

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

**Application Number : 018654/S018 and S029 and S030**

**Trade Name : VERSED**

**Generic Name: Midazolam Hydrochloride**

**Sponsor : Hoffman-La Roche Inc.**

**Approval Date: S018 and S029-December 31, 1996  
S030-March 18, 1997**

Morgan

Food and Drug Administration  
Rockville MD 20857

NDA 18-654/S-018 & S-029

DEC 3 | 1996

Hoffmann-La Roche Inc.  
340 Kingsland St.  
Nutley, New Jersey 07110-1199

Attention: Margaret J. Jack  
Program Director  
Drug Regulatory Affairs

Dear Ms. Jack:

Please refer to your supplemental new drug applications (NDA) dated April 16, 1989 and September 13, 1995, respectively, submitted under section 505 (b) of the Federal Food, Drug, and Cosmetic Act for Versed (midazolam HCl) 5mg/ml and 1 mg/ml vials.

We acknowledge receipt of your amendments for supplemental application S-018 dated September 16, 1994; August 26 and October 22, 1996. We also acknowledge receipt of your amendments for supplemental application S-029 dated June 6 and 27; August 26; September 13; and October 22, 1996.

Supplemental application S-018 provides for label revisions of the Pharmacokinetic Data found under the CLINICAL PHARMACOLOGY SECTION.

Supplemental application S-029 provides for continuous infusion for sedation of intubated mechanically ventilated patients.

We have completed the review of these supplemental applications, 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 revised draft labeling, submitted on October 22, 1996. Accordingly, the applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed revised 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

NDA 18-654/S-018 & S-029

Page 2

**PRINTED LABELING** for approved NDA 18-654. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety or effectiveness of this drug becomes available, revision of that labeling may be required.

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.

Should you have any questions, please contact:

David Morgan  
Consumer Safety Officer  
Telephone: (301) 443-3741

Sincerely yours,

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

NDA 18-654/S-018 & S-029

Page 3

cc:

Original NDA 18-654

HF-2/MedWatch (with draft labeling)

HFD-2/MLumpkin

HFD-92 (with draft labeling)

HFD-103/PBotstein (with draft labeling)

HFD-170/Div. File

HFD-170/CSO/DMorgan / *D. Conner*

HFD-170/Landow/Cerny/Lockwood/Ross/Moody

HFD-101/LCarter

HFD-40/DDMAC (with draft labeling)

HFD-613 (with draft labeling)

HFD-735 (with draft labeling)

DISTRICT OFFICE

HFD-820/New Drug Chemistry Director

drafted: DM/December 24/18654.29a

r/d initials: CMoody/12-30-96

Final: SLiu/12-30-96

APPROVAL (AP)



NDA 18-654/S-030

Food and Drug Administration  
Rockville MD 20857

MAR 18 1997

Hoffmann-La Roche Inc.  
340 Kingsland Street  
Nutley, New Jersey 07110

Attention: Margaret J. Jack  
Program Director

Dear Ms. Jack:

Please refer to your supplemental new drug application dated September 28, 1995, received October 2, 1995, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Versed (midazolam HCl) 5mg/ml and 1mg/ml vials.

We acknowledge receipt of your submissions dated November 18; December 23, 1996; and February 13, 1997.

The supplemental application provides for intramuscular, intravenous, or continuous intravenous infusion for sedation in pediatric patients.

We have completed the review of this supplemental 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 marked-up draft. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed marked-up 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 20 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 supplemental NDA 18-654/S-030. Approval of this submission by FDA is not required before the labeling is used.

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

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 submit one copy to this Division 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

Should a letter communicating important information about this drug product (i.e., a "Dear Doctor" letter) be issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2  
FDA  
5600 Fishers Lane  
Rockville, MD 20852-9787

Please submit one market package of the drug product 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 David Morgan, Consumer Safety Officer, at (301) 443-3741.

Sincerely,



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

cc:

- Original NDA 18-654
- HFD-170/Div. files
- ✓ HF-2/MedWatch (with draft labeling)
- ✓ HFD-002/ORM (with draft labeling)
- ✓ HFD-92/DDM-DIAB (with draft labeling)
- ✓ HFD-103/Office Director (with draft labeling)
- HFD-101/L.Carter
- HFD-170/CSO/D.Morgan
- HFD-170/I.Cerny/L.Landow/J.Ross/A.DSa/C.Moody
- HFD-40/DDMAC (with labeling)
- ✓ HFD-613/OGD (with draft labeling)
- ✓ HFD-735/DPE (with draft labeling)
- ✓ HFD-021/ACS (with draft labeling)
- DISTRICT OFFICE
- HFD-820 /ONDC Division Director
- ✓ HFI-20/Press Office (with draft labeling)

Drafted by: DM/February 25, 1997/versed.30

Initialed by: CPMoody/CW/3/13/97

final: trh/3/13/97

APPROVAL (AP)



NDA 18-654/S029 &amp; S-030

SEP 18 1996

Hoffmann-La Roche Inc.  
340 Kingsland St.  
Nutley, New Jersey 07110-1199

Attention: Margaret J. Jack  
Program Director  
Drug Regulatory Affairs

Dear Ms. Jack:

Please refer to your September 13, and 28, 1995 supplemental new drug applications (NDAs) submitted under section 505 (b) of the Federal Food, Drug, and Cosmetic Act for Versed (midazolam HCl) Injection 5mg/ml and 1 mg/ml vials respectively.

We acknowledge receipt of your amendments dated June 6, 27, and August 26, 1996.

Supplemental application S-029 provides for continuous intravenous infusion of Versed for sedation of intubated mechanically ventilated patients.

Supplemental application S-030 provides for intramuscular, intravenous, or continuous intravenous infusion of Versed in pediatric patients for sedation.

We have completed the review of these supplemental applications as submitted with draft labeling, and they are approvable.

The bulk of the labeling for the two supplements is acceptable as written in your submission dated August 26, 1996. However, there are specific areas of concerns regarding the safe use of the drug in adults and children as proposed in the labeling. Confirmation of the safe use in these populations and revisions in the labeling are needed. Before these supplements may be approved, it will be necessary for you to provide the following:

1. The proposed labeling is very complex, providing dosing information that varies substantially according to body composition (ideal body weight), indication, setting, patient age, concurrent medication and medical conditions. Provide, through some reasonable means, some evidence that the proposed labeling is comprehensible to prescribers of the drug, who would be able to follow the label to select a proper dose and use the drug safely.

2. Since Versed was first approved, there have been a number of practice guidelines proposed for the safe sedation of children. In addition, in connection with a new medication now approved for this use, there has been extensive consideration by experts in this field, of labeling language, to arrive at clear and appropriate wording to provide for safe use. Your labeling needs to be consistent in its use of language with the current standards of practice for prescribers beyond the anesthetic community.
3. The range of doses recommended is internally inconsistent, and might lead to excessively high doses being administered to larger, older children. The dosing guidelines need to be revised to provide patient safety.
4. The proposed labeling and indications need to be more specific as to which indications are and are not being sought for pediatric usage.
5. The Clinical Pharmacology section should be revised to include some information on the pharmacodynamics of midazolam.
6. The proposed labeling is silent on the use of midazolam infusion in unintubated, unventilated patients as part of monitored anesthesia care, ICU practice of conscious sedation. It should either make a direct recommendation for or against such usage.

We are considering discussion of the labeling at a forthcoming meeting of the Anesthetic & Life Support Drugs Advisory Committee.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

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 submit one copy to this Division 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

Within 10 days after the date of this letter, you are required to amend the supplemental applications, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the applications.

These changes may not be implemented until you have been notified in writing that these supplemental applications are approved.

Should you have any questions, please contact:

David Morgan  
Consumer Safety Officer  
Telephone: (301) 443-3741

Sincerely yours, .

*Paula Botstein MD 9/18/96*

Paula Botstein, M.D  
Acting Director  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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

NDA # 18-654 / 524 Trade (generic) names Versed (midazolam)

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.

b. If none of the above apply, explain.

Explain, as necessary, the foregoing items: Senior has submitted supplement #30 for pediatrics  
The data for the supplement is based on an extensive review of the literature.

[Lined area for additional explanation]

*Senior*

12/31/96

Signature of Preparer

Date

cc: Orig NDA  
HFD-170/Div File  
Action Package

**DEBARMENT CERTIFICATION**

**Hoffmann - La Roche Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under 21 U.S.C. 335a (a) and (b), in connection with these applications.**

### PATENT INFORMATION

1. Active Ingredient(s): Midazolam
2. Strength(s): 5 mg/ml
3. Trade Name: VERSED®
4. Dosage Form and Route of Administration: Continuous infusion
5. Applicant (Firm) Name: Hoffmann-La Roche Inc.
6. NDA Number: NDA 18-654
7. First Approval Date: Original NDA approved December 20, 1985  
pending S 029, submitted  
September 13, 1995  
For: Continuous infusion for sedation of  
intubated, mechanically ventilated adult patients
8. Exclusivity: Date first ANDA could be submitted or approved and length of exclusivity period: Three years from date of approval of pending supplement
9. Patent Information:  
Patent number(s) and expiration date(s): 4,280,957, expires December 20, 1999  
Type of Patent: Drug  
Patent Owner: Hoffmann-La Roche Inc.

While this submission was prepared in good faith, no warranty or guarantee is made regarding the accuracy or completeness of the information contained therein.

### CONFIDENTIAL INFORMATION

Since the Supplement to the New Drug Application has not yet been approved, this submission is considered as constituting trade secrets or commercial or financial information which is privileged or confidential within the meaning of the Freedom of Information Act (5 U.S.C. 552). It is requested that this submission not be published until the Supplement to the New Drug Application has been approved.



# FDA CENTER FOR DRUG EVALUATION AND RESEARCH

## DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTIVE DRUGS

HFD 170, Room 9B-45  
5600 Fishers Lane  
Rockville MD 20857

### INTEGRATED EFFICACY & SAFETY REVIEW

NDA #: 18-654 S#30  
Sponsor: Hoffman-La Roche Inc  
Type of Submission: INDA  
Date of Submission: 13 September 1995  
Date Received:  
Date of Review: 1-30 August 1996  
Peer Reviewer: Curtis Wright MD  
Date Cleared Peer:  
Reviewer: Laurence Landow MD

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#### RESUMÉ

This is an Interactive NDA for continuous intravenous infusion of Versed (midazolam) to intubated, adult ICU patients who require sedation during mechanical ventilation. Midazolam has gained widespread acceptance as a safe and effective sedative for patients about to undergo surgery and for conscious sedation during short diagnostic or therapeutic procedures outside the operating room. Off-label use has included sedation of ICU patients who require mechanical ventilation for acute respiratory failure.

Questions that remain unanswered center on safety issues such as appropriate dosage, drug interactions, and potential side-effects of administering this drug continuously, for days or weeks at a time. In an attempt to answer these questions, the sponsor supported three prospective, randomized, double-blind, dose-finding studies in the cardiac and aortic aneurysm repair surgery populations. Based on these and related studies in the literature, the following recommendations can be made for administration of midazolam in the ICU:

i) **Loading Dose:** in the immediate postoperative period following cardiac and major vascular surgery, an appropriate loading dose is approximately 0.01 mg/kg (administered over  $\geq 2$  min) for patients receiving a moderate-dose (25-75 ug/kg loading dose) fentanyl anesthetic, and 0.02 mg/kg; for patients receiving a low-dose (5-20 ug/kg loading dose) fentanyl, or sufentanil or alfentanil anesthetic. Clinical experience and several well-designed studies from the literature suggest that in intubated patients with acute respiratory failure who require sedation for mechanical ventilation, a bolus (administered in divided doses over  $\geq 2$  min) as low as 7 ug/kg in frail, elderly patients, and as high as 200 ug/kg in young, agitated adults, is appropriate.

ii) **Infusion Dose:** an appropriate infusion rate in the immediate postoperative period following cardiac and major vascular surgery is approximately 15 ug/kg-h. Clinical experience and several well-designed studies from the literature indicate that infusion rates for patients in acute respiratory failure depend on a number of clinical factors. Generally speaking, the initial rate in frail, elderly patients is approximately 30 ug/kg-h (0.5 ug/kg-min) whereas in agitated, young adults, rates as high as 200 ug/kg-h (3.3 ug/kg-min) occasionally may be indicated. Infusion rates over time for a given patient are often a function of disease severity; the dose should be assessed periodically and titrated to the lowest effective rate.

The incidence of non-respiratory side-effects – primarily hypotension – is similar to those described in the current labeling for induction of anesthesia. The likelihood of withdrawal symptoms following termination of long-term midazolam administration is minimized by weaning the infusion over several days. There is the potential for several drugs given routinely to ICU patients to interfere with midazolam's metabolism, although the clinical significance of this is as yet unclear.

## INTRODUCTION

Versed (midazolam HCl) is a water-soluble, short-acting benzodiazepine that depresses the central nervous system. It is 95% plasma-protein bound and subject to approximately 55% first pass metabolism. Midazolam is currently approved for three indications: preoperative sedation; intravenous induction of anesthesia; and conscious sedation during therapeutic procedures. A supplemental application (No. 029) to the manufacturer's previous NDA was submitted on 13 September 1995 providing data for a new indication — continuous intravenous infusion for sedation of intubated, mechanically ventilated patients.

Since the late 1980s, intensivists in the US have been using midazolam off-label in order to sedate critically ill patients receiving mechanical ventilation. Independent audits of hospital practices suggest that 25% of the current use of midazolam in the US is for sedation of ICU patients. Midazolam is used as a sedative for over 2,000,000 ICU patient-days yearly. Continuous infusions account for approximately 45 percent of this use. In 30 percent of cases, the duration of administration is for three days or longer.

### The Review Task

There is no doubt that midazolam is safe and effective. Questions that need to be answered with respect to continuous infusions include the following:

- What is the minimum effective dose required to sedate post-surgical patients and ICU patients?
- What are the side-effects of prolonged midazolam infusions?
- Is there tolerance to, or withdrawal from, midazolam infusions?
- What drug interactions (eg, prolonged elimination) are observed when midazolam is administered to ICU patients?

To answer dosing and safety concerns, the sponsor provided data from a variety of supported studies: i) three pivotal dose-finding studies [Martineau et al, Ralley et al, and Teasdale et al]; ii) two repeat-bolus studies [Leslie et al, Ramsey et al]; iii) one continuous infusion study (safety data only) [White et al]; and iv) eight open-label, uncontrolled investigations. In addition, the sponsor generated a detailed literature review of the adult ICU population that included 26 prospective, randomized, controlled, continuous infusion studies (22 of which included a comparator, usually propofol); 23 uncontrolled studies; and more than almost 200 miscellaneous papers (abstracts, case reports) from the world literature. One study, still ongoing, is a pharmacokinetic study using a computer-assisted controlled infusion (CACI).

## CHEMISTRY

Compatibility data for midazolam with 5% dextrose and 0.9% sodium chloride in PVC bags was submitted as a supplement in the application, S-020, dated 4 February 1991 and approved 19 September 1991. The compatibility data show that midazolam Injection, 5 mg/mL, when diluted to a midazolam concentration of 0.5 mg/mL with 5% dextrose or 0.9% sodium chloride is chemically and physically stable for  $\geq 24$  h.

For this NDA, the sponsor has prepared midazolam infusion solutions with PVC tubing to compare its compatibility with the tubing. Midazolam infusion solutions were made up at midazolam concentrations of 0.3 mg/mL and 0.5 mg/mL, diluted with 5% dextrose and 0.9% sodium chloride. The concentration of midazolam was assayed over a 24 h period using HPLC. The data recorded is within the specification limits of %.

From a chemistry viewpoint, the supplement can be approved.

## CLINICAL PHARMACOLOGY

Three dose-ranging studies supported by the sponsor investigated midazolam infusions in ICU patients (for a more complete description of these studies see "Summary of Clinical Studies", below). Two of these (Ralley et al and Teasdale et al) were really safety studies rather than true dose-response studies, because if patients were not at a predetermined level of sedation, the infusion was increased or decreased accordingly. Steady-state plasma concentrations measured in the third study (Martineau et al), in which the dose of midazolam was essentially unchanged throughout the study (whereas the dose of narcotic analgesia was varied), ranged from a mean of 76 ng/mL (range 31-140 ng/mL), 130 ng/mL (40-270), and 205 ng/mL (100-470) for the low, medium, and high treatment groups, respectively. Interim analysis of data collected from a partially completed CACI study indicates that midazolam has a therapeutic window between 50-100 ng/mL for sedation following coronary artery bypass surgery. Similar values were obtained for the low, moderate, and high dose groups with respect to clearance rate, volume of distribution, and elimination half-life and agreed with other studies in the literature.

In their literature review, the sponsor found studies in volunteers that lasted as long as 26 h with infusion rates up to 40 ug/kg-h. Mean plasma clearance in this group ranged from 6.1 to 9.6 mL/min-kg. Mean volume of distribution ranged from 1.0 to 2.7 L/kg. Studies in patients undergoing cardiac, abdominal aortic, and maxillofacial surgery demonstrated a mean plasma clearance and volume of distribution that were similar to those in volunteers, ie, 3.4-10.5 mL/min/-kg and 1.0-3.1 L/kg, respectively. For ICU patients, corresponding values were 0.4-10.3 mL/min/-kg and 0.7-4.6 L/kg, findings that are not unexpected in patients with hepato-renal dysfunction who are typically edematous and hypoalbuminemic. Because of the high variability in Vd and Cl in critically ill patients, cautious dosing should be emphasized. This is reflected in the observation that 14% of patients in the sponsor-supported studies experienced hypotension, most of these cases occurring immediately following the midazolam loading dose.

Midazolam undergoes hepatic metabolism to 1-hydroxy midazolam which is then conjugated and excreted by the kidneys. In the literature review, the sponsor presented several studies that measured levels of the unconjugated metabolite, which were considerably lower than those of the parent compound. This finding, together with the lower receptor affinity and lower relative brain uptake of 1-hydroxy midazolam relative to the parent compound, make it likely that the net pharmacological effect of midazolam administration is attributable to the parent compound. Since the glucuronide is excreted by the kidney, its plasma levels will rise in patients with renal insufficiency. This is not of clinical importance, however, since the glucuronide conjugate is pharmacologically inactive.

## SUMMARY OF CLINICAL STUDIES\*

**Protocol, Enrollment, Randomization, and Evaluability**

Data for three dose-finding, controlled clinical trials were submitted under the sponsor's IND. Two of these were in post-CABG patients (one of which also included 4 patients who had valve replacement), whereas the third was in patients undergoing abdominal aortic aneurysm (AAA) surgery. Except for the first 7 (pilot) patients in Teasdale's CABG study in whom the loading doses were clearly too high, the only patients dropped from any study after being enrolled were in Ralley's group: one low-dose patient had to return to the OR for bleeding <3 h after the infusion was started; two high-dose patients were dropped, one who received the incorrect dose, the other who required a muscle relaxant for excessive shivering.

DOSE-FINDING TRIALS IN ADULT ICU PATIENTS CONDUCTED UNDER THE SPONSOR'S IND					
First Author	Setting	Opioid Technique (ug/kg)	Patients	Loading Dose (mg/kg)	Maintenance Dose (ug/kg-min)
Martineau	AAA Surgery	Load: Fentanyl: 2-10 or Alfentanil: 10-50 or Sufentanil: 1. Maintenance Total: Fentanyl: ≤15; Alfentanil: ≤125; Sufentanil: ≤3.	30 (10 in each of 3 treatment groups)	Low: 0.03 Moderate: 0.06 High: 0.10	Continuous Infusion: Initial: 0.5; Optimal: 0.66 Initial: 1.0; Optimal: 0.83 Initial: 1.5; Optimal: 1.33
Ralley	CABG + Valvular Surgery	Load: Fentanyl: 2-10 or Alfentanil 10-50 or Sufentanil 1. Maintenance Total: Fentanyl: ≤15; Alfentanil: ≤125; Sufentanil: ≤3.	45 (15 in each of 3 treatment groups)	Low: 0.03 Moderate: 0.06 High: 0.09	Continuous Infusion: Initial: 0.5; Optimal: 0.25 Initial: 1.0; Optimal: 0.45 Initial: 1.5; Optimal: 0.40
Teasdale	CABG Surgery	Load: Fentanyl 30. Maintenance Total: Fentanyl ≤75.	30 (10 in each of 3 treatment groups)	Low: 0.015** Moderate: 0.03 High: 0.050	Continuous Infusion: Initial: 0.5; Optimal: 0.25 Initial: 1.0; Optimal: 0.28 Initial: 1.5; Optimal: 0.23

\*\*First 7 patients dropped and excluded from the analysis: Low: 0.03; Moderate: 0.06; High: 0.09 mg/kg.

- Coronary Artery Bypass Graft Surgery**

Methodology for the two studies conducted in patients undergoing CABG surgery, ie, Ralley et al and Teasdale et al, were similar in many respects. Patients were randomized into low, moderate, and high dose midazolam loading and maintenance infusion groups. The patients were comparable in terms of age, body surface area, duration of surgery, and ASA status. Subjects were premedicated with morphine and underwent a "moderate-dose" narcotic regimen with low dose inhalation agent as "background" anesthetic.

They were different, however, in two key respects: i) Teasdale's patients were induced with moderate-dose fentanyl (30 ug/kg), whereas Ralley's patients received either low-dose fentanyl (2-10 ug/kg), or moderate-dose sufentanil or alfentanil; ii) the two studies used inverse sedation scales. A four-step scale was used for Ralley's study (1=unresponsive; 2=asleep, responds to pain; 3= asleep, responds to verbal command; 4=awake), whereas a six step scale was used for Teasdale's study (1=awake; 2=asleep, eyes open to noise; 3=asleep, eyes open to name; 4=asleep, eyes open to touch; 5=asleep, moves to touch; 6=unresponsive). The goal was to achieve the same level of sedation, ie, 2-3 in Ralley's study and 3-5 in Teasdale's. For the purposes of this review, Ralley's sedation scores have been transformed to comply with the results of the other two studies.

\*Throughout this review, conversion to ug/kg assumes patient weight=70 kg.

The following tables show that all three dosing groups had a marked change in sedation scores and that even before they received a revised (downward) midazolam bolus, Teasdale's patients were within the targeted range for sedation of 3-5 (in **bold**):

SEDATION SCORES FOR CABG PATIENTS: RALLEY / TEASDALE							
HOUR	0	0.25	0.5	1	2	4	6
Low Dose	2.3/3.4	4.7/5.3	4.7/5.5	3.6/5.4	3.1/4.4	2.8/3.1	2.6/3.0
Moderate Dose	2.2/3.6	5.3/6.0	5.4/6.0	4.7/6.0	3.6/4.5	2.6/3.9	2.6/3.4
High Dose	2.3/3.5	5.6/5.8	5.6/5.8	5.1/6.0	3.5/5.7	3.6/4.2	2.8/3.6

\* Numbers in bold=sedation within the target range for the study.

MIDAZOLAM INFUSION DOSE (ug/kg-min) FOR CABG PATIENTS: RALLEY / TEASDALE							
HOUR							
Low Dose	0.5/0.5	0.52/0.33	0.3/0.3	0.26/0.28	0.21/0.21	0.22/0.21	0.16/0.24
Moderate Dose	1/0.9	0.97/0.4	0.57/0.4	0.35/0.37	0.23/0.25	0.30/0.21	0.32/0.28
High Dose	1.5/1.5	1.45/0.74	0.75/0.74	0.42/0.62	0.30/0.35	0.32/0.34	0.32/0.25

Rather than reduce the loading dose further in subsequent patients, Teasdale et al elected to reduce the maintenance dose by half. Regrettably, their subjects remained heavily over-sedated (ie, sedation score >5) for almost 2 hours, until the infusion rate was reduced to 12-18 ug/kg-h (0.2-0.3 ug/kg-min). Even though the degree of over-sedation in Ralley's patients was much less, the desired level of sedation was not attained until the dose was decreased to the same rate as in Teasdale's patients, ie, 12-18 ug/kg-h (0.2-0.3 ug/kg-min).

It is likely that pharmacodynamic differences among the synthetic opioids accounted for this observation. Fentanyl, especially in doses as high as 30 ug/kg, has a sedating effect, as opposed to sufentanil or alfentanil. Moreover, the duration of fentanyl's sedative effects is longer than its congeners.

• **Abdominal Aortic Aneurysm Surgery**

The study by Martineau et al was the only dose-finding study conducted in this population. In many respects, the methodology closely resembled that of Ralley et al. For example, the demographics of the patient populations were similar in terms of age, body surface area, duration of surgery, and ASA status. Choice of opioid consisted of low-dose fentanyl or medium-dose sufentanil, or alfentanil. An inhalation agent was used to provide "background" anesthesia. The midazolam dosing schedule was virtually identical, with subjects randomized to receive a midazolam loading dose of 0.03, 0.06, or 0.10 mg/kg, followed by corresponding midazolam infusion rates of 0.5 ug/kg-min (low dose), 1.0 ug/kg-min (moderate dose), or 1.5 ug/kg-min (high dose). There was one noticeable difference -- the sedation scoring system was the same one as Teasdale used (6-step).

SEDATION SCORES FOR ALL THREE DOSE-FINDING STUDIES: RALLEY / TEASDALE / MARTINEAU							
HOUR							
Low Dose	2.3/3.4/1.9	4.7/5.3/3.8	4.7/5.5/3.4	3.6/5.4/3.8	3.1/4.4/3.4	2.8/3.1/3.7	2.6/3.0/3.4
Moderate Dose	2.2/3.6/2.6	5.3/6.0/4.9	5.4/6.0/4.5	4.7/6.0/4.8	3.6/4.5/4.4	2.6/3.9/4.1	2.6/3.4/3.8
High Dose	2.3/3.5/1.4	5.6/5.8/5.1	5.6/5.8/4.7	5.1/6.0/4.8	3.5/5.7/4.4	3.6/4.2/3.9	2.8/3.6/4.0

\*Numbers in bold=sedation within the target range for the study.

The hypothesis was that each group would titrate to a common infusion dose as occurred in the CABG studies. This did not happen, as the treating physicians altered the dose of narcotics analgesics from high (43 mg morphine dose-equivalents) to moderate (34 mg) to low (18 mg) across treatment groups. Accordingly, even though the ultimate infusion rates ranged from ug/kg-h (ug/kg-min) for the three treatment groups, sedation scores were in the desired range as early as the first 30 min of infusion and remained there throughout the study period.

MIDAZOLAM INFUSION DOSE (ug/kg-min) FOR ALL THREE DOSE-FINDING STUDIES: RALLEY / TEASDALE / MARTINEAU							
HOUR							
Low Dose	0.5/0.5/0.5	0.52/0.33/0.5	0.3/0.3/0.5	0.26/0.28/0.47	0.21/0.21/0.55	0.22/0.21/0.6	0.16/0.24/0.6
Moderate Dose	1.0/0.9/1.0	0.97/0.4/1.0	0.57/0.4/1.0	0.35/0.37/0.78	0.23/0.25/0.75	0.30/0.21/0.9	0.32/0.28/0.9
High Dose	1.5/1.5/1.49	1.45/0.74/1.49	0.75/0.74/1.49	0.42/0.62/1.49	0.30/0.35/1.15	0.32/0.34/1.34	0.32/0.25/1.34

### Effect on Concurrent Medication

Since patients enrolled in the two cardiac surgery studies underwent the same procedure and ultimately received the same infusion rate (12-18 ug/kg-h=0.2-0.3 ug/kg-min) of midazolam, it is not unexpected that they would require roughly the same total amount of narcotic analgesia in the post-operative period.

A problem arises when these results are compared with those from the aortic surgery study. At first glance, it might appear that low, moderate, and high dose midazolam groups in Martineau's study ultimately had the same level of sedation. What actually occurred was that low-dose midazolam patients received a total dose of narcotics (morphine equivalents) that was substantially higher than that received by their high dose cohorts. While the practice of using midazolam to reduce analgesic requirements cannot be condoned, it does illustrate midazolam's opioid-sparing effect.

## INTEGRATED ANALYSIS OF EFFICACY

### What is the minimal effective dose for sedation in the ICU population?

#### Cardiac Surgery

i) **Loading Dose:** The fact that Teasdale's patients were too heavily sedated for several hours has important clinical implications. As mentioned previously, even the lowest midazolam loading dose (0.015 mg/kg), combined with the lowest infusion rate (0.5 ug/kg-min), was too large, given putative CNS tissue fentanyl concentrations and fentanyl's pharmacodynamic profile. Accordingly, when moderate-dose fentanyl (eg, 25-75 ug/kg loading dose + supplements prn) is used to induce patients, the recommended midazolam loading dose is approximately 0.010 mg/kg. The fact that Ralley's patients (who received a loading dose of 0.030 mg/kg) were less heavily sedated than Teasdale's during the first hour, lends support to the recommendation that in subjects induced with low-dose fentanyl (ie,  $\leq 10$  ug/kg) or medium-dose sufentanil or alfentanil, a midazolam loading dose of 0.020 mg/kg is appropriate.

ii) **Infusion Dose:** Cardiac surgery patients in these dose-finding studies ultimately achieved the desired level of sedation at a constant infusion rate of 12-18 ug/kg-h (0.2-0.3 ug/kg-min). Accordingly, the recommended initial infusion rate in this population is 15 ug/kg-h (0.25 ug/kg-min).

#### Major Vascular Surgery

Recommendations for AAA patients are less clear. Data from Martineau's study of 30 patients are confounded by a more than two-fold difference (18 mg vs 43 mg) in concurrently administered morphine equivalents between the high and low dose midazolam group. Assuming pain management is being adequately addressed by epidural narcotics/local anesthetics, intravenous opioid infusions, non-steroidals, or PCA, an appropriate dose of midazolam for AAA patients during mechanical ventilation appears to be similar to that for cardiac surgery patients, ie, approximately 0.020 mg/kg loading dose + 15 ug/kg-h (0.25 ug/kg-min) infusion rate.

#### ICU Patients

This seems an appropriate place to outline the demographics of the ICU patient population.

Broadly speaking, this group can be stratified into two subgroups. The first consists of post-operative surgery patients who require short-term mechanical ventilation (ie, <12 h) until they recover from the effects of surgery (eg, blood loss) and anesthesia (ie, drugs that induce acute ventilatory failure – inability to eliminate sufficient CO<sub>2</sub> – by reducing level of consciousness). Results of the three dose-finding studies supported by the sponsor fall into this category.

The second subgroup is comprised of medical and surgical patients who require long-term mechanical ventilation (ie, days to months) for acute respiratory failure – inadequate oxygen uptake in the lungs – subsequent to life-threatening systemic illness, eg, systemic inflammatory response syndrome (ie, ARDS). Acute respiratory failure can last a week or it can last months. Unless patients develop acute respiratory failure on the first day after surgery, hospitalized patients who become hypoxemic acutely rarely receive opioids prior to endotracheal intubation for fear that respiratory drive will be blunted,

necessitating intubation prematurely for iatrogenic reasons. Because this group is extremely heterogenous with respect to several important variables, eg. nature of their illness, number and the extent to which various organs are affected, premorbid physiologic function, age, and mental status, the recommended bolus and infusion doses will, by necessity, cover a wide spectrum. On one end are frail, elderly patients who may require an initial IV bolus as small as 0.5 mg (7 ug/kg). At the other end of the spectrum are young adults, who may require up to 200 ug/kg-h (3.3 ug/kg-min). These doses should be divided and administered over >2 minutes. It is important to point out that in following these dosage recommendations, *caution is advised in those instances when midazolam administration is initiated in preparation for endotracheal intubation.*

As the inflammatory response increasingly impairs hepatic and renal function, appropriate infusion rates often fall below the recommended infusion rates for post-CABG/AAA patients. This phenomenon is most likely due to higher free drug levels resulting from the combined effects of hepato-renal dysfunction, ie, hypoalbuminemia, impaired hepatic glucuronide conjugation, and/or diminished excretion of the major metabolite, 1-hydroxy-midazolam (20% activity of the parent compound). Less well understood as a contributing factor are potential drug interactions specific for the ICU population (see side-effects and drug interactions, below).

## INTEGRATED SUMMARY OF SAFETY

### Is Midazolam Safe to Administer by Continuous Infusion?

There were no deaths or serious injuries attributable to study drug in either Ralley's or Teasdale's investigation. The most frequent adverse event was hypotension, which resolved with conventional treatment. A transient (ie, 15 minute) 50 mmHg decline in systolic blood pressure was noted, however, in the first 15 min of Teasdale's study (due to excessive bolus doses). Transient arrhythmias, one episode of elevated cardiac enzymes, and a pneumothorax also were seen in Teasdale's group, none of which is unexpected in this type of surgery.

One patient (low dose group) in Martineau's study had an adverse event. He experienced postoperative hemorrhage, resulting in hypovolemia, non-cardiogenic pulmonary edema, and a perioperative myocardial infarction. He recovered and was discharged to home. It is unlikely that these events were related to drug infusion. In addition, five patients experienced hallucinations, confusion, or agitation, with no apparent relation to dose. There were no treatment-related alterations in vital signs or laboratory test, despite careful examination for acute withdrawal phenomena.

In formulating this part of the review, the reviewer requested all adverse events associated with midazolam administration reported to the Agency up until 26 February 1996. Key words were "withdrawal," "somnolence," and "prolonged effect." Fourteen cases were identified in which patients (aged 12-60) receiving continuous Midazolam infusions averaging 5-10 mg/h for agitation during mechanical ventilation experienced "withdrawal symptoms," ie, tachycardia, agitation, restlessness, combativeness, sleeplessness, sweating, hallucinations, and, in at least one instance, a grand mal seizure. A common thread running through these reports is that long-term (ie, one or more weeks) infusions were stopped abruptly or weaned from the patient overnight. In many cases, appearance of symptoms was delayed until 12-36 h after termination of the infusion. Typical management included reinstatement of the midazolam infusion and a second weaning trial that lasted several (eg, 3-5) days. Successful outcome with no sequelae was achieved in all cases using this approach.

A review by the sponsor of data supporting the safety of midazolam by continuous infusion to adult ICU patients included material from four primary sources: 1) publications of controlled and uncontrolled trials; 2) publications of clinical pharmacology studies designed to investigate the pharmacokinetics of midazolam; 3) controlled and uncontrolled trials supported by the sponsor, including dose-finding studies; and 4) results of the sponsor's worldwide postmarketing safety monitoring system. Their review of controlled (vs propofol, in most cases) trials published in the medical literature revealed the following. Nine of the studies reported a number of deaths in the respective treatment groups. In the midazolam group (n=299), 1 patient (0.33%) died, whereas in the comparative (propofol by continuous infusion) group (n=270), 8 patients (2.96%) died.

<b>SPONSOR'S SUMMARY OF STUDIES IN WHICH ADULT ICU PATIENTS RECEIVED MIDAZOLAM BY CONTINUOUS INFUSION</b>		
<b>Source of Safety Data</b>	<b>Patient Population</b>	<b>Number of Patients</b>
Controlled Clinical Studies	Medical/Surgical Postoperative Recovery	430 (+ 139 additional patients in 4 controlled studies that did not report the number of patients per treatment group)
Dose-finding Studies	Postoperative Recovery	163 (includes 105 patients from the pivotal Canadian dose-finding studies and studies comparing intermittent bolus vs continuous infusion)
Uncontrolled Studies	Medical/Surgical Postoperative Recovery	319
Pharmacokinetic Studies	Medical/Surgical Postoperative Recovery Healthy Volunteers	325 ~

#### **What Are The Side-Effects Associated with Continuous Midazolam Infusions?**

Because sedation during mechanical ventilation is the primary indication for continuous infusion of midazolam, none of the studies included ventilatory management of the patient among outcome measures. Insofar as time to extubation can be considered a measure of the need for ventilatory support, in studies that compared continuous infusions of midazolam vs propofol, the former was associated with a substantially longer time from termination of infusion to extubation.

Many drugs administered to ICU patients on a routine, round-the-clock basis, inhibit the same enzyme responsible for hepatic 1-hydroxylation of midazolam: cytochrome P450 3A. These include certain histamine-2 antagonists (cimetidine), antibiotics (erythromycin), calcium channel blockers (diltiazem, verapamil), and anti-fungal agents (ketoconazole, fluconazole). Even though this reviewer could not find any published reports of adverse interactions involving midazolam by continuous infusion, it is as yet unclear whether administration of one or more of these substances decreases midazolam metabolism and intensifies its effect, in the face of unchanged infusion rates. None of the dose-finding studies reviewed in this NDA was designed to evaluate drug interactions.

The major side-effect appearing in these dose-finding studies was hypotension, reported in the range of 0-14.3% of patients. Current labeling indicates that the sedative effect of midazolam is accentuated by narcotics administered as premedication for surgery, and therefore recommends that the dosage be adjusted in accord with their use. In patients who have received fentanyl in the 30 ug/kg range, a 14% incidence of hypotension is significant but not unexpected. On the other hand, in ICU patients with acute respiratory failure who are in the initial stage of their disease, hypotension should raise suspicions that other factors are at play.

No neurological or dermatological side-effects were noted in the studies cited.

#### **Is There Tolerance To, Or Withdrawal From, Continuous Midazolam Infusions?**

In the dose-finding studies, there was no evidence that the doses of midazolam specified in the protocols were increased to compensate for tolerance. If anything, the initial doses were titrated down to reach the therapeutic endpoint.

As mentioned previously, there have been a number of reports of symptoms interpreted as signs of withdrawal following prolonged midazolam treatment. Admittedly, this represents a tiny fraction of less than one percent. The fact that most clinicians wean midazolam infusions over several days probably accounts for the low number of AE reports.

**Are There Effects of Prolonged Administration on Steroidogenesis or Hepatic Function?**

Several literature studies looked at the effect of prolonged midazolam infusion on steroidogenesis and found no effect. One controlled trial specifically investigated the effects of continuously infused midazolam on hepatic function and found no adverse effects. Hepatic dysfunction in critically ill patients is more likely due to their underlying disease.

**CONCLUSION**

Findings from the sponsor's three pivotal trials indicate that midazolam administration by continuous infusion is safe and effective for sedating intubated, adult ICU patients during mechanical ventilation. This is consonant with a number of well-designed studies from the literature and corresponds to the clinical impression of intensivists who have been administering midazolam by continuous infusion off-label for more than 5 years.

In particular, the data show that loading doses and infusion rates depend upon a number of factors. These include the setting, plasma levels of opioids, if any, already present in the circulation; patient's age and premorbid status; and severity of disease. Appropriate loading doses (administered over  $\geq 2$  minutes in divided doses) range from \_\_\_\_\_ mg/kg in patients undergoing cardiac and major vascular surgery, and from 0.05 up to 0.2 mg/kg in intubated critically ill patients with acute respiratory failure. In the postoperative setting, corresponding infusion rates are approximately 15 ug/kg-h; in the critically ill population, rates range from approximately 30 ug/kg-h in frail, elderly patients to as much as 200 ug/kg-h in tolerant, young adults. It should be noted that for the average adult, a loading dose of 0.01 mg/kg is less than the 1 mg initial dose recommended in the label. The revised label for this NDA will need to emphasize that extra caution is advised when larger doses are administered to *unintubated* patients in respiratory failure in preparation for endotracheal intubation in the ICU.

In conclusion, within these recommended guidelines, approval of midazolam by continuous infusion should be granted.

## APPENDIX

## A) Literature Search by Sponsor

**Not Supported by the Sponsor:** A literature search to identify publications appearing by April 1994, and presenting original data relevant to the use of midazolam by continuous infusion in adult ICU patients, was conducted by the sponsor. The result was a total collection of 26 publications, with a total enrollment of 1071 patients; of these, 430 actually received midazolam. Of this group, 383 patients received midazolam as the only sedative, while an additional 18 received a combination of Midazolam and morphine and 29 received a combination of midazolam and fentanyl.

All 26 studies were prospective, controlled, parallel-group trials. Eighteen of the studies compared midazolam with propofol, two with isoflurane, and one study each compared midazolam with diazepam, ethanol + clonidine, flunitrazepam, alfentanil + propofol, and morphine. The remaining study compared two dose regimens of midazolam with saline. All but four were randomized (it was not stated whether these four were randomized), one was double-blind, one reported a blinded assessor, and all but one study were conducted at a single center.

In 22 of these studies, the actual number of patients receiving a continuous infusion of midazolam was reported, ie, 430 patients. Midazolam was administered as the only sedative to 383 patients, while an additional 18 received midazolam + morphine and 29 received midazolam + fentanyl. In these same studies, there were 327 patients who received propofol, 60 who received isoflurane, 20 who received morphine, 11 who received flunitrazepam and fentanyl, 9 normal saline, and 7 diazepam. In addition, 40 patients received intermittent bolus doses of midazolam as part of the parallel-group design and 20 patients received a combination of morphine by continuous infusion and intermittent midazolam boluses.

In these 22 studies, the breakdown by patient population was as follows: 8 were in post-cardiac surgery patients, 4 in non-cardiac surgery patients, 1 in a respiratory ICU, and 9 in a mixed medical/surgical ICU.

CONTROLLED CLINICAL TRIALS OF CONTINUOUS MIDAZOLAM INFUSIONS IN ADULT ICU PATIENTS NOT SUPPORTED BY THE SPONSOR						
First Author	Citation	Report Type	# of Patients	Study Design	Treatment Groups	Patient Population
Aitkenhead	<i>Lancet</i>	Full	101	Prospective, Randomized, Open, Comparative	Midazolam vs Propofol	Med/Surg/Trauma
Barvais	<i>Acta Anaesth Belg</i>	Full	14	Prospective, Randomized, Comparative	Midazolam vs Diazepam	CABG
Beyer	<i>Anaesthesist</i>	Full	20	Prospective, Randomized, Open, Comparative	Midazolam vs Propofol	Surg
Boeke	<i>J Drug Develop</i>	Full	10	Prospective, Randomized, Open, Comparative	Midazolam vs Propofol	Surg

<b>CONTROLLED CLINICAL TRIALS OF CONTINUOUS MIDAZOLAM INFUSIONS IN ADULT ICU PATIENTS NOT SUPPORTED BY THE SPONSOR</b>						
Boyle	<i>J Drug Develop</i>	Brief	58	Prospective, Randomized, Open, Comparative	Midazolam vs Propofol	Med/Surg
Carrasco	<i>Chest</i>	Full	88	Prospective, Randomized, Comparative	Midazolam vs Propofol	Med/Surg/Trauma
Chaudhri	<i>Br J Anaesth</i>	Brief	40	Prospective, Randomized, Comparative	Midazolam vs Propofol	CABG
Clarke	<i>J Drug Develop</i>	Brief	20	Prospective, Randomized, Comparative	Midazolam vs Propofol	Neurosurg
Degauque	<i>J Drug Develop</i>	Brief	11	Prospective, Randomized, Comparative	Midazolam vs Propofol	Med (Resp Failure)
Du Gres	<i>J Cardiothoracic Anesth</i>	Abstract	38	Prospective, Randomized, Comparative	Midazolam vs Propofol	Cardiac Surg
Geller	<i>Anesthesiology</i>	Abstract	51	Prospective, Randomized, Comparative	Midazolam vs Propofol	Med/Surg
Glew	<i>J Drug Dev</i>	Brief	29	Prospective, Randomized, Comparative	Midazolam vs Propofol	Med/Surg
Higgins	<i>Anesthesiology</i>	Abstract	80	Prospective, Randomized, Comparative	Midazolam vs Propofol	CABG
Huber	<i>Langenbecks Arch Chir</i>	Brief	52	Prospective, Randomized, Comparative	Midazolam vs Ethanol vs Clonidine	Post-op alcoholic
Kocks	<i>Eur Congress of Anaesth</i>	Abstract	23	Prospective, Comparative	Midazolam + Fentanyl vs Fentanyl + Flunitrazepam	Trauma
Kong	<i>Br Med J</i>	Full	60	Prospective, Randomized, Comparative	Midazolam vs Isoflurane	Surg/Other
Kox	<i>Br J Anaesth</i>	Abstract	30	Prospective, Randomized, Comparative	Midazolam vs Alfentanil vs Propofol	Med/Surg
Ledingham	<i>Resuscitation</i>	Interim	36	Prospective, Randomized, Comparative with Blinded Assessor	Midazolam Bolus + MS infusion vs Midazolam Infusion + MS Bolus vs MS infusion + MS bolus	Med/Surg
Lehmkuhl	<i>J Drug Dev</i>	Brief	60	Prospective, Comparative	Midazolam Bolus vs Midazolam Infusion vs Propofol Infusion	Med/Surg

CONTROLLED CLINICAL TRIALS OF CONTINUOUS MIDAZOLAM INFUSIONS IN ADULT ICU PATIENTS NOT SUPPORTED BY THE SPONSOR						
Pappagallo	<i>Minerva Anestesiol</i>	Full	22	Prospective, Comparative	Midazolam vs Propofol	Med/Surg
Plainer	<i>J Drug Dev</i>	Interim	6	Prospective, Randomized, Comparative	Midazolam + Sufentanil vs Sufentanil + Propofol	Neurosurg
Roekaerts	<i>J Cardiothoracic &amp; Vasc Anesth</i>	Full	30	Prospective, Randomized, Open, Comparative	Midazolam vs Propofol	CABG
Snellen	<i>Int Care Med</i>	Full	40	Prospective, Randomized, Open, Comparative	Midazolam vs Propofol	CABG
Spencer	<i>Int Care Med</i>	Full	60	Prospective, Randomized, Open, Comparative	Midazolam vs Isoflurane	Med/Surg
Westphal	<i>Anesthesiology</i>	Full	27	Prospective, Randomized, Double Blind, Comparative	Midazolam vs saline	CABG
Wolfs	<i>J Drug Dev</i>	Full	34	Prospective, Randomized, Open, Comparative	Midazolam vs Propofol	Surg/Trauma

### B) Trial by Trial Reviews

Twelve of these controlled trials from the literature were published as original articles. Three of these – two in ICU patients (Aitkenhead et al; Carrasco et al), and one in cardiac surgery patients (Westphal et al) a midazolam loading dose of 0.020 mg/kg is appropriate – appearing in leading peer-reviewed journals were carefully examined by this reviewer.

**Aitkenhead AR, Pepperman ML, Willatts SM, et al. Comparison of propofol and midazolam for sedation in critically ill patients. *Lancet* 1989;1:704-709.**

**Introduction:** This prospective, randomized, multi-center, open-label comparative study of propofol vs midazolam for short-term (<24 h) sedation of ICU patients looked at effectiveness of sedation (Ramsey Score), impact on adrenal function, and time required for weaning from mechanical ventilation.

**Methods:** Patients (n=101) aged 16-80 yrs in five institutions were randomized to receive either propofol or midazolam by continuous infusion. A "synacthen test" (ie, known in this country as a Cosyntropin test) was performed immediately after termination of the infusion.

**Results:** One patient never received sedation and was not included in the study data. Four propofol patients died during the study for reasons judged unrelated to sedation.

**Conclusions:** "Propofol and midazolam were comparable in safety and efficacy for sedation; neither drug impaired production of adrenal corticosteroids; recovery time was less variable after discontinuation of propofol than midazolam; weaning from the respirator (*sic*) was achieved faster in propofol patients than in midazolam patients."

**Reviewer's Comments:** The sponsor's review was generally accurate. It omitted the fact that the difference between the groups in terms of weaning following termination of infusion was highly significant – p<0.001 – in favor of propofol.

**Carrasco G, Molina R, Costa J, Soler JM, and Cabre L. Propofol vs midazolam in short-**

*medium-, and long-term sedation of critically ill patients: a cost-benefit analysis. Chest 1993;103:557-564.*

**Introduction:** This randomized, prospective, open label, comparative study of midazolam vs propofol in short-, medium-, and long-term sedation of critically ill patients compared the effectiveness and cost-benefit of the two drugs.

**Methods:** Patients >16 yr old (n=102) were randomly assigned to receive either propofol (n=46) or midazolam (n=42). Within each group, patients were classified into candidates for short-, medium-, or long-term sedation. Desired levels of sedation were defined as end-points. Safety was assessed through hemodynamic parameters, lab test results, recovery time from termination of the infusion to extubation and total time before the patient could be transferred to the floor. **Statistics:** Unpaired t-test or Mann-Whitney U test for between-group comparisons; linear regression to correlate sedation time with extubation and recuperation times, defined as the time when the patient could be transferred to a step-down unit or the floor.

**Results:** Ten patients were ineligible due to exclusion criteria, but it is not clear whether they were randomized and/or exposed to medication. Four patients died during the study period but there is no mention whether they were in the propofol or midazolam group. The remaining 88 patients were analyzed.

Mean Recover Times (h)				
	Event	Midazolam	Propofol	p Value
Short-term group	Time to Extubation	2.5	0.3	<0.05
	Total Recovery Time	3.6	1.0	<0.05
Medium-term group	Time to Extubation	13.5	0.4	<0.05
	Total Recovery Time	21	1.4	<0.05
Long-term group	Time to Extubation	36.6	0.8	<0.05
	Total Recovery Time	54.7	1.8	<0.05

**Conclusion:** "The percent of adequate sedation time was greater for propofol than for midazolam (p<0.05). The time to extubation and recovery to full consciousness was faster with propofol than with midazolam. The time to extubation and time to full recovery correlated with the duration of sedation in patients treated with propofol but not with midazolam."

**Reviewer's Comment:** Review of the study compared to the sponsor's summary was accurate and complete except for the absence of one important finding: as indicated in the accompanying chart (which was provided in the sponsor's review), there was a clinically meaningful and statistically significant shorter time from termination of infusion to transfer out of the ICU in favor of propofol, especially in the medium- and long-term groups.

*Westphal LM, Cheng EY, White PF, Sladen RN, Rosenthal MH, Sung M-L. Use of midazolam infusion for sedation following cardiac surgery. Anesthesiology 1987;67:257-262.*

**Introduction:** This randomized, prospective, open label, placebo-controlled, dose-effect study of midazolam in sedation of post-CABG surgery patients.

**Methods:** Patients (n=27) were randomly assigned to receive either saline, low-dose midazolam (load=0.03 mg/kg + infusion=1.7 mg/kg-h), or high-dose midazolam (load=0.06 mg/kg + infusion=3.4 mg/kg-h) for a duration of 8 h. **Statistics:** X<sup>2</sup>; ANOVA with Bonferroni adjustment; linear regression analysis.

**Results:** All 27 patients were enrolled and completed the study. The control group required significantly more morphine than the two midazolam treatment groups, but the midazolam groups did not differ with respect to morphine requirement. Time to eye opening and response to command was significantly longer in the high dose-dose midazolam than in the control group. Time to spontaneous

ventilation was significantly longer in the low-dose midazolam group than in the control group. There was no significant difference in length of ICU stay among the three study groups.

Postoperative Recovery Times (h) After Arriving in the ICU (Mean ± SEM)*					
Group	First Movement	Eye Opening	Response to Command	Spontaneous Ventilation	Extubation
Saline (placebo)	2.6 ± 0.6	2.9 ± 0.6	3.9 ± 0.6	7.6 ± 1.1	16.2 ± 1.3
Low-dose Midazolam	5.9 ± 1.0	5.9 ± 1.0	6.4 ± 0.8	<b>14.1 ± 1.4</b>	19.2 ± 1.8
High-dose Midazolam	6.2 ± 1.0	6.8 ± 1.0	7.9 ± 1.1	11.9 ± 1.2	19.4 ± 1.4

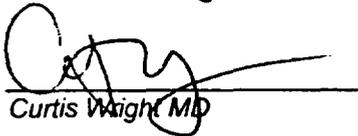
\* Bold=Significantly different from placebo, p<0.05.

Conclusion: Midazolam infusion resulted in a significant decrease in the requirement for morphine. Midazolam infusion increased postoperative recovery time.

Reviewer's Comment: Review of the study compared to the sponsor's summary was accurate and complete except that the original article was more balanced in discussing costs (prolonged emergence time) vs benefits (sedation, amnesia, and anxiolysis) of midazolam administration.

  
 Laurence Landow MD

30 August 1996  
 Date

  
 Curtis Wright MD

8/30/96  
 Date

Medical Officer Review  
Roche NDA 18-654  
Supplement for Midazolam Infusion

**Protocol 910 Ralley (Montreal)**

NDA- 18-654 Midazolam  
Sponsor- Hoffmann La Roche INC.  
Primary Reviewer- Curtis Wright  
Secondary Reviewer- Laurence Landow  
Date of Review- 8/5/96  
Material Reviewed- Jacket 6

**Summary**

This was a three-treatment, randomized, double-blind, dose-controlled study of midazolam in 45 coronary artery bypass graft patients (3 groups of 15 each), who received low dose (0.5 mcg/kg/min), medium dose (1.0 mcg/kg/min) or high dose (1.5 mcg/kg/min) infusions that remained constant in volume but varied in concentration. The hypothesis was that each group would titrate to a common dose (mcg/kg/hr.). Physicians titrated all three groups to the range of \_\_\_\_\_ mcg/kg/hr with acceptable safety.

**Background**

Midazolam is a benzodiazepine sedative used in anesthesia that is most frequently dosed to effect in bolus doses. The sponsor wishes to provide instructions for use by infusion, and has conducted clinical studies to establish the dose. This is one such study. There is no question that midazolam is a sedative, no question that we know the blood level range where the drug is active (these were established in the original NDA and in the evaluation of the cases of drug toxicity associated with improper use of the drug during endoscopy).

The pivotal questions for this application are the suitability of the dose, the effect on use of other medication, and course of recovery from sedation for the patients.

**Protocol**

This protocol started as an open-label study, and was altered to a dose controlled study in a series of amendments before the protocol began. It was supposed to be a patients undergoing single-valve or CABG surgery, but there were only 4 valvular patients out of the 45 studied. Patients scheduled to undergo elective cardiac surgery who had uncomplicated surgery were eligible for the protocol. Excluded were women at risk of pregnancy, pregnant women, patients with severe congestive heart failure, patients with severe lung disease, and patients with severe hepatic or renal disease, history of drug abuse, glaucoma, or recovering from shock or multiple trauma.

All patients had standard premeds (morphine & scopolamine), pentothal induction, and enflurane balanced anesthesia with one of the fentanyl's for analgesia during the procedure and a midazolam bolus of 0.035 mcg/kg just prior to bypass. Patients were then taken to the ICU where they were given morphine 2 mg IV prn for pain. Midazolam was

mixed in one of three strengths, (0.04 mg/mL, 0.08 mg/mL, or 0.12 mg/mL) and started as a bolus of 0.03, 0.06 or 0.10 mg/kg, then an infusion of 0.5, 1.0 or 1.5 mcg/kg/min.

The primary assessment was a categorical FOUR step scale: 4 = Awake, 3 = Asleep, responds to verbal command, 2 = Asleep, responds to pain, 1 = Unresponsive. Physicians were advised to titrate the patients to a target score of 2 or 3 (Asleep but responsive), reduce dosage for a score of 1 (Unresponsive), and increase dosage for a score of 4 (Agitated, Awake or responding to the environment). All dose increases were ordered by volume to protect the blind.

For most patients the infusion period was to be 4-6 hours, with a 12 hour post midazolam observation period. All patients had exit labs and a patient questionnaire.

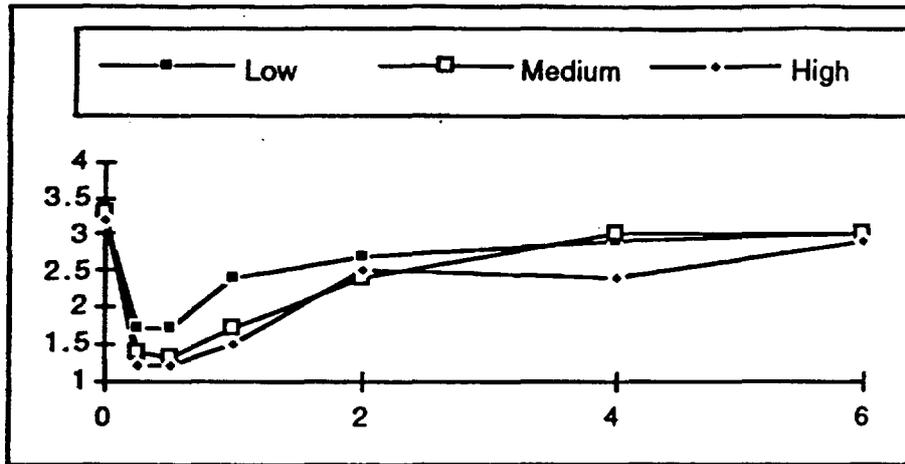
### Enrollment, Randomization, and Evaluability

48 patients were enrolled, two in the high dose group were replaced (patient given non-protocol medication for shivering, patient given wrong midazolam concentration). Of the 45 patients who were eligible some had minor protocol violations, but all were included in the analysis.

Item (MEAN & SD)	Low Dose	Medium Dose	High Dose
AGE	65 (6)	64 (6)	65 (6)
WEIGHT	73 (9)	73 (13)	71 (12)
HEIGHT	68 (2)	66 (4)	66 (2)
DURATION OF SURGERY	204 (41)	215 (47)	206 (29)
MALE	13	11	11
FEMALE	2	4	4
ASA III	13	15	12
ASA IV	2	0	3
CAUCASIAN	15	15	14
Occlusive Disease	14	13	14
Valvular Disease	2	2	1

### Results

All three groups showed a marked change in sedation scores:

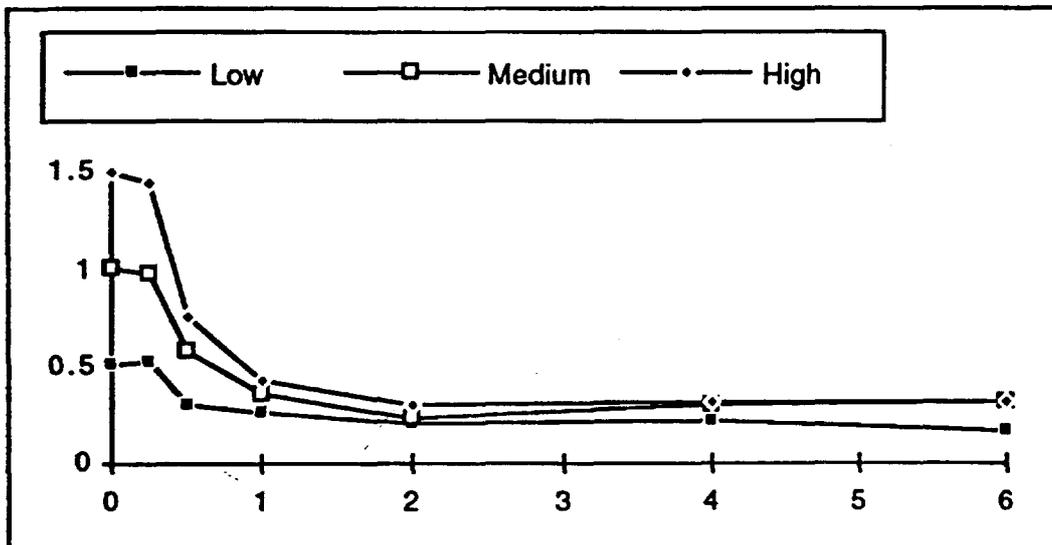


Hours	0	0.25	0.5	1	2	4	6
Low	3.2	1.7	1.7	2.4	2.7	2.9	3
Medium	3.3	1.4	1.3	1.7	2.4	3	3
High	3.2	1.2	1.2	1.5	2.5	2.4	2.9

Except for the inversion, caused by the different scale, the picture is quite similar to trial 912, although far more patients became heavily sedated following the initial bolus dose. This may reflect the addition of both the scopolamine premedication and the bolus of midazolam prior to bypass, or it may reflect a generally deeper anesthesia with greater carry-over of anesthetic effects.

#### Dose of Midazolam by group

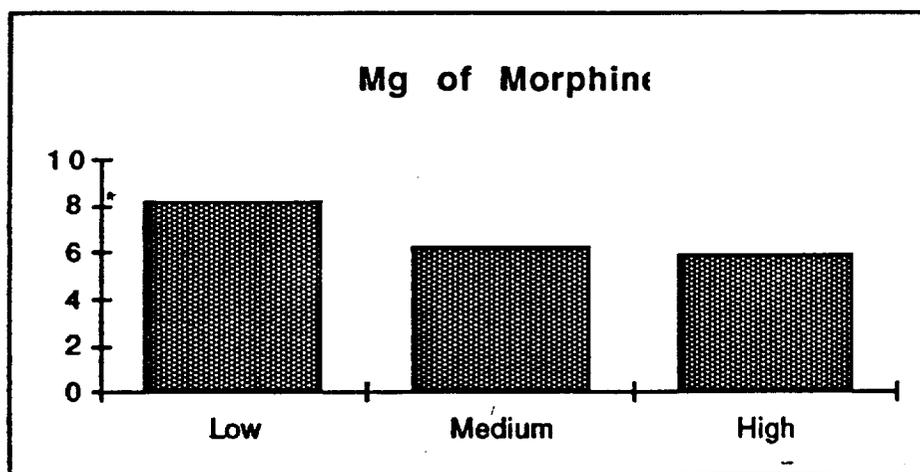
In this study, there was an unequivocal trend toward downward titration in dose (infusion rates in mcg/kg/min).



Hours	0	0.25	0.5	1	2	4	6
Low	0.5	0.52	0.3	0.26	0.21	0.22	0.16
Medium	1	0.97	0.57	0.35	0.23	0.3	0.32
High	1.5	1.45	0.75	0.42	0.3	0.32	0.32

### Effect on Concurrent Medication

We see all three groups down-titrating, and this effect is still reflected in the analgesic usage during midazolam administration.



### Subjective effects

The results of the questionnaires given the subjects were illuminating:

	Low dose	Medium	High Dose
Failed to remember ICU admission	15/15	10/15	15/15
Did not know if it was day or night	13/15	8/15	10/15
No recall of visitors	12/15	10/14	12/14
No recall of anxiety	13/15	8/14	13/15

The impression from the patient questionnaire was that the patients were heavily sedated and amnesic for the period of midazolam administration.

### Efficacy Conclusion

The midazolam infusions caused a dramatic change in level of consciousness, taking the population from "half awake & half drowsing" to "half unresponsive & half responsive only to painful stimuli". In this trial, doses above 0.3-0.5 mcg/kg/min were clearly overly sedating. No efficacy differences beyond downward titration were seen between the groups, as the doses given all patients rapidly converged.

## Safety

There were no deaths or serious injuries during the trial. One patient had a post-operative hemorrhage requiring re-operation, unrelated to the study drug. The most frequent adverse event was mild hypotension, which resolved in all cases with conventional treatment. One patient had marked shivering, treated with vecuronium.

Follow-up lab values were consistent with the surgery performed.

## Conclusion

This was an adequate and well-controlled study. The sponsor's interpretation was that the doses of midazolam were too high. Given group mean scores of 1.2 & 1.4 for the medium and high dose groups, corresponding to 2/3 or 3/4 of the patients being unresponsive to painful stimuli, I agree.

The message from this study is that the dose of midazolam for infusion will need to be titrated, depending on patient factors and on the particular anesthetic technique used. Techniques that involve deeper anesthesia, long-lasting agents or intraoperative benzodiazepines may require lower doses.



Curtis Wright

CC: NDA 18-654  
HFD-170 Division File  
CSO Morgan  
Team Leader Landow  
Reviewer C Wright

Laurence Landow



Medical Officer Review  
Roche NDA 18-654  
Supplement for Midazolam Infusion

**Protocol 912 Martineau & Miller (Ottawa)**

NDA- 18-654 Midazolam  
Sponsor- Hoffmann La Roche INC.  
Primary Reviewer- Curtis Wright  
Secondary Reviewer- Laurence Landow  
Date of Review- 8/5/96  
Material Reviewed- Jacket 6

**Summary**

This was a three-treatment, randomized, double-blind, dose-controlled study of midazolam in 30 patients (3 groups of 10 each), who received low dose (0.5 mcg/kg/min), medium dose (1.0 mcg/kg/min) or high dose (1.5 mcg/kg/min) infusions that remained constant in volume but varied in concentration. The hypothesis was that each group would titrate to a common dose (mcg/kg/hr.). This did not happen, as the treating physicians altered the dose of narcotic analgesics from high (43 mg) to moderate (34 mg) to low (18 mg) across the treatment groups.

The study showed that all three doses of the drug could safely substitute for opiate-induced sedation, with slightly shorter recovery times for the two lower doses.

**Background**

Midazolam is a benzodiazepine sedative used in anesthesia that is most frequently dosed to effect in bolus doses. The sponsor wishes to provide instructions for use by infusion, and has conducted clinical studies to establish the dose. This is one such study. There is no question that midazolam is a sedative, no question that we know the blood level range where the drug is active (these were established in the original NDA and in the evaluation of the cases of drug toxicity associated with improper use of the drug during endoscopy).

The pivotal questions for this application are the suitability of the dose, the effect on use of other medication, and course of recovery from sedation for the patients.

**Protocol**

Patients scheduled to undergo elective abdominal aortic surgery who had uncomplicated surgery were eligible for the protocol. Excluded were women at risk of pregnancy, pregnant women, patients with severe congestive heart failure, patients with severe lung disease, and patients with severe hepatic or renal disease, history of drug abuse, glaucoma, or recovering from shock or multiple trauma.

All patients had standard premeds, pentothal induction, and isoflurane balanced anesthesia with one of the fentanyl's for analgesia during the procedure. Patients were then taken to the ICU where they were given morphine 2 mg IV prn for pain, agitation, fighting the respirator, or tachycardia. Midazolam was mixed in one of three strengths,

(0.04 mg/mL, 0.08 mg/mL, or 0.12 mg/mL) and started as a bolus of 0.03, 0.06 or 0.10 mg/kg, then an infusion of 0.5, 1.0 or 1.5 mcg/kg/min.

The primary assessment was a categorical six step scale (0 Agitated, 1 Awake, 2 Asleep (eyes open to noise), 3 Asleep (eyes open to name), 4 Asleep (eyes open to touch), 5 Asleep (moves to touch), 6 Asleep (Unresponsive). Physicians were advised to titrate the patients to a target score of 3-5 (Asleep but responsive), reduce dosage for a score of 6 (Unresponsive), and increase dosage for a score of 0-2 (Agitated, Awake or responding to the environment). All dose increases were ordered by volume to protect the blind.

For most patients the infusion period was to be six hours, with a 48 hour post midazolam observation period. All patients had exit labs and a patient questionnaire.

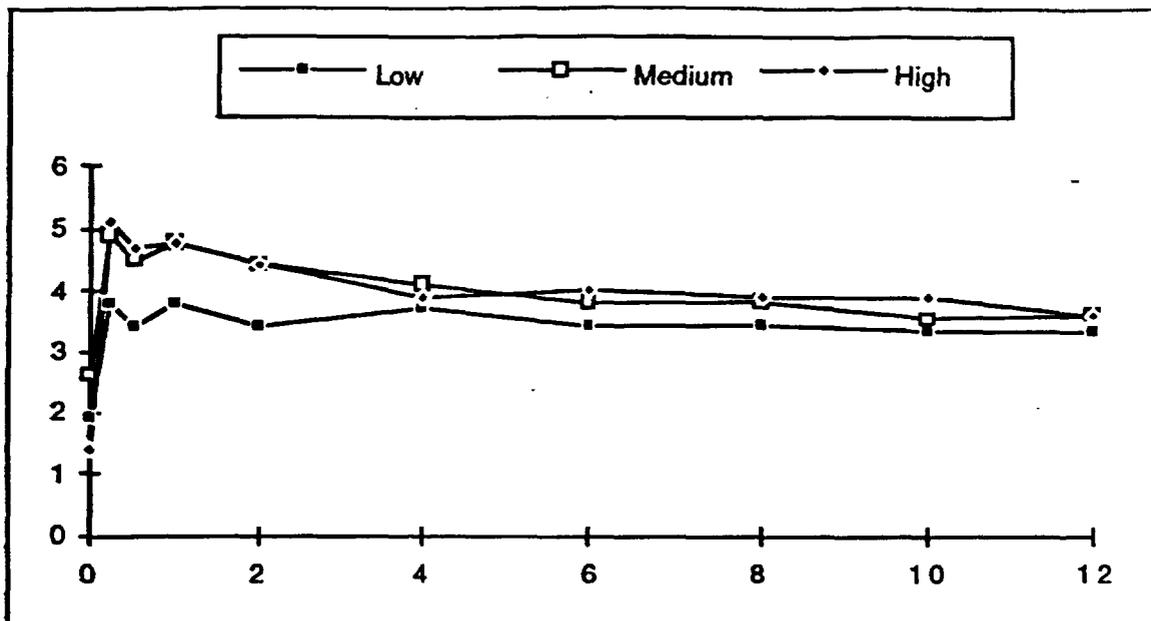
### Enrollment, Randomization, and Evaluability

Thirty patients were enrolled, six had minor weight problems (to heavy, too thin), but all were evaluated and none excluded. The groups were similar in most ways:

Item (MEAN &*SD)	Low Dose	Medium Dose	High Dose
AGE	64 (8.4)	68 (7.4)	70 (5.6)
WEIGHT	69 (7.8)	77 (10.3)	74 (13.6)
HEIGHT	170 (8.8)	172 (9.5)	173 (13.1)
DURATION OF SURGERY	2.6 (0.6)	2.8 (0.7)	2.4 (0.3)
MALE	5	9	7
FEMALE	5	1	3
ASA III	9	10	10
ASA IV	1	0	0
CAUCASIAN	10	10	10
Occlusive Disease	4	3	4
Aneurysm	6	7	6

### Results

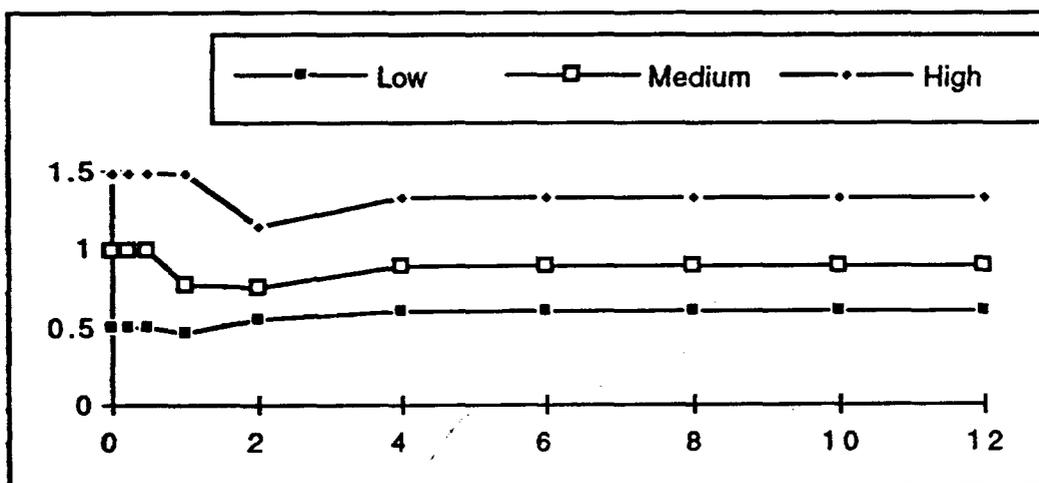
All three groups showed a marked change in sedation scores:



Hours	0	0.25	0.5	1	2	4	6	8	10	12
Low	1.9	3.8	3.4	3.8	3.4	3.7	3.4	3.4	3.3	3.3
Medium	2.6	4.9	4.5	4.8	4.4	4.1	3.8	3.8	3.5	3.6
High	1.4	5.1	4.7	4.8	4.4	3.9	4	3.9	3.9	3.6

### Dose of Midazolam by group

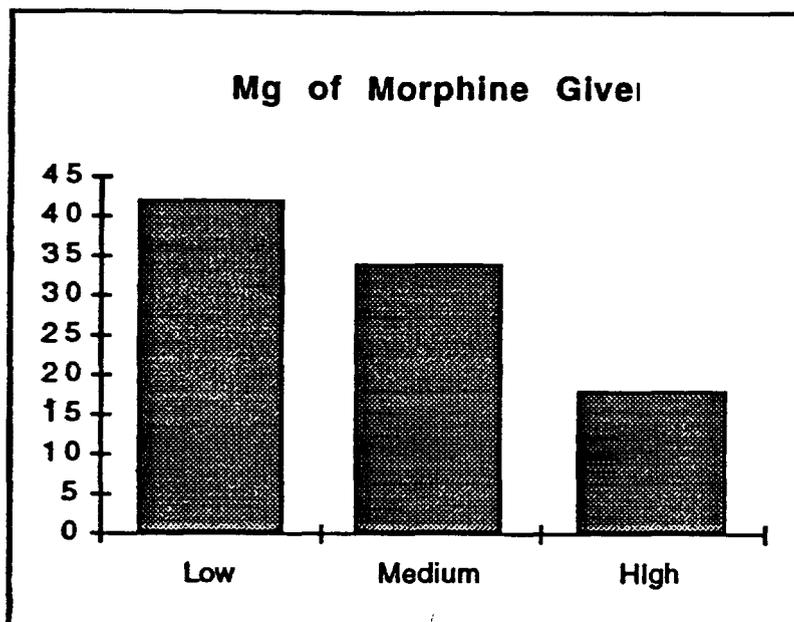
Since this was a titration design, the next step seemed to be to look at the actual doses of drug given (infusion rates in mcg/kg/min).



Hours	0	0.25	0.5	1	2	4	6	8	10	12
Low	0.5	0.5	0.5	0.47	0.55	0.6	0.6	0.6	0.6	0.6
Medium	1	1	1	0.78	0.75	0.9	0.9	0.9	0.9	0.9
High	1.49	1.49	1.49	1.49	1.15	1.34	1.34	1.34	1.34	1.34

## Effect on Concurrent Medication

At first glance, this suggests that all three doses have roughly equal sedating effects, despite a three fold increase in the infusion rate. What actually happened is seen in the next plot which is the total dose of narcotics given to the patients in each group (converted to mg of morphine as some received meperidine or fentanyl).



## Efficacy Conclusion

The midazolam infusions caused a marked reduction in the amount of narcotic needed by the patients to remain comfortable on the ventilator. There is a hint that the highest dose resulted in oversedation seen in the immediate reduction in dosage @ 1 hour, and the lower dosage carried through the study. The efficacy conclusion is that the physicians in the study preferred to adjust the opiate dose, rather than titrate the infusion. Interestingly, the fall in opiate dosage (42->15) is of the same magnitude as the rise in midazolam dose (0.5->1.3).

The data provide some suggestion that the bolus dose for the medium and high dose group are perhaps too high, since at the time of peak effect the average patient's score was 5 (Asleep, responsive to painful stimuli), suggesting that at least some of the patients were unresponsive.

## Safety

One patient (low dose group) had a serious AE. He experienced postoperative hemorrhage, hypovolemia, shock lung from crystalloid, and an intercurrent MI. He recovered and was discharged to home. The relationship to drug was listed as remote, and the reviewer agreed.

Five patients experienced hallucinations, confusion, or agitation, with no dose-relatedness.

There were no treatment related alterations in vital signs or laboratory tests, despite careful examination for acute withdrawal phenomena.

One marked finding in the survey results was the question, "Do you remember being on the breathing machine". Zero of 10 low dose, 6 of 10 medium dose, and 4 of 9 high dose patients were amnesic for the respirator. Patients appear to have an amnesic response to these doses of midazolam.

### Conclusion

This was an adequate and well-controlled study that showed a marked opiate sparing effect from midazolam infusion. It does not support midazolam ALONE in the postoperative patient with post-surgical pain, but does suggest that doses of about 0.5 mcg/kg/min were tolerated and effective for the short term ICU stay. The higher bolus doses and infusion rates may be too high for some patients, as evidenced by some patients being unresponsive and needing downward titration in the medium and high dose groups.

It does not address the risk of either acute withdrawal or precipitated withdrawal following longer infusions.

Curtis Wright



Laurence Landow



CC: NDA 18-654  
HFD-170 Division File  
CSO Morgan  
Team Leader Landow  
Reviewer C Wright

Medical Officer Review  
Roche NDA 18-654  
Supplement for Midazolam Infusion

**Protocol 912 Teasdale (Toronto)**

NDA- 18-654 Midazolam  
Sponsor- Hoffmann La Roche INC.  
Primary Reviewer- Curtis Wright  
Secondary Reviewer- Larry Landow  
Date of Review- 8/7/96  
Material Reviewed- Jacket 7

**Summary**

This was a three-treatment, randomized, double-blind, dose-controlled study of midazolam in 30 patients (3 groups of 10 each), who received a bolus dose of midazolam then either low dose (0.5 mcg/kg/min), medium dose (1.0 mcg/kg/min) or high dose (1.5 mcg/kg/min) infusions that remained constant in volume but varied in concentration. The hypothesis was that each group would titrate to a common dose (mcg/kg/hr.). All patients were initially excessively sedated from the bolus dose, but were titrated to a common dose of 0.2-0.3 mcg/kg/min to good effect.

The study showed good dose finding for the infusion, but the need to titrate the bolus dose.

**Background**

Midazolam is a benzodiazepine sedative used in anesthesia that is most frequently dosed to effect in bolus doses. The sponsor wishes to provide instructions for use by infusion, and has conducted clinical studies to establish the dose. This is one such study. There is no question that midazolam is a sedative, no question that we know the blood level range where the drug is active (these were established in the original NDA and in the evaluation of the cases of drug toxicity associated with improper use of the drug during endoscopy).

The pivotal questions for this application are the suitability of the dose, the effect on use of other medication, and course of recovery from sedation for the patients.

**Protocol**

Patients scheduled to undergo elective coronary artery bypass surgery who had uncomplicated surgery were eligible for the protocol. Excluded were women at risk of pregnancy, pregnant women, patients with severe congestive heart failure, patients with severe lung disease, and patients with severe hepatic or renal disease, history of drug abuse, glaucoma, or recovering from shock or multiple trauma.

All patients had standard premeds (morphine & perphenazine), high dose fentanyl induction (30 mcg/kg IV) with pancuronium, and fentanyl and halothane or fentanyl & isoflurane maintenance (I suspect nitrous oxide was used as part of standard technique).

Patients were then taken to the ICU where they were given morphine 2 -4 mg IV prn for pain, agitation, "fighting the respirator, or tachycardia.

The dose of midazolam was amended during the protocol. It started at the 0.03-0.10 mg/kg bolus such as was in the other site in the study. This was lowered due to signs of excessive sedation in the first 7 patients. In the revised protocol, after the bolus (starting dose of 0.015, 0.03, or 0.05 mg/kg, the infusions were started at 0.5, 1.0 & 1.5 mcg/kg/min, and could be titrated as before.

The primary assessment was a categorical six step scale (0 Agitated, 1 Awake, 2 Asleep (eyes open to noise), 3 Asleep (eyes open to name), 4 Asleep (eyes open to touch), 5 Asleep (moves to touch), 6 Asleep (Unresponsive). Physicians were advised to titrate the patients to a target score of 3-5 (Asleep but responsive), reduce dosage for a score of 6 (Unresponsive), and increase dosage for a score of 0-2 (Agitated, Awake or responding to the environment). All dose increases were ordered by volume to protect the blind.

For most patients the infusion period was to be six hours, with a 48 hour post midazolam observation period. All patients had exit labs and a patient questionnaire.

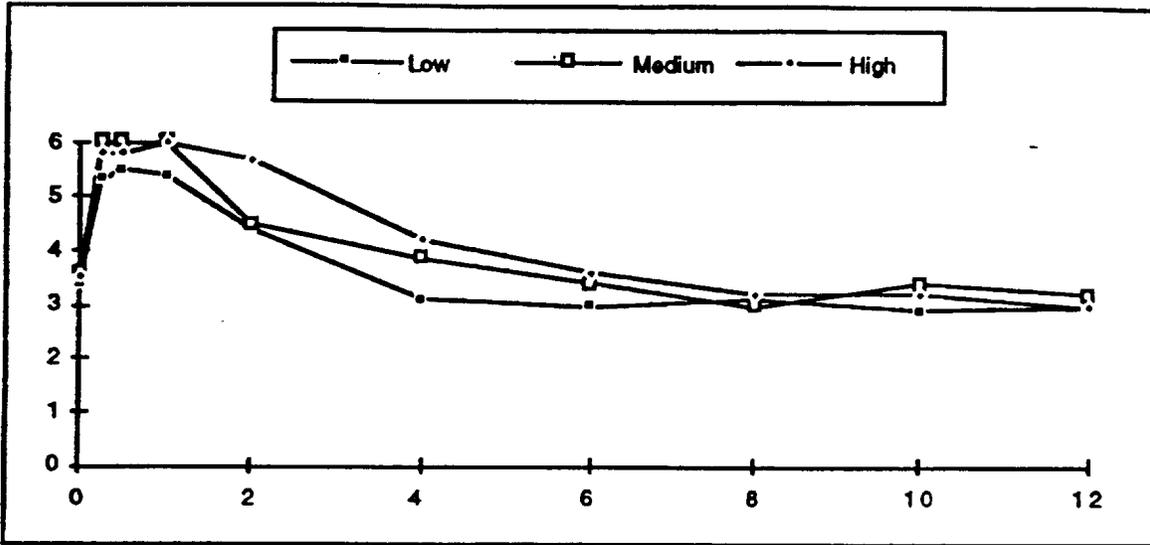
### **Enrollment, Randomization, and Evaluability**

The first 7 patients enrolled were evaluated only for safety, an additional thirty patients were enrolled, five had minor protocol violation problems (the protocol was unwisely restrictive in matters that were unrelated to the study), but all were evaluated and none excluded. The groups were similar in most ways:

Item (MEAN & SD)	Low Dose	Medium Dose	High Dose
AGE	57 (6)	61 (9)	61 (7)
WEIGHT	79 (10)	75 (8)	68 (12)
HEIGHT	170 (8)	172 (9)	165 (12)
DURATION OF SURGERY	2.8 (0.4)	2.8 (0.6)	2.8 (0.5)
MALE	9	9	6
FEMALE	1	1	4
ASA III	10	10	10
ASA IV	0	0	0
CAUCASIAN	8	8	9
BLACK	0	0	1
INDIAN	2	2	0

### **Results**

All three groups showed a marked change in sedation scores:

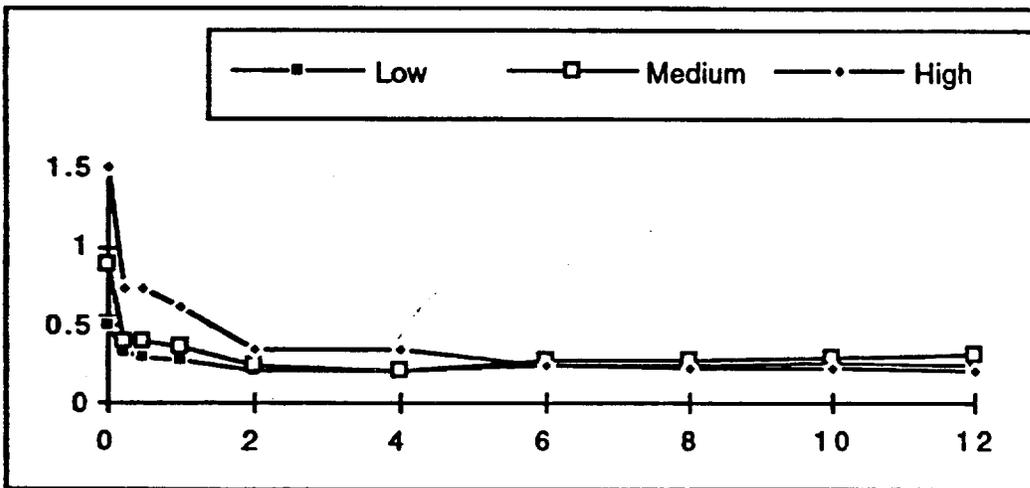


Hours	0	0.25	0.5	1	2	4	6	8	10	12
Low	3.4	5.3	5.5	5.4	4.4	3.1	3	3.1	2.9	3
Medium	3.6	6	6	6	4.5	3.9	3.4	3	3.4	3.2
High	3.5	5.8	5.8	6	5.7	4.2	3.6	3.2	3.2	3

What we see here is that the patients in the medium and high dose groups, even at the reduced dosage, are unresponsive to pain within 15 minutes after the bolus, while in the low dose group things are a bit better, and only half to 2/3 of the patients are anesthetized. The patients have started to recover by 2 hours, and are in good shape by 4.

### Dose of Midazolam by group

Since this was a titration design, the next step seemed to be to look at the actual doses of drug given (infusion rates in mcg/kg/min).

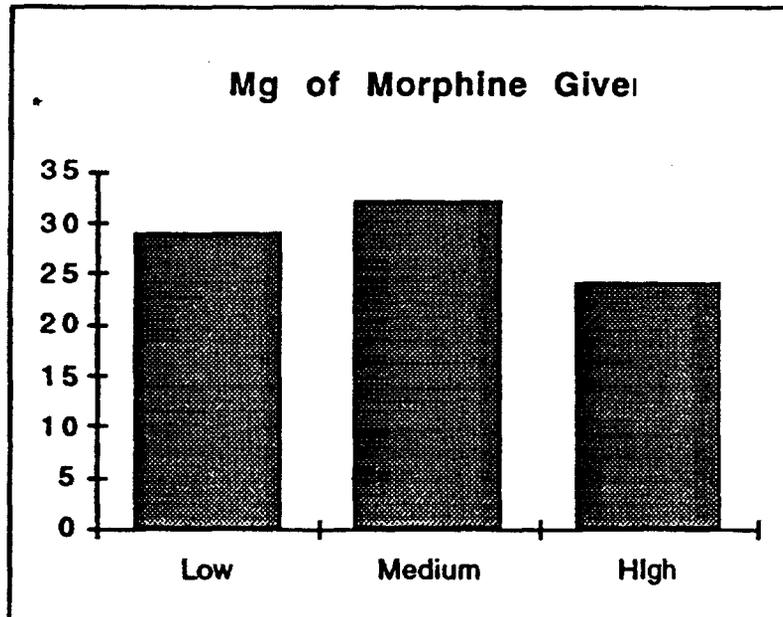


Hours	0	0.25	0.5	1	2	4	6	8	10	12
Low	0.5	0.33	0.3	0.28	0.21	0.21	0.24	0.24	0.27	0.25
Medium	0.9	0.4	0.4	0.37	0.25	0.21	0.28	0.28	0.29	0.31
High	1.5	0.74	0.74	0.62	0.35	0.34	0.25	0.23	0.23	0.21

What we see here is that the physicians quickly detected that the bolus dose was too high, and reduced the dosage in all groups down to a common dose of about 0.2-0.3 mcg/kg/min which seemed to keep the patients in the desired range after the bolus wore off.

### Effect on Concurrent Medication

Since the patients all got about the same amount of midazolam, it is not unexpected that they all required about the same amount of narcotic (converted to mg of morphine as some received meperidine or fentanyl).



### Efficacy Conclusion

The bolus doses in these patients were too high, perhaps far too high, and these patients might have done better with half or a third as much midazolam in the bolus (say 5-15 mcg/kg). The carry away message seems to be that the bolus dose in these studies seems to vary according to the anesthetic technique, and the degree of sedation that is desired for the immediate postoperative setting.

In contrast to the bolus dose, the infusion doses rapidly converged, and do appear to be what is called for.

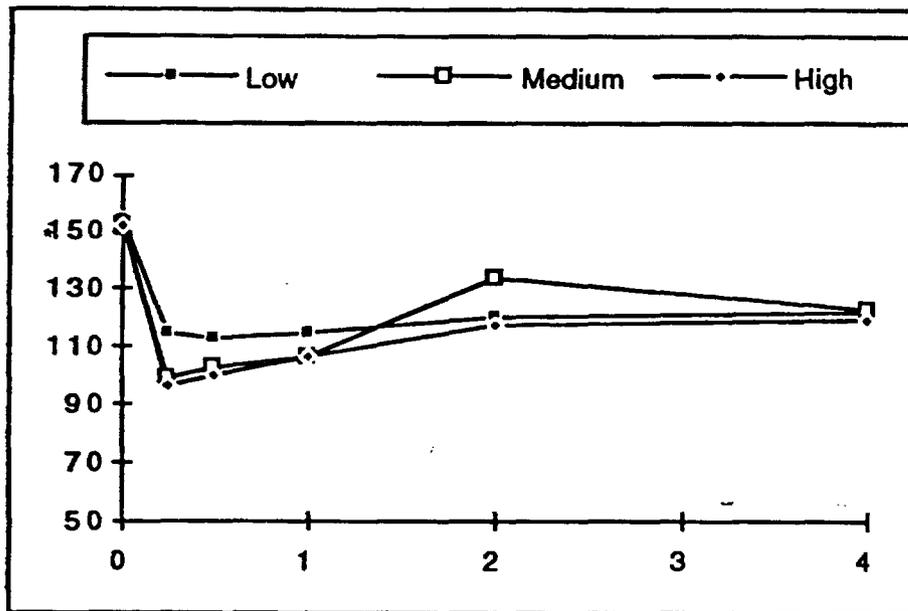
In this study, most of the patients were not amnesic for most of their stay (8-10 in each group remembered the respirator, visitors, etc.).

## Safety

There were no deaths or serious side effects attributable to study drug, though patients in all three treatment groups had transient episodes of either hypotension or hypertension, which responded to therapy. Hypoventilation was not seen (the patients were on ventilators) though it might occur if imprudent minimums were set on the ventilators.

Transient arrhythmias, one episode of elevated cardiac enzymes, and a pneumothorax were seen, again not unexpected.

One unacceptable result of the excessively high bolus doses were 40 & 50 point drops in the systolic blood pressure from the bolus.



Hours	0	0.25	0.5	1	2	4
Low	154	115	113	115	120	122
Medium	152	99	103	107	134	123
High	152	97	100	107	118	119

## Conclusion

This was an adequate and well-controlled study that clearly showed that midazolam bolus and infusion were effective in the ICU. It also showed that the proposed bolus doses were too high for this patient population post-op. It is likely that the size of the bolus dose needed will vary depending on the anesthetic technique, the patient's condition, and the degree of sedation required.

I strongly recommend an integrated review of all the dosing data, and a recommended bolus technique that avoids the kind of excessive sedation seen in this study.

  
Curtis Wright

CC: NDA 18-654  
HFD-170 Division File  
CSO Morgan  
Team Leader Landow  
Reviewer C Wright

Larry Landow  


## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA No; 18-654 S#29

### Midazolam HCl

- 1, 5ml vials containing 5mg midazolam/ml
- 2, 10ml vials containing 1mg midazolam/ml

Hoffmann La Roche Inc  
340 Kingsland Street  
Nutley  
New Jersey 07110 1199

Tradename; Versed

Reviewer: Peter Lockwood MS

Review Start: Thursday, August 1

Submission Date; Sept. 28 1995

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### 1. BACKGROUND

Versed (midazolam HCl) is a water soluble short-acting benzodiazepine central nervous system depressant. It is 95% plasma protein bound over the concentration range encountered in clinical usage and is subject to approximately 55% first pass metabolism. The main metabolite is 1-hydroxy midazolam which is pharmacologically active but much less than the parent has a half-life of about 0.8 hrs. Midazolam is currently approved under the above mentioned NDA for three indications in adults, namely (1) for preoperative sedation following intramuscular administration, (2) for conscious sedation prior to short diagnostic, therapeutic or endoscopic procedures following intravenous administration and (3) for induction or adjunct to general or regional anesthesia.

All these approved indications pertain to short term use of injectable midazolam in adults. A supplemental application No. 029 to this NDA was submitted September 13, 1995 providing data for the following new indication in adults:

- continuous intravenous infusion for sedation of intubated, mechanically ventilated patients.

### 2. SYNOPSIS

The pharmacokinetic component of this submission included a summary of 21 publications of the pharmacokinetics of midazolam administered by continuous intravenous infusion and four studies supported by the sponsor. The literature submission reaffirmed the ranges of the Vd and Cl parameters for midazolam in healthy adults. These were 1-3 L/kg and 3-10ml/min/kg, respectively. Infusions ranged from 0.01-0.2mg/kg/hr, which is well within the range disseminated in the package insert. No life threatening adverse events were reported and all adverse events resolved after treatment was discontinued.

In critically ill patients the Cl may well be reduced (range 0.4-10ml/min/kg) and the Vd may either increase or decrease (range 0.7-4.6L/kg). The infusion rate in these patients ranged from 0.003-0.21mg/kg.

**Three dose ranging studies investigated infusions of 0.03, 0.06 and 0.09 mg/kg/hr to ICU patients who were mechanically ventilated following abdominal aortic surgery. This is the infusion range reflected in the package insert (i.e. 0.02-0.1mg/kg/hr). These were really safety studies rather than true dose response studies, because if patients were not at a predetermined level of sedation, the infusion was increased or decreased accordingly. The number of dosage adjustments for each treatment group for each center and each study was similar. There is marginal evidence that there were fewer dosage adjustments for the low dose treatment group.**

Steady state plasma concentrations measured in study 912 (Ottawa center) ranged from 31 to 140 ng/ml (mean 76ng/ml), 40 to 270ng/ml (mean 130ng/ml) and from 100 to 470ng/ml (mean 205ng/ml) for the low medium and high treatment groups respectively. There was no clinically significant difference in sedation levels, although the optimum sedation level was more rapidly obtained with the high infusion rate treatment group. Tolerance to midazolam was not apparent in these infusion studies.

Interim analysis of data collected from a partially completed computer assisted continuous infusion study indicated that midazolam has a therapeutic window between 50 and 100 ng/ml for sedation following coronary artery bypass with underlying residual opioids from the anesthesia. Modeling pharmacokinetic data with NONMEM indicated that midazolam PK was best described by a three compartment model. Using the PK parameters determined from this, the desired therapeutic window was simulated using the a dosing schedule of 5-10 mg/hr for the first hour, 3-6mg/hr for the second and third hours and 2-4 mg/hr beyond 3 hours.

3. **COMMENTS & RECOMMENDATIONS (not to be sent to the sponsor but to be discussed with review team).**
  - 1) The "Continuous Infusion" paragraph in the pharmacokinetic section of the label conveys no useful information and should be removed.
  - 2) The continuous infusion section in the dosing section of package insert should be amended to indicate that the loading dose be infused over 2-several minutes as opposed to "given slowly or infused over several minutes".
  - 3) Because of the high variability in Vd and Cl in critically ill patients, cautious dosing at the lower end of the suggested dose ranges should be emphasised.

- 4) Tolerance is not addressed in the package insert. This should be noted together with the fact that increases in doses to account for this will be accompanied by prolongation of the half-life.

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#### 5. PHARMACOKINETICS

##### 5.1. literature review

The number of subjects studied in the 21 reports amounted to 282. This included 43 healthy volunteers in 6 studies, 109 surgical patients in 5 studies and 130 critically ill patients in 10 studies. Midazolam infusion was continued for up to 27 days. The ranges of administered doses generally were;

loading dose; 0.02-0.5mg/kg  
 maintenance dose; 0.01-0.4mg/kg/hr

### **5.1.1. studies of healthy volunteers**

Infusion durations in healthy volunteers were up to 26 hours with infusion rates up to 0.04mg/kg/h. The range of mean plasma clearance in healthy volunteers was 6.1- 9.6 ml/min/kg. The range of mean volume of distribution was 1.0-2.7 L/kg. Details of the studies conducted in healthy volunteers are displayed in table V1-B-7; Appendix 1.

### **5.1.2. midazolam kinetics after surgical procedures**

The pharmacokinetics of midazolam were evaluated when midazolam was used in the postoperative period following surgical procedures, as a component of anesthesia during the procedure itself, or both. Infusion durations generally fell in the range of 4-24 hours. When a loading dose was administered it ranged from 0.01-0.05mg/kg. The time frame over which this was administered was not specified. The maintenance dose administered ranged from 0.01-0.2 mg/kg/hr. The duration of infusion ranged from 8-24 hours.

The patients in these studies tended to be young adult or elderly. Most appeared to be healthy at the time of surgery, but were undergoing major procedures such as myocardial revascularization, abdominal aortic reconstruction or other intra-abdominal procedures, or maxillofacial surgery. Midazolam was generally one of many pharmacologic agents administered. Other classes of coadministered medications included opiates, anticholinergics, neuromuscular blockers, barbiturates, and volatile general anesthetics.

The range of mean plasma clearance was 3.4-10.5 ml/min/kg. The range of mean volume of distribution was 1.0-3.1 L/kg. The pharmacokinetics of midazolam determined in these studies are displayed in Table VI-B-8, Appendix 1. These are similar to values reported in Supplement 30 where it was reported that for individuals between 1-18 years of age, the mean CL ranged from 3-13ml/min/kg. Similarly the mean Vd ranged from 0.6-2.7 L/kg.

### **5.1.3. Midazolam Infusion in Critically Ill Patients on Mechanical Ventilation**

Most patients confined to intensive or critical care units receive mechanical ventilation for various reasons including postoperative recovery, serious medical illness, or trauma. Ten studies included this patient population. Most of these studies included elderly patients suffering from dysfunction of multiple organs and major abnormalities of cardiac output, and receiving multiple medications. Kinetic parameters for midazolam in these studies were quite variable, with clearances ranging from values in the normal range to those that are substantially reduced from normal. Likewise, values of elimination half-life ranged from those usually expected for individuals of corresponding age to values that were greatly prolonged.

The range of mean plasma clearance was 0.4- 10.3 ml/min/kg. The range of mean volume of distribution was 0.7-4.6 L/kg. The infusion duration ranged from 23 to 649 hours. The loading dose where administered ranged from 0.07-0.5 mg/kg. The maintenance dose ranged from 0.003-0.21 mg/kg/hr. Details of dosing and pharmacokinetic parameters determined in these studies are displayed in Table VI-B-9; Appendix 1.

### **5.2. Midazolam Metabolites**

Plasma concentrations of  $\alpha$ -hydroxy-midazolam were reported in some of these studies. When levels of the unconjugated metabolite were described, they were considerably lower than those of the parent compound (Crevat-Pisano et al 1986; Driessen et al 1989; Dirksen et al 1987; Miller et al 1994). This finding, together with the lower receptor affinity and lower relative brain uptake of  $\alpha$ -hydroxy-midazolam relative to those of the parent compound (Arendt et al 1987), make it likely that the primary pharmacological effect of midazolam administration is attributable to the parent compound. In some studies plasma levels of  $\alpha$ -hydroxy-midazolam glucuronide were also reported (Driessen et al 1991; Vree et al 1989; Dirksen et al 1987; Oldenhof et al 1988). Levels of the glucuronide conjugate exceeded those of intact  $\alpha$ -hydroxy-midazolam. Since the glucuronide is excreted by the kidney, its plasma levels will rise in patients with renal insufficiency. This is not of clinical importance in short term infusion (<24 hrs), since the glucuronide conjugate is pharmacologically inactive. However with prolonged infusion in very sick ICU patients (e.g with acute renal failure due to circulatory shock or hypotension), this accumulation may displace the equilibrium to deglucuronidation resulting in elevated  $\alpha$ -hydroxy-midazolam. Driessen et al., 1991, who studied the pharmacokinetics of midazolam, the hydroxylated metabolite and its conjugate in ICU patients administered prolonged midazolam infusions, reported that in 6 patients who developed acute renal failure, unconjugated hydroxy midazolam levels were lower than the parent drug. This suggests that the deglucuronidation is unlikely to be of any clinical importance.

### **5.3. Studies Supported by the Sponsor**

Pharmacokinetic investigations were undertaken as part of three dose-ranging studies and one prospective, open-label study of midazolam administered by continuous intravenous infusion that were supported by the sponsor. The three dose-ranging studies (by Martineau and Miller; Teasdale et al; and Ralley et al) are completed. The prospective, open-label study (Reves et al) is ongoing; this is a multi-center trial of the safety and efficacy of midazolam administered to patients following cardiac surgery by computer-assisted continuous infusion (CACI).

**5.3.1. Study by Martineau and Miller (Ottawa site) and Study by Teasdale (Toronto site)**

The 60 patients in this 2 center study received midazolam by continuous intravenous infusion during mechanical ventilation in the ICU, following abdominal aortic surgery. The patients were 50 to 75 years of age, with a mean age of 67.6. They were randomly assigned to one of six dosage groups. Three dosage regimens were at an Ottawa center and three dosage regimens at a Toronto center. Dosage regimens are detailed in Table 1 and Table 2.

**Table 1; Theoretical and Actual Infusion Rates Studied; Toronto site**

group	bolus	infusion (mg/kg/hr)		time to optimal sedation (mins)
	mg/kg	theoretical	actual	
1	0.015	0.03		
2	0.03	0.06		
3	0.05	0.09		

**Table 2; Theoretical and Actual Infusion Rates Studied; Ottawa site**

group	bolus mg/kg	infusion (mg/kg/hr)		time to optimal sedation (mins)	mean plasma conc at end of infusion
		theoretical	actual		
1	0.03	0.03	0.036 ± 0.011		76.1 ± 31.6
2	0.06	0.06	0.054 ± 0.031		132.7 ± 70.5
3	0.1	0.09	0.080 ± 0.041		206.6 ± 106.2

Mean duration of infusion was approximately 17 hours for both centers. (Further details of the patients and methods are shown in Table VI-B-3 and Table VI-B-4, under Miller et al.) For the Ottawa site, the differences in infusion rates were associated with differences in midazolam plasma concentrations (see Table 2). There was no significant difference in the time to optimal sedation although the time to recovery was faster for the low and medium dose groups compared to the high dose group at 2 hours ( $p=0.3$ ). There was no significant difference between duration of artificial ventilation, postoperative sedation and stay in the ICU for any group.

Pharmacokinetic variables were independent of infusion rates. Similar values were obtained for the three groups with respect to total clearance rates, volumes of distribution, and elimination half-lives. The values are within the ranges

determined in other studies. (These latter values are shown in Table VI-B-8, under Miller et al.)

Plasma samples were collected at the Toronto center and analyzed. Data for 5 patients indicated that plasma concentrations of midazolam persisted or increased in the 24 hours following termination of infusion. The sponsor speculates that this was a consequence of poor chromatography by the contract research organization. This reason is speculative because chromatographic records could not be accessed for appraisal because they had been discarded. There was no pharmacokinetic analysis of this data.

The mean time to optimal sedation at the Toronto center was reported as approximately 200 minutes. This is inconsistent with the results reported by the Ottawa center. No explanation is offered by the sponsor and does not appear consistent with the sedation scale scores during midazolam administration. Mean sedation scores during the recovery period were very similar for the three treatment groups.

### 5.3.2. Study by Ralley et al. (protocol no 910)

This study was similar in design to the two previous studies reported. Results from this study supported the previously mentioned findings; i.e. no clinically significant difference in sedation. The time to optimum sedation was similar to the results obtained at the Ottawa site in study 912. Plasma samples were also collected at this site but there was no PK analysis of the data.

Table 3; Theoretical and Actual Infusion Rates Studied; Montreal site

group	bolus	infusion (mg/kg/hr)	time to optimal sedation (mins)
	mg/kg	theoretical	
1	0.015	0.03	
2	0.03	0.06	
3	0.05	0.09	

#### 5.4. PK-PD relationship

Mean midazolam concentration-time curves during sedation and decay curves for midazolam, and  $\alpha$ -hydroxy-midazolam, for patients representative of each group were obtained from the publication by Miller et al 1994 and are shown in Figure 1. For low rate infusion, steady state plasma concentrations ranged from 76 ng/ml (mean 76 ng/ml), for the medium infusion rate, steady state plasma concentrations were between 40 to 270 ng/ml (mean 130 ng/ml) and for the fast infusion plasma concentrations ranged from 205 ng/ml (mean 205 ng/ml). Despite the differences in infusion requirements all groups were optimally sedated 95% of the time. The obscurity of the PK/PD relationship in this instance is likely to be attributable to the coadministration of narcotics during the postoperative sedation period.

The proportion of patients requiring dosage adjustments in the three groups did not differ significantly. Upon discontinuation of midazolam, a relatively rapid decline in the level of sedation was observed in all groups (see Figure 2). However the early recovery phase was prolonged in the higher infusion rate treatment groups.

Figure 1; Midazolam and hydroxy-midazolam plasma concentration decay curves for representative patients in the low medium and fast infusion rate treatment groups

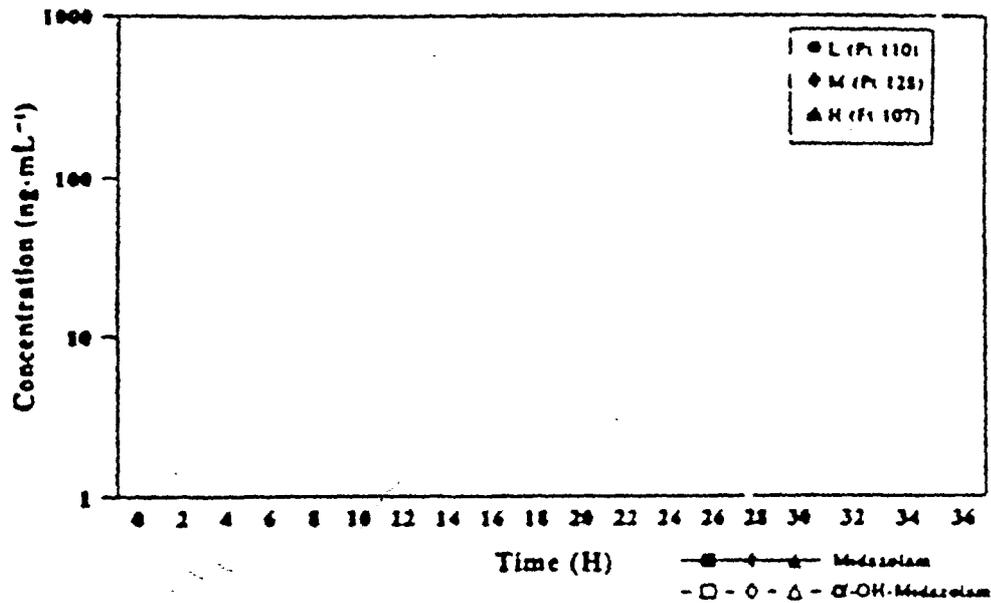
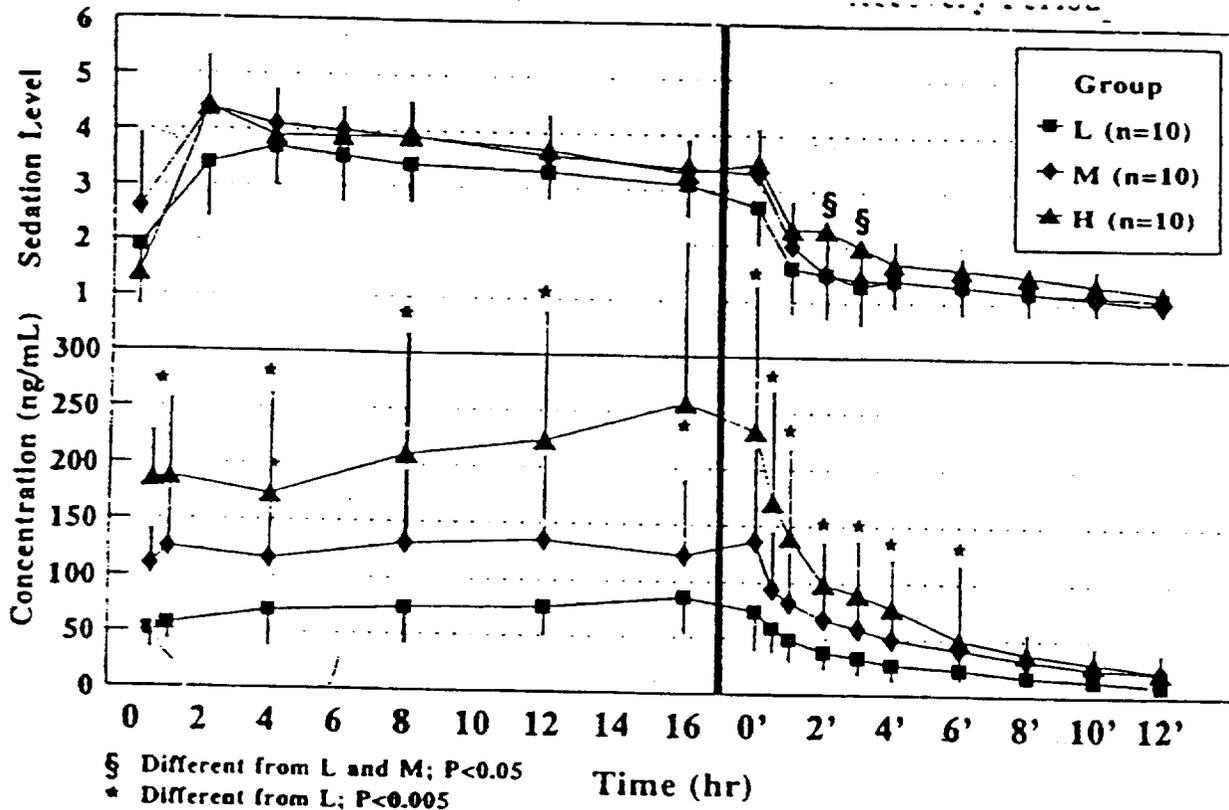


Figure 2; Mean sedation levels and corresponding mean midazolam plasma concentrations



### 5.5. Adverse Events

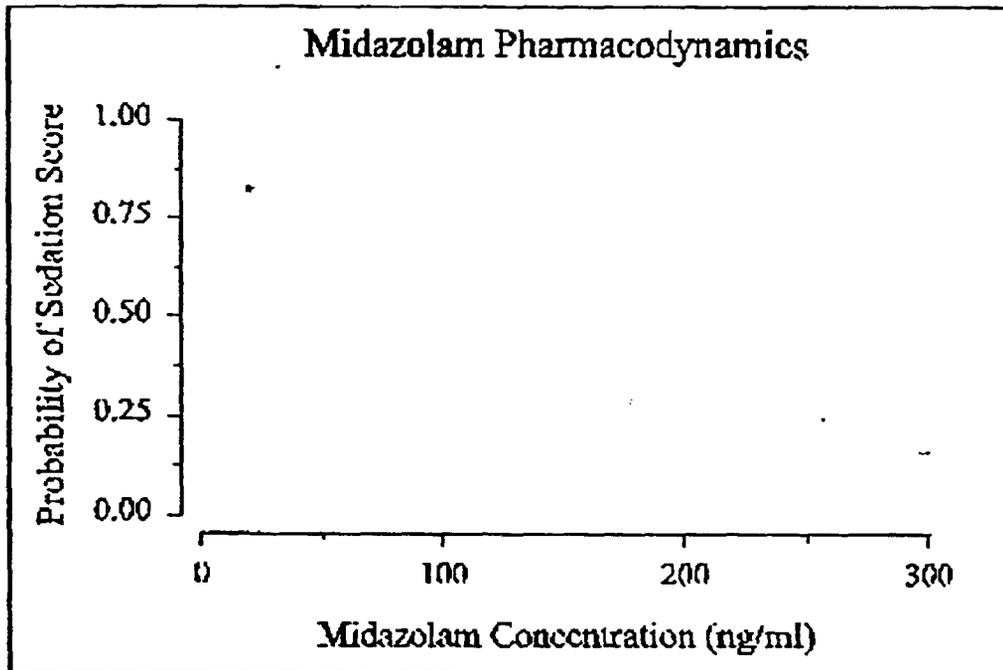
Most patients in these studies experienced at least one adverse event. None of these events were assessed to have a probable relationship with the study drug. Cardiovascular events were the most common. Both hypertensive and hypotensive events were apparent which resolved after cessation of treatment. No correlation was conducted between plasma levels and adverse events.

### 5.6. Open Study of Computer-Assisted Continuous Infusion

This is an ongoing multi-center study involving three study sites. Each site is to enroll thirty patients for a study of the safety, efficacy, pharmacokinetics, and

pharmacodynamics of midazolam administered by computer-assisted continuous infusion (CACI) for sedation during mechanical ventilation following coronary artery bypass grafting (CABG). An interim analysis has examined the pharmacokinetic data for twenty-five patients and the pharmacodynamic data for fifteen patients. The relationship between plasma concentration and sedation level was determined with logistic regression using NONMEM (see Figure 3).

**Figure 3; Probability of a sedation score relative to midazolam plasma concentration determined by logistic regression**



This suggests that the probability of obtaining a score greater than 2 ranges from 70%-90% at plasma concentrations of 150-200 ng/ml. The probability of obtaining a sedation score < 5 at this concentration ranges from 10-20%. This is the basis for the claim that the therapeutic window is between 50-100ng/ml. Using parameters determined from the fitting of a three compartment model to the pharmacokinetic data using NONMEM, the desired therapeutic window could be simulated using the following dosing schedule;

First hour: 5-10 mg/hr, Second and third hours: 3-6 mg/hr, beyond 3 hours: 2-4 mg/hr. After infusions of more than 4 hours duration, return to a fully alert state may take 6-10 hours after stopping midazolam application.

6. SIGN-OFF

Reviewed by: .....

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Thursday, August 15, 1996

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**7. APPENDIX 1; TABLES**

Table VI-B-1 Published Pharmacokinetic Studies of Midazolam Continuous Infusion in Healthy Volunteers: Subjects and Methods									
Reference	Study Design	Sample Size	Target Population	Concomitant Medications	Dose		Duration	Sampling Plan	
					Loading (mg/kg)	Maintenance (mg/kg/h)			
Greenblatt et al 1993	Prospective 3-way crossover.	8	Healthy volunteers.	None	0.1 mg/kg (3 Sections: see duration)	0.07	1 min 60 min 180 min	Not reported.	
Handel et al 1988	Prospective, placebo-controlled, randomized, double-blind, crossover, drug-interaction study.	8	Healthy, drug-free volunteers. Age range 21-35 yrs. Weight 54-85 kg. 44% male.	nitrendipine 20 mg P.O. or placebo	0.035	0.07	6 h	-Zero time and 0.5; 1.0; 1.5; 2.0; 2.17; 2.33; 2.5; 2.75; 3; 3.5; 4.5; 6; 7; 8; 9; 10 h after MDZ injection.	
Klotz & Reimann 1984	Prospective	6	-Healthy, drug-free male volunteers. -Age range 26-42. -Weight range 66-82 kg.	None	0.025	0.05	26 h	Blood samples during infusion: 1, 2, then q2h to 26 h	
Klotz et al 1985a	Prospective, randomized, 3-way crossover study.	8	Healthy men taking no other drugs. Age 24-46 yrs. Weight 62-85 kg.	Placebo; or cimetidine 800 mg P.O.; or Ranitidine 300 mg P.O.	0.025	0.05 (over 30 s)	10 h	-Before MDZ injection. -0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10 h after injection.	
Klotz et al 1985b	Prospective, double-blind, crossover study of MDZ and antagonist interaction	6	-Healthy drug and alcohol free men. -Age range 28-42. -Weight 63-82 kg. -Normal sleep-wake pattern.	Ro 15-1788 2.5 mg, or placebo injected double-blind in random order at 2h and 8h after MDZ infusion start.	0.025-0.040	0.07	8 h	Venous blood at infusion start, and 0.5, 1, 1.5, 2, 2.25, 2.5, 2.75, 3, 3.5, 4, 5, 6, 25, 5.5, 5.75, 6, 6.5, 7 and 8h after infusion start.	
Lauven et al 1982	Prospective, pharmacokinetic study.	7	Fasting, healthy trial subjects.		Continuously variable according to target plasma level. Total dose 35.5 mg. [0.36] <sup>1</sup>	NA (over 15 s)	1 h	-10 min. before infusion start. -10, 20, 30, 40, 50, 60, 62, 65, 67, 70, 75, 80, 90, 105, 120, 135, 150, 160, 210, 240 min. After infusion start.	

<sup>1</sup> Calculated, based on mean weight from publication.

<sup>2</sup> Calculated as follows: (Total dose - Loading dose)/mean weight.

**Table VI-B-3  
Published Pharmacokinetic Studies of Midazolam Continuous Infusion in Surgical Patients: Patients and Methods**

Reference	Study Design	Sample Size	Target Population	Reasons for ICU Admission and Other Health Status Characteristics	Concomitant Medications	Dose		Duration	Sampling Plan
						Loading (mg/kg)	Maintenance (mg/kg/h)		
Miller et al 1994	Randomized, double-blind, dose finding	30	Patients post abdominal aortic surgery in ICU, 50-75 yrs of age.	Surg	morphine 2 mg IV prn.; nifedipine 10 mg sublingual q10-15 min. prn or nitroglycerin infusion to maintain systolic blood pressure <160 mmHg; propranolol 1 mg prn if heart rate >100 bpm	Low Dose (L): 0.03 0.03 Optimal: 0.04 Med. Dose (M): 0.06 0.06 Optimal: 0.05 High Dose (H): 0.09 0.09 Optimal: 0.08	<24h mean 16.2h	6, 12, 24 h -Prior to administration and at 30 min, 60 min, q4h until infusion stop. -Prior to any change in MDZ infusion rate. -At infusion stop. -Following infusion stop; 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 18, 24, 36, 48 h	
Westphal et al 1987	Prospective, randomized, double blind, dose-finding, placebo-controlled.	27	Post-CABG patients, mechanically ventilated.	Surg	morphine 1-2 mg IV prn; sodium nitroprusside; trimethaphan; dopamine	I - placebo II - 0.023* III - 0.048*	placebo 0.012* 0.024*	8 h	Blood samples: -Before loading dose, then q2h for the first 12 h post-op.

\* Calculated, based on mean weight from publication.

Table VLB-4 Published Pharmacokinetic Studies of Midazolam Continuous Infusion in Surgical Patients: Patients and Methods (Cont.)				
Reference	Assay Method	Analytes	Outcome Analysis Plan	Comments
Driessen et al 1989	HPLC	MDZ and metabolites	-AUC calculated using trapezoid rule. -Elimination half-life calculated using least squares analysis of log concentration-time, using ② least 3 data points/pl. -Total body clearance = total dose/AUC. -Volume of distribution = total body clearance/elimination rate constant.	
Maitre et al 1989	Protein binding in pre-dose plasma by equilibrium dialysis. -GLC with electron capture detection. Lower limit of detection 1 ng/mL	MDZ	Two approaches were used. First approach: -Non-compartmental moment analysis to assess kinetics in each patient. -AUC and AUMC were calculated using trapezoidal rule. -Elimination clearance (CL <sub>e</sub> ), mean residence time (MRT), apparent volume of distribution at steady state (V <sub>ss</sub> ) were obtained. Second approach: -Non-linear regression program NONMEM to obtain average kinetic parameters for the group of patients fitting data to a 2 compartment model and then a 3 compartment model. The authors then selected which model was more appropriate.	
Mathews et al 1987	GLC	MDZ	-Clearance = infusion rate/concentration at steady state. -Terminal slope from least squares regression using log concentration-time data from 2h after infusion stop. -1/2 = log <sub>2</sub> terminal slope	
Miller et al 1994	Gas chromatography with electron capture detection.	Plasma MDZ Plasma α-OH-MDZ Urine α-OH-MDZ	-Non-compartmental analysis. -Linear regression to obtain best log-linear fit to concentration vs. time data and elimination constant k <sub>12</sub> obtained. -AUC by trapezoidal and extrapolation methods. -Vd=total dose MDZ/(AUC x k <sub>12</sub> ). -Total clearance = Total dose/AUC.	
Westphal et al 1987	GC w/ electron capture	MDZ	Steady-state concentration for each pt was mean of concentrations during the infusion period. Clearance = infusion rate/steady state concentration.	No other sedative-hypnotic/or analgesic drugs were given.

Kinetics of Midazolam Infusion After Surgical Procedures									
Reference	Subjects	Age (yrs)	Infusion Dose		Infusion Duration (h)	Elimination t <sub>1/2</sub> (h)	Total Clearance	Volume of Distribution	Concomitant Medications
			Loading Dose (mg/kg)	Maintenance Dose (mg/kg/h)					
Driessen et al 1989	20	mean 23.5	None	0.08* starting with anesthesia	24	mean 2.1 (1.5-5.3)	mean 10.5 mL/min/kg	2.3 L/kg	Pipitranide (n=13)
Maitre et al 1989	12 <sup>1</sup>	mean 64.5 (53-81)	None	0.21*	4	10.6	mean 3.42 mL/min/kg	1.4 L/kg	Nitroglycerin; dopamine, adrenaline, nitroprusside, morphine (pm)
Mathews et al 1987	9 by infusion	56	0.03*	0.03*	mean 16	4.5 (2.0-7.1)	5.58 mL/min/kg		Morphine (pm)
	10 by intermittent bolus	50	0.03*	0.03*	mean 16	5.1 (3.3-7.1)	NR		
	1 pt. in infusion group	55	0.04*	0.04*	16	15.6	3.93 mL/min/kg		
Miller et al 1984	30	50-75	Low: 0.03	Low: optimal, 0.04	mean 16.2	6.2	6.3 mL/min/kg	3.3 L/kg	Morphine, vasoactive agents (pm)
			Medium: 0.05	Medium: optimal, 0.05				3.0 L/kg	
			High: 0.1	High: optimal, 0.08				3.1 L/kg	
					Mean for all groups 6.3	Mean for all groups 5.9 mL/min/kg			
Westphal et al 1987	9	56	0.01*	0.01*	8		mean 5.3 mL/min/kg (2.5-8.6)		Morphine, nitroprusside (pm); trimethaphan (n=4); dopamine (3)
			0.05*	0.024*					
Age						2.8			

Table VIB-8

Kinetics of Midazolam Infusion After Surgical Procedures

Reference <sup>1</sup> Subjects	Age (yrs)	Infusion Dose		Infusion Duration (h)	Elimination t <sub>1/2</sub> (h)	Total Clearance	Volume of Distribution	Concomitant Medications
		Loading Dose (mg/kg)	Maintenance Dose (mg/kg/h)					
IV Injection		[single doses]			(1.8-6.4)			

1 Patients with severe liver or renal disease excluded.  
 2 Patients divided into groups to study effects of epidural versus total intravenous anesthetics.  
 a Calculated, based on mean weight from publication.

Kinetics of Midazolam Infusion in Critically Ill Patients on Mechanical Ventilation									
Reference/Subjects	Age (yrs)	Infusion Dose		Infusion Duration	Elimination t <sub>1/2</sub> (h)	Total Clearance	Volume of Distribution	Concomitant Medications	
		Loading Dose (mg/kg)	Maintenance Dose (mg/kg/h)						
Behne 1987	21-79	None	0.10 <sup>a</sup> (n=10) 0.16 <sup>b</sup> (n=4) (Unknown, n=2)	24h	Calculated 1.5-7.4 (n=6) Estimated 15-50 (n=4)	1.0-21.36 mL/min/kg		Piritramide, thalamandol, opioids, neuroleptics, catecholamines, vasoactive agents, etc.	
Byatt et al 1984	66 <sup>1</sup>	None	0.003-0.045 <sup>a</sup>	144h	19.4			Indotropic support, papaveretum, erythromycin	
	3,6 <sup>2</sup>		0.03-0.34 <sup>a</sup>	96h	8.9			Papaveretum, chloral hydrate, erythromycin	
	56		0.008-0.043 <sup>a</sup>	144h	15.8			Bronchodilators, erythromycin	
Dirksen et al 1987	13-70	0.06 <sup>a</sup>	0.048-0.063 <sup>a</sup>	80-360h	4-12	0.4-5.2 <sup>a</sup> mL/min/kg		Nicomorphine (n=6)	
		2.4 (n=1)	0.6 (n=1)						
Driessen et al 1991	Non-ARF <sup>3</sup> 47.6 (n=33) ARF 62.3 (n=6)	0.07 <sup>a</sup>	Initial: 0.07-0.21 Actual Means: non ARF: 0.16 <sup>a</sup> ARF: 0.14 <sup>a</sup>	mean: 145 (47-477)h  mean: 322 (38-650)h	mean 7.6  mean 13.2 (n=4)	3.0 <sup>a</sup> mL/min/kg  1.8 <sup>a</sup> mL/min/kg	1.6 <sup>a</sup> L/kg  2.1 <sup>a</sup> L/kg	Nicomorphine (n=19), Inotropic agents (14), pancuronium (6), gentamycin (5), H <sub>2</sub> blockers (5)	
Melacrida et al 1992	50 (19-70)	0.23 <sup>a</sup> (over 15 min)	mean: 0.14 <sup>a</sup>	mean: 33.6 (19.2-60)h	mean 5.4 (3.8-7.7)	mean 6.3 mL/min/kg (4.0-9.8)	mean 3.1 L/kg (1.6-4.8)	Morphine (n=6)	
Michalk et al 1988	57 (30-78)	0.2	NA	309h	mean 3.8	5.2 mL/min/kg (calculated <sup>4</sup> )	2.23 L/kg	Phenoperidine, ranitidine	
Odenhof et al 1988	58 range (32-85)	0.06 or 0.12 <sup>a</sup>	0.05-0.1	20-326h	1.4-39.7	1.1-9.1 <sup>b</sup> mL/min/kg	0.7-4.6 L/kg	Narcotic analgesics and/or muscle relaxants (n=16); neuroleptics or diazepam (4)	

**Table VLB-9**  
**Kinetics of Midazolam Infusion in Critically Ill Patients on Mechanical Ventilation**

	Reference <sup>a</sup> Subjects	Age (yrs)	Infusion Dose		Infusion Duration	Elimination t <sub>1/2</sub> (h)	Total Clearance	Volume of Distribution	Concomitant Medications
			Loading Dose (mg/kg)	Maintenance Dose (mg/kg/h)					
Shafer et al 1990	4 case studies	40 <sup>1,2</sup>	0.1 <sup>a</sup>	0.014 <sup>a</sup>	23	16	0.29 mL/min/kg	0.37 L/kg	Dopamine, phenylephrine, diazepam, haloperidol
		68 <sup>1</sup>	0.1 <sup>a</sup>	0.036 <sup>a</sup>	48	26	1.79 mL/min/kg	2.49 L/kg	Dopamine
		33	0.5	0.41 <sup>a</sup>	101	14	2.66 mL/min/kg	2.31 L/kg	Diazepam, morphine, haloperidol
		42	0.1	0.123 <sup>a</sup>	16	15	4.02 mL/min/kg	1.79 L/kg	None
Shelly et al 1987	6 case studies	76 68 <sup>1</sup> 54 62 <sup>1</sup> 60 <sup>1,2</sup>	None	0.035 <sup>a</sup> 0.097 <sup>a</sup> 0.057 <sup>a</sup> 0.054 <sup>a</sup> 0.117 <sup>a</sup>	10 26 143 39 369	2.5 13.9 2.5 18 Not given <sup>a</sup>	Not given <sup>a</sup> 1.8 mL/min/kg 7 mL/min/kg 1 mL/min/kg 0.67 mL/min/kg <sup>a</sup> 8.2 mL/min/kg <sup>10</sup> 0.5 mL/min/kg <sup>10</sup> 1.3 mL/min/kg <sup>11</sup>	Not given <sup>a</sup> 2.23 L/kg 1.51 L/kg High Not given <sup>a</sup> 0.98 L/kg <sup>10</sup> 0.98 L/kg <sup>11</sup>	Morphine, renitidine; dopamine (n=5); other vasoactive agents, misc. other drugs (pm)
Vree et al 1989	16	22-81	0.07 or 0.14 <sup>b</sup>	0.07-0.21 <sup>b</sup>	36-649	2.0-9.4 (Calculated)	0.8-10.3 <sup>b</sup> mL/min /kg	0.4-3.8 <sup>b</sup> L/kg	Nicomorphine, vasoactive agents, misc. other drugs (pm)
Approved labeling for IV injection				[single doses]		2.8 (1.8-6.4)			

1 Pt had renal dysfunction or failure.  
2 Pt had hepatic dysfunction or failure.  
3 ARF = acute renal failure (creatinine clearance < 25 mL/min).  
4 Three pts sedated for 2 courses of treatment and produced 2 sets of data.  
5 Patient not at steady state when infusion discontinued.  
6 No samples during decay period.  
7 Assuming average pt weight of 70 kg.  
8 Clearance on day 4  
9 Clearance on day 14  
10 Pt had first course of midazolam infusion discontinued on day 5.  
11 Second course of midazolam infusion.  
12 Calculated, based on mean weight from publication.  
13 Calculated, based on average weight of 70 kg

## 8. APPENDIX 2; REFERENCES

Arendt RM, Greenblatt DJ, Liebisch DC, Luu MD, Paul SM. Determinants of benzodiazepine brain uptake: lipophilicity versus binding affinity. *Psychopharmacology* 1987;93:72-76.

Crevat-Pisano P, Dragna S, Granthil DC, Coassolo P, Cano JP, Francois G. Plasma concentrations and pharmacokinetics of midazolam during anaesthesia. *J Pharm Pharmacol* 1986;38:578-582.

Driessen JJ, Vree TB, Guelen PJM. The effects of acute changes in renal function on the pharmacokinetics of midazolam during long-term infusion in ICU patients. *Acta Anaesthesiol Belg* 1991;42:149-155.

Driessen JJ, Dirksen MS, Rutten JM, Santman F, van Egmond J, Vree TB. Continuous infusion of midazolam during anaesthesia and postoperative sedation after maxillofacial surgery. *Acta Anaesthesiol Scand* 1989;33(2):116-121.

Dirksen MSC, Vree TB, Driessen JJ. Clinical pharmacokinetics of long-term infusion of midazolam in critically ill patients--preliminary results. *Anaesth Intensive Care* 1987;15(4):440-444.

Miller DR, Martineau RJ, Hull KA, Vallee F, LeBel M. Optimizing sedation following major vascular surgery: a double-blind study of midazolam administered by continuous infusion. *Can J Anaesth* 1994;41(9):782-93.

Oldenhof H, de Jong M, Steenhoek A, Janknegt R. Clinical pharmacokinetics of midazolam in intensive care patients, a wide interpatient variability? *Clin Pharmacol Ther* 1988;43:263-269.

Vree TB, Shimoda M, Driessen JJ, Guelen PJM, Janssen TJ, Termond EFS, van Dalen R, Hafkenscheid JCM, Dirksen MSC.

*Handwritten note:*  $3 - 16/2$

## 8. APPENDIX 2; REFERENCES

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Vree TB, Shimoda M, Driessen JJ, Guelen PJM, Janssen TJ, Termond EFS, van Dalen R, Hafkenscheid JCM, Dirksen MSC.

Chemistry Review #2	1. Division HFD-170	2. NDA Number 18-654
3. Name and Address of Applicant  Hoffmann-La Roche Inc. 340 Kingsland Street Nutley, NJ 07110-1190		4. Supplement Number      Date  SE2 -029/13-Sep.-95  SE2- 030/28-Sep.-95
5. Name of Drug  VERSED Injection (midazolam HCL)	6. Nonproprietary Name Midazolam Hydrochloride	
7. Supplement Provides for:  SE2-029- *provides for continuous intravenous infusion for sedation of intubated, mechanically ventilated adult patients.  SE2-030-provides for intravenous (including continuous infusion) or intramuscularly for sedation of intubated, mechanically ventilated pediatric patients		8. Amendment(s)  9/13/96
9. Pharmacological Category  Anesthetic	10. How Dispensed  Rx	11. Related Documents
12. Dosage Form Injection	13. Potency(ies) 1 mg/ml      and      5 mg/ml	
14. Chemical Name and Structure    see USAN		

**15. Comments**

The applicant has responded to my fax dated Aug. 1, 1996 as follows:

**Comment:** In the communication dated September 13, 1995, Section II Summary of Application, under Simulated Intravenous Infusion, indicate at what temperature this 24 hour data was recorded and clarify the absence of sterility data and pH monitoring. (Include specification limits)

**Response:** Since the purpose of the study was to simulate an intravenous infusion done at ambient room temperature, the experiment was conducted at that condition. The recommended storage temperature for the undiluted product is 59° to 89°F (15° to 30° C).

The pH specification limits for the product are 3.0 - 3.6. There are no specifications for the diluted product in infusion solutions. However, the drug has been shown to be physically and chemically stable up to 24 hours at room temperature when diluted ten-fold in standard unbuffered infusion solutions (0.9% sodium chloride or D 5W). The pH of the diluted solutions through the course of this study was between 3.4 and 3.7

It was not the purpose of this study to monitor sterility. It is expected that the hospital pharmacy follows aseptic techniques for withdrawals, mixing and transfers. In such a situation, maintenance of sterility is dependent on procedures followed by the end user. The manufacturer can only guarantee the sterility of the product being sold based on process validation and compendial release criteria for injectable products.

**Comment:** We call to your attention that the labeling for the reconstituted preparation should contain some indication as to temperature of reconstituted solution.

**Response:** Since the marketed product is labeled for storage at room temperature and dilution and infusion are done at room temperature, we did not feel it necessary to specify the temperature of the diluted solution in the label. However, we will add to the label that the diluted solution can be stored at room temperature, 59° to 89°F (15° to 30° C) for up to 24 hours.

Responses - acceptable

16. Conclusions and Recommendations

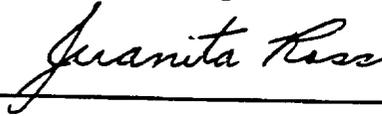
From a chemistry manufacturing and controls standpoint this supplement is acceptable; therefore it is recommended for approval.

17. Name

Signature

Date

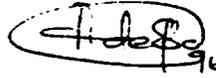
Juanita Ross



9/18/96

Team Leader

Albinus D'Sa



9/18/96

CC:

NDA 18-645/Se2-029, Se2-030

HFD-170/Division File

HFD-170/JMRoss

HFD-170/Morgan

HFD-170/LandowL.

Doc ID: N18654.AnS

Chemistry Review #1	1. Division HFD-170	2. NDA Number 18-654
3. Name and Address of Applicant  Hoffmann-La Roche Inc. 340 Kingsland Street Nutley, NJ 07110-1190		4. Supplement Number      Date  SE2 -029/13-Sep.-95  SE2- 030/28-Sep.-95
5. Name of Drug  VERSED Injection(midazolam HCL)	6. Nonproprietary Name Midazolam Hydrochloride	
7. Supplement Provides for:  SE2-029- * provides for continuous infusion for sedation of intubated, mechanically ventilated patients.  SE2-030- provides for continous infusion for sedation of intubated, mechanically ventilated pediatric patients		8. Amendment(s)
9. Pharmacological Category  Anesthetic	10. How Dispensed  Rx	11. Related Documents
12. Dosage Form Injection	13. Potency(ies) 1 mg/ml      and      5 mg/ml	
14. Chemical Name and Structure    see USAN		

**15. Comments**

1. All approved uses to date have pertained to short-term administration and these supplements are for continuous infusion.
2. No new dosage form of VERSED has been developed for the new indications.
3. In regard to the chemistry aspects of these efficacy supplements, the Midazolam solutions will be diluted to the desired concentrations using 5% Dextrose Injection or 0.9% Sodium Chloride Injection.
4. Compatability data of VERSED with 5% Dextrose and 0.9% Sodium Chloride in PVC bags was submitted as a supplement in the application, S-020, dated Feb. 4, 1991 and approved Sept. 19, 1991. The compatability data submitted at that time showed that Versed Injection, 5 mg/ml, when diluted to a midazolam concentration of 0.5 mg/ml with 5% Dextrose Injection or 0.9% Sodium Chloride is chemically and physically stable for at least 24 hours.

Therefore the VERSED labeling was revised to include this compatability data. See Dosage and Administration section of the package insert.

5. In these current supplements, the applicant has prepared midazolam infusion solutions with PVC tubing to compare its compatability with the tubing. Midazolam infusion solutions were made up at midazolam concentrations of 0.3 mg and 0.5 mg/ml diluted with 5% Dextrose and 0.9% Sodium Chloride. The concentration of midazolam was assayed over a 24 hour period using a stability-indicating HPLC method and the data recorded is within the specification limits of 90%-110%.  
SEE data in supplement S-029.

**16. Conclusions and Recommendations:**

The following questions were faxed to the applicant:

1. In the communication dated September 13, 1995, Section II, Summary of the Application, under Simulated Intravenous Infusion, indicate at what temperature this 24 hour data was recorded and clarify the absence of sterility data and pH monitoring. (include specification limits)
2. We call to your attention that the labeling for the reconstituted preparation should contain some indication as to temperature of the reconstituted solution.

17. Name	Signature	Date
Juanita Ross	<i>Juanita Ross</i>	Jul. 26, 1996
18. Team Leader: Albinus D'Sa	<i>Albinus D'Sa</i>	9/18/96

CC:

NDA 18-654  
HFD-170/Division File  
HFD-170/JMRoss  
HFD-170/Morgan  
Doc ID: N18654.2 SU

TO: Ms. Margaret Jack  
Senior Manager

FROM: Ms. Juanita Ross  
Review Chemist

SUBJECT: NDA 18654/SE2-029 and SE2-030  
Versed (midazolam HCL)

In the communication dated September 13, 1996, Section II Summary of Application, under Simulated Intravenous Infusion, indicate at what temperature this 24 hour data was recorded and clarify the absence of sterility data and pH monitoring. ( Include specification limits)

We call to your attention that the labeling for the reconstituted preparation should contain some indication as to temperature of reconstituted solution.

## Midazolam Dosing

The instructions for dosing midazolam are complex, and internally inconsistent, reflecting the divergent data sources. The review team has tried to synthesize the data from: the pediatric literature, the existing label, current anesthetic practice, the PK analysis, and the studies in adults and children in the supplement, including the flumazenil study.

### We define four distinct patient populations:

Elderly, debilitated and/or medicated adults (responsible for early MDZ casualties)

Healthy adults and children age 6 and older (most tolerant group)

Children one month to five years of age (at risk population)

Neonates and premature children (24 weeks EGA to 44 weeks EGA)

### We define three distinct practice settings:

Premedication and Conscious Sedation (Patients are in areas where they are monitored, and may be resuscitated, but full life support may not be available)

Anesthesia and Monitored Anesthesia care (Patients are under the continuous observation of a practitioner able by training and equipment to provide age and size appropriate full life support).

ICU Sedation: Sedation in an environment able to provide monitoring, resuscitation and frequent dosage adjustment on an individual basis.

### We believe four things to be true:

1. Children under age 6 require larger doses for sedation and require full life support to be available to be safely sedated. They cannot be safely sedated with less.
2. Alcoholic or benzodiazepine tolerant patients may require larger doses.
3. Doses must be adjusted to Ideal Body Weight for the morbidly obese (> 30% over Ideal Body Weight).
4. Patients who have received other drugs require lower midazolam doses

### Using these ideas we have the following proposed dosing scheme:

	Old/Sick & Medicated	Adults and Children >6	Children <6	Neonates & Premature
Premedication & Conscious Sedation	1-3.5 mg/70-kg 0.15-0.5 mg/kg	2-5 mg/70kg 0.3-0.7 mg/kg	Unsafe	NA
Anesthesia and MAC	1-10 mg/70kg 0.15-0.15 mg/kg	2-20 mg/70kg 0.03-0.30 mg/kg	3-30 mg/70kg 0.045-0.45 mg/kg	NA
ICU Infusions (to start)	0.015 mg/kg/hr	0.030 mg/kg/hr	0.060 mg/kg/hr	0.03 mg/kg/hr* 0.060 mg/kg/hr**

\* Under 32 weeks

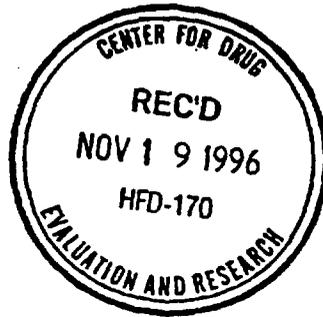
\*\* over 32 weeks

Do you agree? Do you have suggestions?



**Roche Pharmaceuticals**

A Member of the Roche Group



Hoffmann-La Roche Inc.  
340 Kingsland Street  
Nutley, New Jersey 07110-1199

Direct Dial (201) 812-3719  
Fax (201) 812-3700/3554

November 18, 1996

Food and Drug Administration  
Division of Anesthetic, Critical Care and  
Addiction Drug Products, HFD-170  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research  
ATTN.: DOCUMENT CONTROL ROOM 9B-30  
5600 Fishers Lane  
Rockville, Maryland 20857-1706

Re: **NDA 18-654**  
**VERSED® (midazolam HCl) Injection**  
**Supplement 030**

Reference is made to the approvable letter from the Agency for Supplement 030 dated September 18, 1996 and to the meeting with the Division held on October 10, 1996 to discuss various issues related to the labeling of VERSED for the pediatric indications. Reference is also made to the introduction and list of questions to be discussed at the Anesthetic and Life Support Pediatric Subcommittee Meeting regarding labeling of parental VERSED (Midazolam) for use in pediatric patients scheduled for December 18, 1996.

In preparation for the Advisory Committee meeting and in response to a request by the Agency, the sponsor has discussed these labeling issues with consultants, and has revised the VERSED label to address all the issues raised by the Division in their review of Supplement 030. This revised labeling is provided in Appendix A of this submission. This labeling is a composite label for Supplements 018 (pharmacokinetics) and 029 (adult continuous infusion) as well as Supplement 030 (pediatric indications). In the sponsor's opinion, the revised label included in this submission will provide for the safe and effective use of VERSED in adult and pediatric patients.

The issues for discussion at the December 18 Advisory Committee meeting which are also addressed in this revised label include:

1. Definition of terms with respect to sedation
2. Labeling of VERSED for use in neonates
3. Monitoring
4. IV Access
5. Dosing Guidelines for Pediatrics

**DUPLICATE**



### 1. Definition of Terms With Respect to Sedation:

In the previous VERSED label, terms such as conscious sedation and preoperative sedation were used to describe the pharmacological response to the administration of VERSED when in fact sedation, anxiolysis and amnesia are the targeted endpoints of VERSED administration. These terms were somewhat confusing to the medical community because a clear consensus on the definition of these terms does not exist. However sedation is viewed by medical professionals as a continuum where patients may move easily from light to deep sedation with the potential loss of protective reflexes. For this reason sedatives should be titrated and continuous monitoring of respiratory and cardiac function is required. In order to more clearly communicate the pharmacological effects of VERSED, the terms conscious sedation and preoperative sedation have been replaced with sedation/anxiolysis/amnesia and the need for continuous monitoring is reinforced throughout this revised label. A new MONITORING subsection was added to the DOSAGE AND ADMINISTRATION section which also includes a beginning paragraph discussing the definition of sedation.

### 2. Labeling VERSED for Use in Neonates

This label clearly attempts to present the risks of VERSED administration in this population so that the medical professional may assess the benefits versus the risks. The BOXED WARNING now includes a neonate subsection addressing the risks of rapid bolus administration and the potential for severe hypotension and seizures in this population. Other sections of the label which address the use of VERSED in neonates include CLINICAL PHARMACOLOGY: Pharmacokinetic subsection; WARNINGS: Usage in Preterm Infants and Neonates subsection; PRECAUTIONS: Pediatric Use subsection; ADVERSE REACTIONS: Neonates subsection and DOSAGE AND ADMINISTRATION: Usual Neonatal Dose subsection.

The CONTRAINDICATIONS section also now includes a contraindication concerning rapid bolus injection in all populations.

In addition the Agency previously requested if the dosing recommendations for neonates was based on a limited number of patients (24) included in an article by Jacqz-Aigrain and if there were additional data such as population kinetics available in neonates. A response to these inquiries prepared by Dr. Charles Cote and Dr. Helen Karl is presented in Appendix B.

### 3. Monitoring

This revised VERSED labeling reinforces the continuous monitoring of all patients. Specifically the BOXED WARNING includes a statement as per the "Practice Guidelines on Sedation and Analgesia for non-Anesthesiologists" by the American Society of Anesthesiologists Task Force published in Anesthesiology, Volume 8, Feb. 1996, page 459. In addition the WARNINGS, PRECAUTIONS and the DOSAGE AND ADMINISTRATION sections of the VERSED label also include monitoring recommendations for patients receiving VERSED. These latter monitoring recommendations are also in accord with the American Academy of Pediatrics "Guidelines for Monitoring and Management of Pediatric Patients During and After Sedation for Diagnostic and Therapeutic Procedures" published in Pediatrics Volume 89, June 1992. In the latter section of the VERSED label a MONITORING subsection has been added addressing continuous monitoring in all patients.



Division of Anesthetic, Critical Care and  
Addiction Drug Products. HFD-170  
November 18, 1996  
Page 3

#### 4. IV Access

The need for intravenous access is discussed in the OVERDOSAGE section of the VERSED label as well as in the new MONITORING subsection of the DOSAGE AND ADMINISTRATION section. These recommendations are also made in accordance with the American Academy of Pediatrics and their guideline entitled, "Guidelines for Monitoring and Management of Patients During and After Sedation for Diagnostic and Therapeutic Procedures" published in Pediatrics Volume 89, June 1992.

#### 5. Dosing Guidelines for Pediatrics

The DOSAGE AND ADMINISTRATION section of the label have been revised with respect to the pediatric dosing guidelines. Specifically an upper limit for the IM dose of 10 mg is now included in the dosing guidelines. When VERSED is administered intravenously by intermittent injection to pediatric patients, doses based on the age and weight of the patient are presented in the label along with a maximum recommended dose. This maximum recommended dose is 6 mg for patients 6 mo. to 5 yrs. age group and 10 mg for pediatric patients 6 years of age and older.

It is the opinion of the sponsor that the revised label presented in Appendix A addresses all the concerns raised by the Agency during their review of Supplement 030 and will provide for the safe and effective use of VERSED in all targeted populations including pediatric and neonatal patients. Please note that the issue concerning benzodiazepines and glaucoma discussed at the October 10 meeting has not been resolved yet in the VERSED label. We are currently evaluating all the published and unpublished data available on this topic and will revise the applicable statements in the label at a later date.

We understand that the Advisory Committee meeting will be discussing pediatric labeling only and not Supplements 018 and 029. In addition we would like to remind the Agency that we are still awaiting the final approval of Supplement 029 which the Agency agreed to complete before the resolution of the labeling issues for the pediatric supplement.

If you have any questions concerning this submission, please contact the undersigned by phone at 201-812-3719 or via fax at 201-812-3700 or 3554.

Sincerely,

HOFFMANN-LA ROCHE INC.

Margaret J. Jack  
Program Director  
Drug Regulatory Affairs

MJJ/gsm  
Attachments  
HLR No. 1996-2226

Department of Health and Human Services Food and Drug Administration <b>APPLICATION TO MARKET A NEW          DRUG, BIOLOGIC, OR AN          ANTIBIOTIC DRUG FOR HUMAN USE</b> Title 21, Code of Federal Regulations, Parts 314 & 601.		<b>FOR FDA USE ONLY</b> Application Number	
<b>APPLICANT INFORMATION</b>			
Name of Applicant <b>Hoffmann-La Roche Inc.</b>		Date of Submission November 18, 1996	
Telephone Number ( Include Area Code ) (201) 812-3719		Facsimile (FAX) Number ( Include Area Code ) (201) 812-3700/3554	
Applicant Address (Number, Street, State, Country, and Zip Code or Mail Code): Hoffmann-La Roche Inc. 340 Kingsland Street Nutley, NJ 07110-1199		Authorized U.S. Agent, name & Address (Number, Street, State, and Zip Code telephone & FAX Number) if applicable Margaret J. Jack Hoffmann-La Roche Inc. 340 Kingsland Street, Bldg. 719/4 Nutley, NJ 07110-1199	
NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE NUMBER (if previously issued) 18-654			
<b>PRODUCT DESCRIPTION</b>			
Established Name (e.g., Proper name, USP/USAN name) midazolam hydrochloride		Proprietary Name (trade name) if any VERSED	
Chemical/Biochemical Name (if any)		Code Name (if any) Ro 21-3981	
Dosage Form: vial	Strengths: 5 mg/ml and 1 mg/ml	Route of Administration: I.V. and I.M.	
Proposed Indications for Use: Sedation via continuous infusion and sedation of pediatric patients			
<b>APPLICATION INFORMATION</b>			
APPLICATION TYPE (check one) <input type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50) <input type="checkbox"/> ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGIC APPLICATION (21 CFR part 601)			
IF A NDA, IDENTIFY THE APPROPRIATE TYPE <input type="checkbox"/> 505 (b)(1) <input type="checkbox"/> 505 (b)(2) <input type="checkbox"/> 507			
IF AN ANDA, or AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION			
Name of Drug		Holder of Approved Application	
TYPE OF SUBMISSION (check one) <input type="checkbox"/> Original Application <input checked="" type="checkbox"/> Amendment to a Pending Application <input type="checkbox"/> Resubmission <input type="checkbox"/> Presubmission <input type="checkbox"/> Notification <input type="checkbox"/> Establishment Description Supplement <input type="checkbox"/> SUPAC Supplement <input type="checkbox"/> Efficacy Supplement <input type="checkbox"/> Labeling Supplement <input type="checkbox"/> Chemistry, Manufacturing & Controls Supplement			
REASON FOR SUBMISSION Provide revised draft labeling for Supplement 030			
PROPOSED MARKETING STATUS (Check one) <input type="checkbox"/> Prescription Product (Rx) <input type="checkbox"/> Over-The-Counter Product (OTC)			
Letter		This application is <input checked="" type="checkbox"/> Paper <input type="checkbox"/> Paper and Electronic	
Number of Volumes Submitted			
<b>ESTABLISHMENT INFORMATION</b>			
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.			
Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs and DMFs referenced in the current application)			

MJJ/gsm

HLR No. 1996-2226

This submission contains the following items (check all that apply)

	1. Index
x	2. Labeling (check one) <input checked="" type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
	3. Summary (e.g. 21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing and control information (e.g. 21 CFR 314.50 (d)(1))
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (1))
	5. Nonclinical pharmacology and toxicology section (e.g 21 CFR 314.50 (d) (2))
	6. Human pharmacokinetics and bioavailability section (e.g 21 CFR 314.50 (d) (3))
	7. Clinical Microbiology (e.g 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g 21 CFR 314.50 (d) (5))
	9. Safety update report (e.g 21 CFR 314.50 (d) (5) (vi) (b))
	10. Statistical section (e.g 21 CFR 314.50 (d) (6))
	11. Case report tabulations (e.g 21 CFR 314.50 (f) (1))
	12. Case report forms (e.g 21 CFR 314.50 (f) (1))
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. Establishment description ( 21 CFR Part 600, if applicable )
	16. Debarment certification
	17. Field copy certification
	18. User Fee Cover Sheet ( Form FDA 3397 )
x	19. Other (Specify) Provide revised labeling as requested by the Division

**CERTIFICATION**

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to, the following:

1. Good manufacturing practice regulations in 21 CFR 210, 211, 606 and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610 and/or 609.
4. In the case of a prescription drug product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72 and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the controlled substance act, I agree not to market the product until the drug enforcement administration makes a final scheduling decision.

The data and information in this submission have been reviewed and are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

Signature of responsible official or agent <i>Margaret Jack</i>	Typed name and title Margaret J. Jack Program Director Drug Regulatory Affairs	Date November 18, 1996
--	---	---------------------------