6. SIGN-OFF

Reviewed by: .....

Peter Lockwood, MS; Thursday, August 15, 1996
Pharmacokineticist

Draft; Initialed by; .....

Dale Conner PharmD, Thursday, August 15, 1996

Distribution:
HFD-170/DIV/File
HFD-170 NDA 18-654; S29 (Original Copy)
HFD-170/CSO/Millie Wright
HFD-205 FOI
HFD-870 ML Chen/ Chron/Drug Review

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)		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	0.07	0.035	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	5	-Healthy, drug-free male volunteers. -Age range 26-42. -Weight range 66-82 kg.	None	0.05	0.025	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.	0.05 (over 30 s)	0.025	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 26-42. -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 5h after MDZ infusion start.	0.07	0.025-0.040	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, 5.25, 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.		NA 0.13[a] (over 15 s)	Continuously variable according to target plasma level. Total dose 35.5 mg. [0.36][1]	1 h	-10 min. before infusion start. -10, 20, 30, 40, 50, 60, 62, 65, 67, 70, 75, 80, 90, 105, 120, 135, 150, 180, 210, 240 min. After infusion start.

a Calculated, based on mean weight from publication.
1 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)		
									6, 12, 24 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 Dosing[a]: 0.03 0.03ptimal: 0.04 Med. Dosing[a]: 0.06 0.06ptimal: 0.05 High Dosing[a]: 0.09 0.0ptimal: 0.08	<24h mean 16.2h	-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[a] III - 0.048[a]	placebo 0.012[a] 0.024[a]	6 h	Blood samples: -Before loading dose, then q2h for the first 12 h post-op.

[a] Calculated, based on mean weight from publication.

Table VI-B-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 @ least 3 data points/pt. -Total body clearance = total dose/AUC. Volume of distribution = total body clearance/elimination rate constant.	
Meitre 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 (CLe), mean residence time (MRT), apparent volume of distribution at steady state (V_{ss}) 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. -$t_{1/2}$ = $\log_e 2$/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_el obtained. -AUC by trapezoidal and extrapolation methods. -Vd=total dose MDZ/(AUC x k_el). -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.

Table VI-B-5

Kinetics of Midazolam Infusion After Surgical Procedures

	Refereed Subjects	Age (yrs)	Infusion Dose		Infusion Duration (h)	Elimination t½ (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	0.06[a] starting with anesthesia	24	mean 2.1 (1.5-5.3)	mean 10.5 mL/min/kg	2.3 L/kg	Piritramide (n=13)
Maitre et al 1989	12[1]	mean 64.5 (53-81)	None	0.21[a]	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	58	0.03[a]	0.03[a]	mean 18	4.5 (2.0-7.1)	5.58 mL/min/kg		Morphine (pm)
	10 by intermittent bolus	50	0.03[a]	0.03[a]	mean 18	5.1 (3.3-7.1)	NR		
	1 pt. in infusion group	55	0.04[a]	0.04[a]	16	15.6	3.93 mL/min/kg		
Miller et al 1994	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		6.2	5.9 mL/min/kg	3.0 L/kg	
			High: 0.1	High: optimal. 0.08		6.5	5.7 mL/min/kg	3.1 L/kg	
						Mean for all groups 6.3	Mean for all groups 5.9 mL/min/kg	Mean for all groups 3.1 L/kg	
Westphal et al 1987	9	56	0.01[a]	0.01[a]	8		mean 5.3 mL/min/kg (2.5-6.6)		Morphine, nitroprusside (pm); trimethaphan (n=4); dopamine (3)
	9	62	0.05[a]	0.024[a]	8		mean 4.8 mL/min/kg (4.1-7)		
App[illegible]oling for						2.6			

Hoffmann-La Roche, Inc. – VERSED®

NDA 18,654

Table VI-B-8

Kinetics of Midazolam Infusion After Surgical Procedures

	Reference Subjects	Age (yrs)	Infusion Dose		Infusion Duration (h)	Elimination t½ (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.

Table VI-B-9

Kinetics of Midazolam Infusion in Critically Ill Patients on Mechanical Ventilation

	Referenced Subjects	Age (yrs)	Infusion Dose		Infusion Duration	Elimination t½ (h)	Total Clearance	Volume of Distribution	Concomitant Medications
			Loading Dose (mg/kg)	Maintenance Dose (mg/kg/h)					
Behne 1987	16	21-79	None	0.10[a] (n=10) 0.16[a] (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		Pirlramide, thalamanol, opioids, neuroleptics, catecholamines, vasoactive agents, etc.
Byatt et al 1984	3 case studies	68[1]	None	0.003-0.045[a]	144h	19.4			Inotropic support, papaveretum, erythromycin
		3.8[2]		0.03-0.34[a]	96h	8.9			Papaveretum, chloral hydrate, erythromycin
		56		0.008-0.043[a]	144h	15.8			Bronchodilators, erythromycin
Dirksen et al 1987	8	13-70	0.06[a]	0.048-0.063[a]	80-360h	4-12	0.4-5.2[a] mL/min/kg		Nicomorphine (n=6)
			2.4 (n=1)	0.6 (n=1)					
Driessen et al 1981	39	Non-ARF[3] 47.6 (n=33)	0.07[a]	Initial: 0.07-0.21 Actual Means: non ARF: 0.18[a]	mean: 145 (47-477)h	mean 7.6	3.0[a] mL/min/kg	1.6[a] L/kg	Nicomorphine (n=19), inotropic agents (14), pancuronium (8), gentamycin (5), H_2 blockers (5)
		ARF 62.3 (n=6)		ARF: 0.14[a]	mean: 322 (38-650)h	mean 13.2 (n=4)	1.8[a] mL/min/kg	2.1[a] L/kg	
Melacrida et al 1992	6	50 (19-70)	0.23[a] (over 15 min)	mean: 0.14[a]	mean: 33.6 (19.2-60)h	mean 5.4 (3.8-7.7)	mean 6.3 mL/min/kg (4.0-8.8)	mean 3.1 L/kg (1.6-4.8)	Morphine (n=6)
Michalk et al 1988	9	57 (30-78)	0.2	NA	309h	mean 3.8	5.2 mL/min/kg (calculated*)	2.23 L/kg	Phenoperidine, ranitidine
Oldenhof et al 1988	17[4]	58 range (32-85)	0.06 or 0.12[a]	0.05-0.1	20-326h	1.4-39.7	1.1-9.1[b] mL/min/kg	0.7-4.6 L/kg	Narcotic analgesics and/or muscle relaxants (n=16); neuroleptics or diazepam (4)

Table VI-B-9

Kinetics of Midazolam Infusion in Critically Ill Patients on Mechanical Ventilation

	Reference/ Subjects	Age (yrs)	Infusion Dose		Infusion Duration	Elimination t½ (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[1,2]	0.1[5]	0.014[5]	23	16	0.29 mL/min/kg	0.37 L/kg	Dopamine, phenylephrine, diazepam, haloperidol
		68[1]	0.1[5]	0.036[5]	48	26	1.79 mL/min/kg	2.49 L/kg	Dopamine
		33	0.5	0.41[4]	101	14	2.66 mL/min/kg	2.31 L/kg	Diazepam, morphine, haloperidol
		42	0.1	0.123[3]	16	15	4.02 mL/min/kg	1.79 L/kg	None
Shelly et al 1987	6 case studies	76	None	0.035[5]	10	2.5	Not given[6]	Not given[6]	Morphine, ranitidine; dopamine (n=5); other vasoactive agents, misc. other drugs (pm)
		68[1]		0.097[5]	26	13.9	1.8 mL/min/kg	2.23 L/kg	
		54		0.057[5]	143	2.5	7 mL/min/kg	1.51 L/kg	
		62[1]		0.054[4]	39	18	1 mL/min/kg	High	
		60[1,3]		0.117[5]	369	Not given[6]	0.67 mL/min/kg[6]	Not given[6]	
							8.2 mL/min/kg[6]		
		76[1,3]		0.077[4]	159	21[10]	0.5 mL/min/kg[10]	0.88 L/kg[10]	
						7.8[11]	1.3 mL/min/kg[11]	0.98 L/kg[11]	
Vree et al 1989	18	22-81	0.07 or 0.14[b]	0.07-0.21[b]	36-649	2.0-9.4 (Calculated)	0.8-10.3[b] mL/min /kg	0.4-3.8[b] 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 (creatine 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.
p Calculated, based on mean weight from publication.
b Calculated, based pm 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.

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.

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 intravenius infusion for sedation of intubated, mechanically ventilated adult patients. SE2-030-provides for intravenous (including continous 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 ([redacted]% 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	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% Dectrose 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 compatabilty 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 Simlulated 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	Juanita Ross	Jul. 26,1996
18. Team Leader: Albinus D'Sa		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 synthsize 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?

NDA SUPPL AMEND
SE2-030 (AL)

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