 14 REFERENCES

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SECTION 15 APPENDICES

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