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APPLICATION NUMBER:NDA 20-942

PHARMACOLOGY REVIEW(S)

Review and Evaluation of Pharmacology/Toxicology Data
Division of Anesthetic, Critical Care & Addiction Drug Products
HFD-170/Kathleen Haberny

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Information to sponsor Yes (✓) No ()

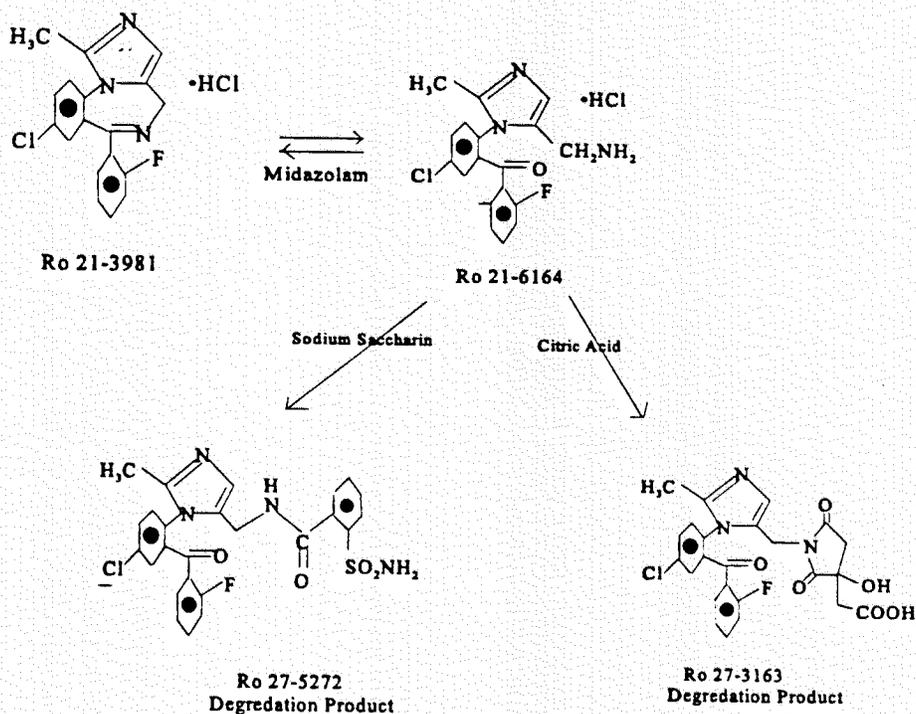
Sponsor: Hoffmann-La Roche Inc., 340 Kingsland Street, Nutley, NJ 07110-1199

Manufacturer: Hoffman-La Roche Inc., 340 Kingsland Street, Nutley, NJ 07110-1199
F. Hoffmann-La Roche Ltd., Basle, Switzerland CH-4070

Drug Name: Versed® (midazolam hydrochloride)

Chemical Name: 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine hydrochloride

Structure:



NDA 20-942

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Molecular Weight: 362.25

Relevant INDs/NDAs/DMFs: IND NDA 18-654

Drug Class: Benzodiazepine central nervous system depressant

Indication: Sedation, anxiolysis and amnesia prior to diagnostic, therapeutic or endoscopic procedure or before induction of anesthesia in pediatric patients

Note: Portions of this review were excerpted directly from the sponsor's submission.

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Clinical Formulation (and components):

Component	Amount (g/100 ml)	
	Pre-clinical Studies	Clinical Formulation
Ro 21-3981/000 (de novo) (Midazolam, lot #C-185136)	0.200	0.200
✓ Sorbitol solution (70% w/w)		
✓ Glycerin		
✓ Disodium Edetate		
✓ Sodium Benzoate		
✓ Sodium Saccharin		
✓ Citric Acid, Anhydrous		
✓ Sodium Citrate		
✓ D&C Red #33		
✓ Artificial cough syrup flavor or Tutti-Frutti flavor #134813		
✓ Artificial bitterness modifier		
✓ Hydrochloric Acid		
✓ Purified water qs to 100 ml		

Route of Administration: Oral**Studies Reviewed within this Submission:**

Midazolam Syrup (Ro 21-3981): An Acute (Single Dose) Oral (Intubation) Toxicity Study in Two-Week Old Rats Followed by a Two-Week Observation Period (Study No. 06827). Research Report No. N-138782.

Midazolam Syrup (Ro 21-3981): A Two-Week Oral (Intubation) Toxicity Study in Two-Week Old Rats (Study No. 06958). Research Report No. N-139383.

The remaining portion of this review summarizes information provided in published literature reports on midazolam, in Micromedex Inc. (TOMES Plus®) Vol. 34 (1987-1997), previously reviewed studies submitted under NDA 18-654 and studies conducted under IND

Introduction/Drug History:

Midazolam is a short acting benzodiazepine sedative-hypnotic, approved for intramuscular and intravenous administration in adult and pediatric patients prior to diagnostic, therapeutic and endoscopic procedures, and prior to general anesthesia. Oral midazolam (Dormicum®) tablets have been used in the treatment of insomnia in adults since 1986 outside the United States, and

for the prevention of night terrors in children. This application is for an oral syrup midazolam formulation for preoperative sedation in pediatric patients.

In adults, the recommended therapeutic intravenous dose for conscious sedation is 10-10.5 mg up to age 45, decreasing to 7-7.5 mg at ages 55-64, 5-5.5 mg at ages 65-74, 3.6 mg at ages 75-84 and 2.3 mg at ages 85 and above. Intramuscular midazolam, at approximately 5 mg up to age 60 and 1-3 mg at ages over 60 years, is used for preoperative sedation and anxiolysis. Pediatric patients have required higher doses than adults, on a mg/kg basis. The recommended intramuscular doses in children are 0.1-0.15 mg/kg IM (not to exceed 10 mg total dose) for sedation. For intermittent IV administration in children, the recommended doses are 0.05-0.1 mg/kg (up to 0.6 mg/kg total dose) at ages 6 months to 5 years, 0.025-0.05 mg/kg (up to 0.4 mg/kg or 10 mg) at ages 6-12 years, and the adult dose at ages 12-16. The proposed pediatric oral VERSED® dose is 0.5 mg/kg up to a maximum dose of 20 mg. Younger patients may require higher doses of up to 1.0 mg/kg at ages 6 months to 6 years, and older pediatric patients (up to 16 years of age) may require lower doses of 0.25 mg/kg.

The pharmacology, toxicity and efficacy of midazolam, in parenteral and oral form, are well known. Oral midazolam in the proposed formulation, has been administered to more than 480 pediatric patients by the sponsor. Additionally, more than 3000 pediatric patients received oral midazolam in studies reported in the literature.

PHARMACOLOGY

Midazolam pharmacologic effects include anxiolysis, sedation, hypnosis, skeletal relaxation and anticonvulsant effects. Oral midazolam has also produced partial or complete amnesia of surgical experience. Midazolam anxiolytic, sedative and hypnotic effects are mediated by inhibition of gamma-aminobutyric acid (GABA) neurotransmission at the limbic, thalamic and hypothalamic levels of the central nervous system (CNS). Skeletal relaxation is produced by inhibition of spinal polysynaptic and monosynaptic afferent pathways, blockade of excitatory synaptic transmission and depression of motor nerve and muscle function. The anticonvulsant activity of midazolam is mediated by inhibition of the spread of seizure activity.

SAFETY PHARMACOLOGY

Vital Functions: Midazolam increased heart rate in female renal hypertensive dogs at doses of 0.3-10 mg/kg IV. Blood pressure was decreased transiently by 20-55 mm Hg in barbiturate and chloralose anesthetized dogs given midazolam maleate at 4-20 mg/kg IV. Midazolam respiratory effects were decreased (30%) minute volume of respired air in the same dogs. There were no effects on ECG.

Drug interactions: Midazolam bioavailability was increased with cimetidine or ranitidine administration. Midazolam potentiated the respiratory depressant effects of CNS depressants (e.g., opiates, barbiturates, alcohol, other anesthetics) and antagonized the cardiovascular stimulatory effects and delirium associated with ketamine administration. In pigs, midazolam (0.06 mg/kg IV) delayed the onset of bupivacaine-induced (2 mg/kg/min) ventricular dysrhythmias, seizures and increased blood pressure and heart rate, but not the bupivacaine dose required to produce cardiovascular collapse. Aminophylline inhibited the sedative effect of midazolam. Midazolam has shown no interactive effects with the neuromuscular blockade

induced by succinylcholine or pancuronium. There was a greater than additive effect when midazolam was combined with alcohol in rats, due to the effects of alcohol on midazolam binding (potentiation at the benzodiazepine receptor). Valproate increased midazolam brain levels in rabbits by displacing plasma binding sites. Midazolam suppressed paraoxon-induced seizures in male Sprague-Dawley rats. In the sciatic nerve-tibialis anterior muscle preparation of the anesthetized cat, midazolam (0.3 mg/kg IV) enhanced vecuronium and pancuronium induced 50% neuromuscular block. Midazolam at an initial loading dose of 3 mg/kg given over 20 minutes followed by continuous infusion of 21 μ g/kg/min for 5 hours potentiated enflurane anesthesia, reducing the EC50 for enflurane (concentration required to oppose responding to noxious stimulation by tail clamping, in 50% animals) by 55% in mongrel dogs. No interaction with the Ca²⁺ channel antagonist nitrendipine has been demonstrated. Nitrous oxide did not alter midazolam induced decreases in cerebral blood flow in rats. The hypnotic effects of midazolam were potentiated by alfentanil at low doses (15 μ g/kg) in man. Midazolam induced interference with motor performance was antagonized by Ro 15-1788 and CGS 8216. Midazolam antagonized soman induced seizures and neuronal degeneration in the entorhinal cortex, caudate nucleus, and hippocampus in monkeys. In male Sprague-Dawley rats, midazolam (2.5 mg/kg IV) antagonized lidocaine (15.2 mg/kg IV) induced convulsions but not mortality. Midazolam decreased the dose of thiopentone required to produce anesthesia in patients undergoing minor elective surgery.

PHARMACOKINETICS/ADME

In animals, absorption of intramuscular (IM) midazolam is rapid and nearly complete (90%). The onset of action of IM midazolam is approximately minutes, with maximal effects at minutes and the duration of action is approximately 2 hours (range hours). After intramuscular administration of 2.5 mg midazolam HCL, the maximum plasma concentration (C_{max}) reaches 200 ng/ml (range ng/ml) at approximately 45 minutes (T_{max}). Oral midazolam is rapidly absorbed, with a T_{max} of approximately 1 hour.

In animals, midazolam given intravenously is widely distributed. The highest concentrations were found in the liver, kidneys, lungs, fat, and heart. At physiologic pH, midazolam is highly lipophilic, and crosses the blood-brain-barrier and placenta. At 0.075 mg/kg IV, the half-life is 68 minutes, the apparent V_d is 0.23 l/kg, and clearance is approximately 13 ml/kg/min.

Midazolam is extensively metabolized in the liver by hydroxylation to the pharmacologically active, but less potent 1-hydroxymethylmidazolam and 4-hydroxymidazolam. A small fraction of 1-hydroxymethylmidazolam is hydroxylated to the non-active metabolite 1-hydroxymethyl-4-hydroxymidazolam. The hydroxylated forms undergo glucuronidation to form conjugates that are eliminated primarily by the kidney. Midazolam excretion occurs as conjugated metabolites (45-57% total dose as 1-hydroxymethylmidazolam, small amounts of conjugated 4-hydroxymidazolam and 1-hydroxymethyl-4-hydroxymidazolam, and <0.03% as unchanged drug).

In humans, oral midazolam is rapidly absorbed, with an onset of action of 10 minutes and duration of action of approximately 30-45 minutes. The short duration of action is predominantly due to the high metabolic clearance and rapid rate of elimination. Midazolam is widely distributed, with an apparent volume of distribution (V_d) of 0.8-2.5 l/kg (range l/kg). The time to maximum plasma concentration (T_{max}) is hours, and the estimated oral midazolam bioavailability is approximately 24%-49% (after 7.5-15 mg), in adult patients. The

Tmax in pediatric patients (ages 6 mo-<16y) for midazolam syrups is approximately 0.17-2.65h after a dose of 0.25-1.0 mg/kg. The absolute bioavailability of VERSED is 36%. Midazolam is highly protein bound (95%-97% in adults and children over 1 yr) to albumin.

In man, midazolam undergoes hepatic metabolism by α -hydroxymidazolam (active metabolite), which is then glucuronidated. α -hydroxymidazolam glucuronide is excreted renally (63%-80%). Other metabolites, 4-hydroxy (3% dose) and 1,4-dihydroxy (1% dose), are also excreted in urine. There is little fecal elimination (approximately 2-10% oral dose). The elimination half-life is 1.4-4.9 h, the apparent clearance is 0.87-2.4 L/kg in adults, and the elimination half-life for VERSED is 2.22-6.83 h after 0.25-1.0 mg/kg PO in children 6mo-<16y. The mean clearance in pediatric patients is approximately 1.0-4.5 L/kg after oral administration. The efficacy of oral and IV midazolam are similar at similar plasma concentrations of combined midazolam and α -hydroxymidazolam. The level of sedation induced by midazolam has been found to be correlated to plasma concentration. The elimination half-life was increased and clearance decreased, and therefore bioavailability was increased in elderly males. However, there was no difference in volume of distribution (Vd) with age in that study. Further, there were no differences in pharmacokinetic parameters with regard to age in females. The Vd and $t_{1/2}$ (elim) increased in obese patients, but no differences were found for Cl or bioavailability.

Mean pharmacokinetic parameters in pediatric patients (reproduced from the Draft Package Insert, NDA 20-942): Midazolam pharmacokinetics are linear from 0.25-1.0 mg/kg (up to 40 mg) within and across age groups from 6 mo to <16 yrs. Absolute bioavailability was 36% and was not affected by pediatric age or weight. The AUC_{0-∞} ratio for α -hydroxymidazolam:midazolam was higher after oral than after IV treatment in children, and higher in children than in adults.

Age Group	Dose VERSED® (mg/kg)	Tmax (h)	Cmax (ng/ml)	t _{1/2β} (h)	AUC _{0-∞} (ng.h/ml)	Vd _{B/F} (l/kg)	Cl/F (ml/min/kg)
6m-<2y	0.25 (n=1)	0.17	28	5.82	68	30.7	62
	0.50 (n=1)	0.35	66	2.22	152	10.2	53
	1.00 (n=1)	0.17	61	2.97	224	19.1	75
2y-<12y	0.25 (n=18)	0.72	63	3.16	138	9.6	40
	0.50 (n=18)	0.95	126	2.71	306	8.1	37
	1.00 (n=18)	0.88	201	2.37	743	7.0	38
12y-<16y	0.25 (n=4)	2.09	29	6.83	155	15.8	32
	0.50 (n=4)	2.65	118	4.35	821	5.7	17
	1.00 (n=2)	0.55	191	2.51	566	5.7	27

TOXICOLOGY

Single Dose Toxicology

The IV LD₅₀s for the 2.5 mg base equivalents/ml formulation in mice, rats and rabbits were 34-67, 29 and >5 mg/kg respectively. The LD₅₀s for the same formulation given IM in mice, rats and rabbits were >25, >5 and >2.5 mg/kg respectively. In Beagle dogs, IV midazolam maleate at 10 mg/kg resulted in muscle relaxation, licking, salivation, ataxia, inability to stand, swimming

movements, loss of placing reflex, dazed appearance, disoriented behavior, emesis and sedation. No hemolysis was produced in beagle dogs after administration of 0.7 mg/kg IV (1.0, 2.5 or 5.0 mg base equivalents/ml) over 30 seconds. However, moderate hemolysis was observed in the 10 mg/ml formulation.

Oral toxicology studies were conducted in mice, rats, rabbits and dogs. The oral LD₅₀ (mg/kg) values were observed as follows (reproduced in part from NDA 20-942):

	Substance			Tablet
	Midazolam Base	Midazolam Maleate (new method of synthesis)	Midazolam Maleate (old method of synthesis)	
Mice (CD-1, CF-1)	858	258-457	251-383	
Adult Rats (CD)	362	221	258	
Neonatal Rats (CD)	160	-	-	
Rabbits (New Zealand White)	614	-	-	

Midazolam maleate was lethal in 3/4 Beagle dogs at 300 mg/kg PO, with deaths occurring on days 1, 5 and 8 after drug administration. Adverse effects observed in dogs at 100-300 mg/kg PO were ataxia, elevated alkaline phosphatase, serum urea nitrogen, and SGPT levels. In a pyramiding dose study, Beagle dogs were administered 3, 10, 30 and 100 mg/kg midazolam maleate PO; observations were emesis and mucoid stool at all doses; ataxia, disorientation, dazed appearance, salivation and decreased motor activity at ≥ 10 mg/kg; elevated white blood cell (polymorphonuclear leukocytes and lymphocytes) counts, slight elevation of SGPT and alkaline phosphatase at 100 mg/kg; decreased glucose and elevated SGOT at all doses.

In comparison, adverse effects in clinical studies included agitation, involuntary movements, hyperactivity, combativeness, emesis, nausea and respiratory events (hypoxia, laryngospasm, rhonchi, coughing, respiratory depression, airway obstruction, upper-airway congestion, and shallow respirations). Allergic dermatitis, primary skin irritation, urticaria, allergic rhinitis, and serum sickness have been reported after IV midazolam infusion in adult and pediatric patients. Overdose in humans produced symptoms typically reported with benzodiazepines at high doses including diminished reflexes, confusion, impaired coordination, somnolence, sedation, coma and altered vital signs (respiratory rate, blood pressure, pulse rate). Deaths have been reported due to respiratory depression and respiratory arrest after coadministration of midazolam and opioid analgesics. In one clinical study, midazolam (0.05 mg/kg IV) increased fentanyl-induced hypoxemia and apnea, but had no effect on respiratory rate when given alone.

Repeat Dose Toxicology

Male and female B6C3F1 mice administered 1.2-1.3, 8.2-8.5 and 56-58 mg/kg dietary midazolam maleate for 4 weeks showed elevated white blood cell counts in mid-dose males and in high dose males and females, elevated glucose in high dose females, increased absolute and relative liver weights in high dose males and females and increased relative liver weights in mid-dose males. Adverse effects observed in mice, given 1, 9 and 80 mg/kg/d dietary midazolam maleate for 24 months, were increased mortality rate (high dose males), decreased white blood cell counts (high dose males), preputial and urinary tract inflammation with urinary bladder distension (high dose males), increased body weight gains (high dose males and mid and high

dose females), increased absolute and relative liver weights and hepatocellular hypertrophy (mid and high dose males, high dose females), and increased adrenal cortical hypertrophy (high dose females). Midazolam at 80 mg/kg/d (27x to 54x the recommended dose of 0.35 mg/kg in the human child on a mg/m² basis, in the mouse and rat respectively) PO for 24 months was associated with increased incidence of hepatic tumors (primary adenomas or carcinomas) in female mice and benign thyroid follicular cell tumors in male rats.

Toxicologic observations, in CD rats administered 0.5, 1.6 or 5.0 mg/kg/d IM midazolam base daily for 15-17 days, were dose-related ataxia, slow/loss of righting reflex, leg dragging, and hyperexcitability lasting ≤ 2 hours. Decreased body weight gain and food consumption were observed in male rats, and chronic active myositis at the injection site were found in all midazolam treated rats.

After oral administration (1, 7 or 50 mg/kg/d midazolam maleate in the diet) for four weeks, adverse effects were decreased alkaline phosphatase levels in high dose female rats, and higher absolute and relative liver weights in high dose male and female rats. In the nine week study, midazolam at 1.0, 4.0, and 16 mg/kg/d PO was associated with dose-related sedation, ataxia, and loss of righting reflex. In a thirteen week study of Fullinsdorf albino rats given 50, 100 or 200 mg/kg/d midazolam maleate in the diet, observations were increased absolute liver weights at all doses in both males and females, increased mean absolute thyroid weights in mid and high dose male rats and high dose female rats, increased mean thyroid weights at the high dose in both sexes, dose-related decreases in mean body weights and mean net body weight gain in female rats, decreased hemoglobin and red blood cells and moderate proteinuria in high dose female rats. In the necropsy, lobular delineation of the liver was observed in rats at all doses and increased fat and acidic mucopolysaccharide content in the liver was found in high dose females.

Adverse effects, observed in male and/or female Sprague Dawley rats administered 80 mg/kg/d dietary midazolam maleate for 24 months in the carcinogenicity study, were decreased serum glucose, increased serum urea nitrogen, albuminuria, increased hepatic masses or nodules and mottled livers, increased liver, thyroid, kidney and adrenal gland weights, and decreased testes and pituitary gland weights. Histopathology findings were centrilobular hepatocytic hypertrophy and centrilobular fatty change in the liver, and benign follicular tumors of the thyroid gland. In the same study, observations at 1 and 9 mg/kg/d included increased body weight and food consumption, increased liver weights, and centrilobular hepatocytic hypertrophy and centrilobular fatty change in the liver.

Rabbits administered 0.1, 0.5 or 2.5 mg/kg/d IV midazolam maleate daily for 2 weeks showed dose-related sedation, loss of righting reflex, ataxia, muscle relaxation, rapid and shallow respiration, and muscular twitching in the mid and high dose groups, and hypnosis in the high dose group. A slight decrease in prothrombin time was observed at the mid and high dose, and liver weights were reduced at the high dose.

Subacute toxicity in Beagle dogs (at 0.1, 0.5 or 2.5 mg/kg/d IV daily for two weeks) was observed as transient, dose-related sedation, ataxia, muscle relaxation, licking, chewing, biting, hyperactivity, retching and emesis. There were no drug related effects on clinical laboratory parameters, gross anatomic or histologic observations except focal changes at the injection site. Similar results were found in the subacute IM study in dogs. Oral midazolam maleate (5.0, 15 and 45 mg/kg/d for thirteen weeks) in Beagle dogs increased relative liver weight (to total body

weight) in the high dose group, produced slight proteinuria in the high dose group, and produced a dose-related increase in serum alkaline phosphatase (reversible after two weeks).

In the one year study, oral midazolam (1.0, 7.0 and 45 mg/kg/d) administered to Beagle dogs resulted in decreased body weight gain (mid and high dose), persistent signs of CNS depression (e.g., ataxia, depression, dazed appearance, mid and high dose), decreased hemoglobin and hematocrit (high dose), increased serum alkaline phosphatase (mid and high dose) and gamma glutamyltranspeptidase activities (high dose), enlarged liver (mid and high dose), hepatic parenchymal cell hypertrophy (mid and high dose), altered cytoplasmic staining (mid and high dose), yellow-brown granules in parenchymal cells (mid and high dose), eosinophilic cytoplasmic inclusions (mid and high dose), all reversible after 14 weeks recovery except in one of seven high dose dogs. At 1 mg/kg/d PO for one year, emesis was observed for 26 weeks in the dogs. No signs of withdrawal were observed after the 53-week treatment was discontinued.

Carcinogenicity

There was no evidence of carcinogenic potential in rats and mice given dietary midazolam at 1 and 9 mg/kg/d PO for two years. At 80 mg/kg/d (27x to 54x the recommended dose of 0.35 mg/kg in the human child on a mg/m² basis, in the mouse and rat respectively) PO for 24 months, midazolam was associated with increased incidence of hepatic tumors (primary adenomas or carcinomas) in female mice and increased benign thyroid follicular cell tumors in male rats. Adverse effects observed in the mice were increased mortality rate, decreased white blood cell counts, inflammation of the prepuce and urinary tract with distended urinary bladders in males; increased body weight gains, increased absolute and relative mean liver weights and hepatocellular hypertrophy in both sexes; and increased adrenal cortical hypertrophy in female mice. Adverse effects in the rats were decreased serum glucose in high dose males and females, increased serum urea nitrogen in high dose females, albuminuria in high dose males, increased hepatic masses or nodules in high dose females and mottled livers in high dose males and females.

Reproductive Toxicology

In the Segment I study, male and female CD rats were administered midazolam maleate at 1.0, 4.0 and 16 mg/kg/d PO (1/2x-7x the human dose of 0.35 mg/kg on a mg/m² basis) from 62 days prior to mating through mating in males and through lactation day 21 in mated females. Midazolam treatment produced dose-related pharmacologic effects (ataxia, voracious behavior), but had no effect on gonadal function, mating behavior, conception rate, early and late stages of gestation, parturition, lactation, neonatal viability, and pup growth.

In the Segment II study in female Fullinsdorf albino mice, midazolam maleate (at 30, 60 or 120 mg/kg/d PO, up to approximately 30x the oral human dose of .35 mg/kg on a mg/m² basis, gestation days 6-15) had no effects on reproductive and litter parameters. There were no treatment-related embryotoxic, fetotoxic or teratogenic effects, and no effects on pup survival or growth.

In the teratology study in CD rats, midazolam maleate (0.2, 1.0, or 4.0 mg/kg/d IV on gestation days 7-15) at 1/3x-8x the clinical IV dose of 5 mg (60 kg patient, on a mg/m² basis) had no effect on percent animals pregnant, number of corpora lutea and implants, mean litter size, mean fetal body weight, distribution of fetuses by sex, number of fetuses born dead, resorption rate, percent

litters showing resorptions, number of pups born dead, viability, lactation indices, or mean pup weight at birth. However, post-implantation loss (pups found dead at birth + resorbed fetuses and/or cannibalized pups) was increased 13% and 16% in the mid and high dose dams, respectively, that delivered normally. Because this was not observed in dams that underwent caesarean section, the increase in post-implantation loss in the rats allowed to deliver normally was attributed to cannibalization. There were no increases in external, soft tissue or skeletal abnormalities.

Female New Zealand white rabbits were administered midazolam maleate (0.2, 0.6 or 2.0 mg/kg/d IV, 1x-8x the clinical IV dose of 5 mg in a 60 kg patient on a mg/m² basis) on gestation days 7-18, in a Segment II study. Maternal effects observed during high dose treatment were sedation and decreased body weight gain. There were no effects on percent rabbits pregnant, mean number of corpora lutea, mean litter size, fetal body weight, crown-rump length, 24-hour viability, distribution by sex, resorption rate and percent litters with resorptions. There were no drug-related effects on external, soft tissue and skeletal abnormalities. Oral midazolam administered at 25, 50 or 100 mg/kg/d (approximately 100x the clinical oral dose of 0.35 mg/kg on a mg/m² basis, gestation days 6-18) to pregnant Swiss hare rabbits produced dose-related decreases in weight maternal gain and decreased fetal body weights, but no embryotoxic or teratogenic effects.

In the Segment III Perinatal and Postnatal evaluation in CD rats, midazolam maleate (0.2, 1.0 or 4.0 mg/kg/d IV, up to 8x the high clinical IV dose of 5 mg in a 60 kg patient on a mg/m² basis) administered daily from gestation day 15 through lactation day 21, was associated with maternal ataxia, increased cannibalism and reduced maternal weight gain in the mid and high dose groups. There were no external or visceral malformations, no skeletal abnormalities or variations, and no effects on late fetal development, delivery, lactation, neonatal viability or pup growth.

Oral midazolam maleate at 10, 25 and 50 mg/kg/d (up to 23x the oral clinical dose of 0.35 mg/kg on a mg/m² basis) was administered to pregnant CD rats on gestation day 15 through lactation day 4. Observations were dose-related CNS depression, reduced food consumption, increased fetal and neonatal loss (50% deaths by day 4 at 50 mg/kg/d), and increased cannibalization. In another segment III study in female CD rats administered 1, 5 and 20 mg/kg/d PO midazolam maleate (up to 9x the oral clinical dose on a mg/m² basis) from gestation day 15 through lactation day 20, ataxia and slightly reduced weight gain were observed. There were no adverse effects on litter size, gestation length, parturition, live-birth, viability and lactation indices, late fetal development or pup growth.

Genotoxicology

The mutagenic potential of midazolam maleate was tested in *in vitro* and *in vivo* microbial and mammalian test systems. In the Ames Test, midazolam was not mutagenic in *Salmonella typhimurium* strains TA1538, TA98, TA1537, TA1535 and TA100 at up to 500 µg/plate, or in *Escherichia coli* WP2uvrA at up to 278 µg/plate with or without metabolic activation with S9 homogenate under the conditions of this study. There were no forward mutations in V79 cells derived from Chinese hamster lung cells treated with midazolam at up to 150 µg/ml with or without metabolic activation. Midazolam was also not mutagenic in *Saccharomyces cerevisiae* D7 at up to 288 µg/ml, human lymphocytes at up to 100 µg/ml with and 50 µg/ml without metabolic activation, and *in vivo* in the micronucleus test at up to 800 mg/kg PO.

Studies on Degradation Products, Impurities, Intermediates and Metabolites

The following potential degradation products and intermediates, and their LD₅₀ values, were identified:

Substance	Identity	LD ₅₀ (mg/kg)	
		P.O.	I.P.
Ro 21-5561	Degradation Product	(CF-1 Mice) 1700-3800 (CD Rats) 2500	(CF-1 Mice) 1800-2000 (CD Rats) >2000
Ro 5-3367	Degradation Product	(CF-1 Mice) 2500-2800	-
Ro 22-6135	Degradation Product	(CF-1 Mice) >4000	-
Ro 5-3510	Degradation Product	(CF-1 Mice) 3100->4000	-
Ro 5-4373	Degradation Product	(CF-1 Mice) >4000	-
Ro 21-5344	Degradation Product	(CF-1 Mice) 1600-2100 (CD Rats) 2400	(CF-1 Mice) 920-1100 (CD Rats) 1100
Ro 22-5260	Degradation Product	(CF-1 Mice) >4000 (CD Rats) >4000	(CF-1 Mice) 880-1000 (CD Rats) 650
Ro 22-5261	Degradation Product	(CF-1 Mice) >4000 (CD Rats) >4000	(CF-1 Mice) 1500-2000 (CD Rats) 1000
Ro 22-5606	Degradation Product	(CF-1 Mice) >4000 (CD Rats) >4000	(CF-1 Mice) 1400-1600 (CD Rats) 760
Ro 21-5533	Intermediate (synthetic precursor, old synthesis)	(CF-1 Mice) 170-180 (CD Rats) 130	(CF-1 Mice) 110-120 (CD Rats) 83
Ro 21-5751	Intermediate (synthetic precursor, new synthesis)	(CF-1 Mice) >4000 (CD Rats) >4000	(CF-1 Mice) 250-450 (CD Rats) 980

Toxicity of the principal metabolite, 1-hydroxymethylmidazolam, was studied in rats and Beagle dogs. Male Fullinsdorf albino rats were administered the metabolite at 1.0 or 2.5 mg/kg/d IV daily for two weeks. Observed toxicity were ataxia and sedation, tail swelling, and increased leukocytes in the high dose group and reduced body weight gain in both treated groups. In the necropsy examination, lymphocytic infiltration and local small necrotic foci in the liver and interstitial lymphocytic infiltration in the kidneys were observed. Male Beagle dogs administered the metabolite at 1.0 or 2.5 mg/kg/d IV for two weeks showed ataxia, sedation, and increased induration of the cephalic veins. There were no effects on body weight or laboratory values.

Special Toxicology Studies: Juvenile Studies

Midazolam Syrup (Or 21-3981): An Acute (Single Dose) Oral (Intubation) Toxicity Study in Two-Week Old Rats Followed by a Two-Week Observation Period (Study No. 06827). Research Report No. N-138782.

Note: Testing Facility: Department of Toxicology and Pathology at Hoffmann-La Roche Inc., Nutley, NJ. Study Dates: February 27, 1996 - April 2, 1996. GLP and Quality Assurance statements signed and present.

Methods: Two-week old male and female rats

weights 28-38 g) were administered a single dose of midazolam (Ro 21-3981/000) syrup (2 mg/ml, cherry Lot No. C-185136, tutti-frutti lot No. C-185146) or syrup vehicle (cherry Lot No. L-185286, tutti-frutti Lot No. L-185296) by oral intubation as follows (reproduced from the original NDA 20-942, n=5/sex/treatment group):

Group	Formulation Flavor	Midazolam Concentration (mg/ml)	Dose (mg/kg)	Dose Volume (ml/kg)
A	cherry	0	0	30
B	cherry	2	60	30
C	tutti-frutti	0	0	30
D	tutti-frutti	2	60	30
AA*	cherry	0	0	30
BB*	cherry	2	60	30
CC*	tutti-frutti	0	0	30
DD*	tutti-frutti	2	60	30
E	cherry	0	0	5
F	cherry	2	10	5
G	cherry	0	0	10
H	cherry	2	20	10
I	cherry	0	0	20
J	cherry	2	40	20
K	tutti-frutti	0	0	5
L	tutti-frutti	2	10	5
M	tutti-frutti	0	0	10
N	tutti-frutti	2	20	10
O	tutti-frutti	0	0	20
P	tutti-frutti	2	40	20

*The treatments for Groups A, B, C and D were repeated due to high rate of mortality in rats that received 30 ml/kg dose volume. The observations were body weights (baseline and weekly), clinical signs and mortality (3x dosing day, 2x daily thereafter), and gross necropsy examinations (at 2 weeks).

Results: There was one death at 40 mg/kg tutti-frutti midazolam (n=10, sex not provided) several minutes after drug administration. In rats given 60 mg/kg active drug in 30 ml vehicle, there were 10/10 and 6/10 deaths (repeated test) after cherry flavored and 9/10 and 8/10 (repeat test) deaths after tutti-frutti flavored midazolam. In comparison, 8/10 and 4/10 rats died after 30 ml cherry vehicle and 2/10 and 6/10 rats died after 30 ml tutti-frutti vehicle administration. Most deaths in the rats given 30 ml vehicle (sex not provided) occurred within 1-2 days after treatment (number of rats not described) and the deaths were attributed to dehydration by the sponsor. The highest non-lethal dose was 20 mg/kg midazolam (40x the HRD of 0.5 mg/kg on a mg/kg basis and 9x on a mg/m² basis) in either flavor. The LD50 was not determined in this study.

Mean body weights and weight gain were slightly but not significantly lower in surviving

midazolam treated compared to placebo vehicle treated rats over 14 days. Clinical observations in midazolam treated rats were dose related decreased motor activity, slow or loss of righting reflex, tremors, muscle relaxation, respiratory depression, unkempt, diarrhea, weakness and ataxia persisting 1 - 2 days. Signs in rats given placebo were tremors, decreased motor activity, slow righting reflex, muscle relaxation, respiratory depression, unkempt, diarrhea or no signs. The NOAEL was not established in this study. The LOAEL was 10 mg/kg PO midazolam.

In the rats that died after treatment with 30 ml/kg vehicle with either placebo or 60 mg/kg midazolam, necropsy examination showed distended stomachs, intestines and urinary bladders, and dilated pelvises. No abnormal gross pathology was found in surviving rats at any dose.

Discussion:

The highest non-lethal dose in this study was 20 mg/kg midazolam (9x the HRD on a mg/m² basis). The lowest lethal dose was 40 mg/kg midazolam (tutti-frutti). Thirty-three of 40 rats administered 60 mg/kg midazolam in 30 ml, and 20 of 40 rats administered 30 ml placebo vehicle died, most within 2 days of dosing. The sponsor attributed the deaths in these animals to dehydration. However, there were significantly more deaths in the midazolam (60 mg/kg) group than in the placebo syrup group. In comparison, the LD50 in adult rats (see NDA 18-654) was 29 mg/kg - 50 mg/kg IV (approximately equivalent to 116 mg/kg - 200 mg/kg PO at 25% bioavailability).

The NOAEL was not established in this study. The LOAEL was 10 mg/kg PO midazolam. Effects were consistent with those of the benzodiazepine class of drugs and included dose related decreased motor activity, slow or loss of righting reflex, tremors, muscle relaxation, respiratory depression, unkempt, diarrhea, weakness and ataxia persisting 1 - 2 days. Several of these effects (tremors, decreased motor activity, slow righting reflex, muscle relaxation, respiratory depression, unkempt, diarrhea) were observed in placebo treated animals.

Clinical pathology, performed for one rat at 60 mg/kg only, revealed a blood glucose level of 38 mg/dl and increased hematocrit (52%). Gross examination at necropsy showed distended stomachs, intestines and urinary bladders, and dilated pelvises in rats that died after a dose volume of 30 ml/kg, with and without midazolam at 60 mg/kg. No abnormal gross pathology was found in the remaining, surviving rats at any dose.

Midazolam Syrup (Ro 21-3981): A Two-Week Oral (Intubation) Toxicity Study in Two-Week Old Rats (Study No. 06958). Research Report No. N-139383.

Note: Testing Facility: Department of Toxicology and Pathology at Hoffmann-La Roche Inc., Nutley, NJ. Study Dates: February 17, 1997 - March 12, 1997. Quality Assurance and GLP statements signed and present.

Methods: Male and female Sprague-Dawley rats

ages 2 weeks, weights 39.4 - 43.8 g, n=9/sex/treatment) were administered oral midazolam cherry flavored syrup at 5 mg/kg/d (2.5 ml/kg) or 10 mg/kg/d (5 ml/kg), with (Lot No. L-188307) and without (Lot No. 188297) the degradation products Ro 27-3163 (5.0%) and Ro 27-5272 (0.7%), by oral intubation once daily for two weeks. Degradation product exposure in this study was estimated to be 5.7x - 20x maximum human exposure from midazolam syrup when stored for up to 18 months. The placebo vehicle was cherry syrup (Lot No. L- 188317, 5 ml/kg).

Observations were mortality, moribundity and clinical signs (1x daily), body weights (baseline and 2x weekly), necropsy examination (macroscopic and microscopic), hematology (at end of treatment), and bone marrow smears, clinical chemistry and urinalysis (at necropsy).

Histopathology examinations were conducted on: adrenal glands, aorta, bone (proximal femur and sternum), brain, cecum, cervix, colon, duodenum, epididymides, esophagus, eyes, heart, ileum, jejunum, kidneys, Harderian gland, liver, lung (with mainstem bronchi), lymph node (mesenteric and submaxillary), mammary gland, ovaries, pancreas, parathyroid glands, pituitary gland, prostate gland, rectum, salivary gland (submaxillary), sciatic nerve, seminal vesicles, skeletal muscle (hind limb), skin, spinal cord, spleen, stomach, testes, thymus, thyroid glands, tongue, trachea, urinary bladder, uterus, vagina and gross lesions/masses.

Results: There were no deaths at any midazolam dose (0, 5 and 10 mg/kg/d PO) with or without the degradation products Ro 27-3163 and Ro 27-5272. Three rats were sacrificed in extremis (1 animal at 5 mg/kg/d and 2 animals at 10 mg/kg/d, all non-degraded), due to gavage errors that were later confirmed by histology. There were no treatment-related changes in body weights or weight gains. Clinical signs in all midazolam treated rats were decreased motor activity, persisting several hours after dosing. There were several changes in hematology parameters that were not dose related, were within historical limits and were not considered to be treatment related. Serum chemistry and urinalysis showed no treatment-related changes.

In the necropsy examination in rats that were sacrificed at the end of the study, there were no abnormal treatment related gross pathology observations. Macroscopic examination of the rats sacrificed during treatment showed evidence of gavage error (thorax abscess, lung adhesion). Liver weights were increased in the surviving animals at 5 mg/kg/d (non-degraded formulation) and 10 mg/kg/d (degraded and non-degraded formulation) midazolam. Histopathology results are presented in the following table, for observations that were increased in active drug treated, compared to placebo treated animals.

	Vehicle (n=9/sex)	5 mg/kg Degraded (n=9/sex)	10 mg/kg Degraded (n=9/sex)	5 mg/kg Non- degraded (n=9/sex)	10 mg/kg Non- degraded (n=9/sex)
Squamous metaplasia, trachea	1 Female	0	0	0	1 Male, 3 Females
Ultimobranchial thyroid cyst	0	1 Female	2 Males, 1 Female	1 Female	2 Males
Pericarditis	0	0	0	0	2 Females
Chronic esophageal inflammation	0	1 Male, 1 Female	2 Males	1 Male, 1 Female	2 Females
Alveolitis eosinophil, lung	0	0	1 Male	0	1 Female
Pleuritis	0	0	0	0	2 Females
Alveolitis eosinophil	0	0	1 Male	0	1 Female
Lymphoid depletion	0	0	0	0	2 Females
Acute thymus inflammation	0	0	0	0	1 Female
Vacuolar change, liver	0	0	0	0	1 Female
Acute inflammation, aorta	0	0	0	0	2 Females
Progressive nephropathy, kidney	1 Female	1 Male, 3 Females	1 Male, 2 Females	3 Females	2 Females

Discussion: Daily administration of either non-degraded or degraded (5% degradation product Ro 27-3163 and 0.7% Ro 27-5272) midazolam at up to 10 mg/kg/d PO for two weeks resulted in no treatment related deaths, changes in body weights or weight gains, or changes in hematology, serum chemistry and urinalysis parameters in 2 week old male and female rats. Decreased motor activity was observed in all midazolam treated rats. There were no gross pathology changes, but mean liver weights were increased at 5 mg/kg/d (non-degraded) and 10 mg/kg/d (degraded and non-degraded formulation) midazolam. The change in liver weights was without accompanying histopathologic changes except for vacuolar change in the liver in one female (at the high dose non-degraded formulation). Adverse histopathology findings were infrequent and observed in both degraded and non-degraded products. Therefore, no increase in adverse effects were attributed to the degradation products Ro 27-3163 or Ro 27-5272. Several histopathology observations (e.g., esophageal inflammation, tracheal metaplasia) were probably caused by gavage error. The histopathology results weakly suggest toxicity; however the incidence of microscopic pathology was low, there was little evidence for a dose-response effect, and the observations were not consistent across sexes. Therefore, there appears to be no specific target organ of toxicity. The NOAEL in this study was not established due to increased liver weights in all non-degraded midazolam treated (at 5 and 10 mg/kg/d), and in 10 mg/kg/d degraded midazolam treated rats. The LOAEL was 5 mg/kg/d.

OVERALL SUMMARY AND DISCUSSION

Midazolam is a short acting benzodiazepine sedative-hypnotic, approved for intramuscular and intravenous treatment, and here proposed for oral administration in a syrup formulation to pediatric patients prior to surgical procedures. The proposed dose is 0.25-1.0 mg/kg up to a maximum dose of 20 mg. The pharmacology, toxicology and efficacy of midazolam are well known. This submission included two special toxicity studies, addressing acute and repeat dose oral midazolam in juvenile rats.

In addition to sedation and hypnosis, midazolam produces anxiolysis, skeletal relaxation and has anticonvulsant activity, predominantly through inhibition of gamma-aminobutyric acid neurotransmission in the central nervous system. Midazolam can produce mild transient increases in heart rate, decreased blood pressure and decreased minute volume of respired air. Midazolam bioavailability is increased with cimetidine or ranitidine co-administration. Midazolam increases the respiratory depressant effects of other central nervous system depressants including opioids, barbiturates and alcohol, and antagonizes the cardiovascular stimulatory effects of ketamine. Midazolam also potentiates enflurane and thiopentone anesthesia. There are no interactive effects with the neuromuscular blocker succinylcholine, but midazolam enhanced vecuronium and pancuronium induced neuromuscular block in the sciatic nerve-tibialis anterior muscle preparation of the anesthetized cat. Midazolam delays bupivacaine induced dysrhythmias, seizures, increases in blood pressure and heart rate, and suppresses seizures induced by paraoxon, soman and lidocaine.

In clinical studies the peak plasma concentration (C_{max}) increased with pediatric age and with dose after oral administration, from approximately 28-63 ng/ml at 0.25 mg/kg to 61-200 ng/ml at 1 mg/kg. The time to maximum plasma level (T_{max}) increased with pediatric age but not with midazolam dose, from approximately 10-20 minutes at ages six months to two years, to two hours at ages twelve to sixteen years. The onset of action of oral midazolam in pediatric patients was ten minutes, duration of action 30-45 minutes, absolute bioavailability 36%, half-life

2.2-5.8 hours (at ages six months to two years) to 2.5-6.8 hours (at ages twelve to sixteen years), and AUC 68-224 ng.h/ml (at ages six months to two years) to 155-566 ng.h/ml (at ages twelve to sixteen years) after 0.25-1.0 mg/kg PO. PK data from juvenile animals are not available.

Oral midazolam is rapidly absorbed and widely distributed, with highest concentrations found in the liver, kidneys, lungs, fat and heart. Midazolam is highly lipophilic and crosses the blood brain barrier and the placenta. Midazolam is metabolized in the liver by enzymes to alpha-hydroxymidazolam (63%-80% dose), 4-hydroxymidazolam (3% dose) and 1,4-dihydroxymidazolam (1% dose), and later glucuronidated prior to elimination by the kidney. A small fraction is eliminated in feces. Clearance is decreased with increasing pediatric age, from ages six months to 16 years.

Single dose toxicity studies were conducted in mice, adult and juvenile rats, rabbits and Beagle dogs. The LD50 values for midazolam base in adult mice, rats and rabbits were 858, 362 and 614 mg/kg PO, respectively. In comparison, the oral LD50 in neonatal rats was 160 mg/kg. Midazolam was lethal in 75% Beagle dogs, 1-8 days after oral treatment with 300 mg/kg. Adverse effects observed in the dogs at 100-300 mg/kg PO were ataxia, elevated alkaline phosphatase, serum urea nitrogen and SGPT levels. In another study, adverse midazolam effects in Beagle dogs were emesis, mucoid stool, decreased glucose and elevated SGOT at 3-100 mg/kg PO and ataxia, disorientation, dazed appearance, salivation and decreased motor activity at 10-100 mg/kg PO. At 100 mg/kg PO, elevated white blood cell counts (polymorphonuclear leukocytes and lymphocytes), SGPT and alkaline phosphatase were observed at 100 mg/kg PO. In comparison, adverse effects reported in adult and pediatric patients included agitation and involuntary movements, emesis, nausea and respiratory events (e.g., hypoxia, laryngospasm). No change in respiratory rate was observed at 0.05 mg/kg IV midazolam alone in one study, although midazolam at that dose increased fentanyl-induced hypoxemia and apnea.

Repeat dose toxicity of midazolam was studied in several species. Hepatotoxicity, indicated by increased or decreased liver weights, centrilobular hepatocytic hypertrophy, fatty change, hepatic masses or nodules, mottled liver and other changes, was observed in mice (at 8.5-80 mg/kg/d PO), rats (1-80 mg/kg/d PO), rabbits (0.1-2.5 mg/kg/d IV) and dogs (7-45 mg/kg/d PO) given midazolam daily for four weeks to 24 months. Other adverse effects of repeated dosing in animals were increased or decreased white blood cell counts, increased or decreased body weight gain, urinary inflammation, increased adrenal cortical weight or adrenal cortical hypertrophy, increased thyroid and kidney weights, decreased testes and pituitary gland weights, decreased serum glucose, increased serum urea nitrogen and albuminuria, increased or decreased alkaline phosphatase, decreased hemoglobin or red blood cells or hematocrit, proteinuria and increased gamma glutamyltranspeptidase activity.

The carcinogenic potential of midazolam was studied in mice and rats. Midazolam at 80 mg/kg/d PO for 24 months was associated with an increase in the incidence of hepatic tumors in female mice and benign thyroid follicular cell tumors in male rats. This dose represented 27x and 54x the recommended dose of 0.35 mg/kg in the pediatric patient on a mg/m² basis in the mouse and rat respectively.

Midazolam had no effects on fertility or general reproductive performance in CD rats at up to 7x the human dose of 0.35 mg/kg. Midazolam was not teratogenic in mice at up to 120 mg/kg/d PO

(30x the HRD), CD rats at up to 4 mg/kg/d IV (8x the HRD) or in rabbits at up to 2 mg/kg/d IV or 100 mg/kg/d PO (8x and 100 x the HRD respectively). There were no adverse effects on perinatal and postnatal development in rats at up to 4 mg/kg/d IV or 50 mg/kg/d PO (8x and 50x the HRD respectively).

Midazolam was not mutagenic in the Ames test in *Salmonella typhimurium* (500 µg/plate) or *E. Coli* (278 µg/plate) with or without metabolic activation with S9, in V79 cells derived from Chinese hamster lung cells (150 µg/ml with or without metabolic activation), in *Saccharomyces cerevisiae* D7 (288 µg/ml), in human lymphocytes (100 µg/ml with and 50 µg/ml without metabolic activation) or *in vivo* in the micronucleus test at up to 800 mg/kg PO.

The oral LD50s for the degradation products labeled Ro 21-5561, Ro 5-3367, Ro 22-6135, Ro 5-3510, Ro 5-4373, Ro 21-5344, Ro 22-5260, Ro 22-5261 and Ro 22-5606 were 1600-4000 mg/kg PO in mice and/or rats. The LD50s for the synthetic precursors ranged from 130 mg/kg to 180 mg/kg in rats and mice respectively for Ro 21-5533 and were 4000 mg/kg in both mice and rats for the intermediate Ro 21-5751. The toxicity of the principal metabolite was studied in rats and Beagle dogs. Adverse effects in male rats administered 1-2.5 mg/kg/d IV 1-hydroxymethylmidazolam for two weeks were ataxia, sedation, tail swelling, increased leukocytes and reduced body weight gain, with lymphocytic infiltration and local necrotic foci in the liver and interstitial lymphocytic infiltration in the kidneys observed in the necropsy examination. The same doses in male Beagle dogs induced ataxia, sedation and increased induration of the cephalic veins.

Special toxicology studies were conducted for this application, evaluating the effects of single dose and repeated dose oral midazolam syrup in juvenile rats. In the acute oral toxicity study, male and female two-week old rats received placebo or midazolam at 10, 20, 40 or 60 mg/kg in cherry and tutti-frutti flavored syrup with a dose volume of 5, 10, 20 or 30 ml/kg by oral intubation. One of 20 rats administered 40 mg/kg midazolam died within several minutes after dosing. Thirty three of 40 rats administered midazolam at 60 mg/kg in 30 ml/kg syrup (cherry and tutti-frutti) died while 20/40 given 30 ml/kg syrup alone died. The deaths occurred within 1-2 days after treatment and were attributed to dehydration by the sponsor. However, it is noted that there were significantly more deaths in the midazolam (60 mg/kg) group than in the placebo syrup group. The highest non-lethal dose was 20 mg/kg midazolam PO (9x the HRD on a mg/m² basis), the lowest lethal dose was 40 mg/kg PO (18x the HRD) and the LD50 was not determined. Midazolam was lethal in >75% rat pups at 60 mg/kg PO (27x the HRD). In comparison, 50% rat pups given vehicle died during the study. In a previous study (see NDA 18-654) the LD50 in adult rats was 29 mg/kg-50 mg/kg IV (approximately equal to 116 mg/kg-200 mg/kg PO given 25% bioavailability). Clinical observations, conducted over 14 days post-drug treatment, revealed decreased motor activity, slow/loss of righting reflex, tremors, muscle relaxation, respiratory depression, unkempt appearance, diarrhea, weakness, and ataxia. These effects were consistent with those of the benzodiazepine class of drugs and several of these effects (tremors, decreased motor activity, slow righting reflex, muscle relaxation, respiratory depression, unkempt, diarrhea) were observed in placebo treated animals. The LOAEL was 10 mg/kg PO midazolam and the NOAEL was not established in this study. Gross necropsy examination of the rats that died after treatment showed no abnormal pathology.

In the repeated dose study, two-week old rats were administered placebo syrup or midazolam syrup at 5 mg/kg/d or 10 mg/kg/d, either with or without the degradation products Ro 27-3163 (at 5.0%) and Ro 27-5272 (at 0.7%), daily by oral intubation for two weeks. The estimated

degradation product exposure was 5.7x-20x the maximum human exposure from midazolam syrup when stored for up to 18 months. The results showed no treatment related deaths, changes in body weights or weight gains, or changes in hematology, serum chemistry and urinalysis parameters. Decreased motor activity was observed in all drug treated neonatal rats. There were no gross pathology changes, but mean liver weights were increased at 5 mg/kg/d (non-degraded) and 10 mg/kg/d (degraded and non-degraded formulation) midazolam. The change in liver weights was without accompanying histopathologic changes except for vacuolar change in the liver in one female (at the high dose non-degraded formulation). Adverse histopathology findings were infrequent and observed in both degraded and non-degraded products. Therefore, no increase in adverse effects were attributed to the degradation products Ro 27-3163 or Ro 27-5272. Histopathology observations suggested potential toxicity although several findings were probably caused by repeated irritation during dosing. The incidence of microscopic pathology was low, there was little evidence for a dose-response effect, and the observations were not consistent across sexes. Therefore, there appears to be no specific target organ of toxicity. The LOAEL was 5 mg/kg/d PO midazolam, and the NOAEL was not established. In comparison, in a previous study (see NDA 18-654) adult rats were administered up to 5 mg/kg/d IM midazolam (60x the suggested human IM dose) for two weeks. In that study, dose related CNS depression, hemorrhage at the injection sites and injection site myodegeneration, myonecrosis, focal hemorrhage and mixed inflammatory cell infiltration were reported. However, there were no reports of increased liver weights and histopathology findings other than at the injection site in the adult rats. This suggests increased toxicity of midazolam in juvenile compared to adult rats.

CONCLUSIONS

Special Toxicology Studies: Acute and Repeated Dose Toxicity in Juvenile Rats

Acute Toxicity

- Highest non-lethal dose 20 mg/kg PO (9x HRD on a mg/m² basis), lowest lethal dose 40 mg/kg PO (18x HRD), increased mortality in midazolam treated pups (>75%) at 60 mg/kg PO (27x HRD) compared to controls (50%).
- Adverse effects: dose-related decreased motor activity, slow/loss of righting reflex, tremors, muscle relaxation, respiratory depression, unkempt, diarrhea, weakness, ataxia. NOAEL not established (<10 mg/kg PO), LOAEL 10 mg/kg PO.
- No abnormal gross pathology.

Subchronic Toxicity (2 wks)

- Decreased motor activity in all treated rats at 5-10 mg/kg/d, daily for 2 weeks, with and without the degradation products Ro 27-3163 Ro 27-5272. No treatment related deaths, changes in body weights or weight gains, or changes in hematology, serum chemistry and urinalysis parameters. There were no significant gross pathology changes.
- Mean liver weights increased at 5 mg/kg/d (non-degraded) and 10 mg/kg/d (degraded and non-degraded formulation) midazolam, without accompanying histopathologic changes

except for vacuolar change in the liver in one female (at the high dose non-degraded formulation).

- Histopathology findings were infrequent, observed in both degraded and non-degraded products, not dose-related, and not consistent across sexes. Therefore, there was no specific target organ of toxicity and no increase in adverse effects were attributed to the degradation products Ro 27-3163 or Ro 27-5272. Several histopathology observations (e.g., esophageal inflammation, tracheal metaplasia) were probably caused by gavage error.
- NOEL not established due to increased liver weights in all non-degraded midazolam treated (at 5 and 10 mg/kg/d), and in 10 mg/kg/d degraded midazolam treated rats. LOEL 5 mg/kg/d.

Labeling Review

The Carcinogenesis, Mutagenesis and Impairment of Fertility, and Pregnancy sections of the proposed package insert were submitted as follows:

The following changes to the proposed package insert are recommended:

RECOMMENDATIONS

This NDA is approvable from a pharmacology/toxicology point of view with the following recommendations. It is important to consider that although higher doses of midazolam may be needed with decreasing pediatric age to achieve the desired level of sedation, there is preclinical evidence that midazolam toxicity may be increased in younger pediatric patients. This is based on reports in the literature of a decrease in lethal dose (LD50) by more than 50% in neonatal (160 mg/kg PO) compared to adult (at 362 mg/kg PO) rats. Also, in the special toxicology study in neonatal rats reported in this submission, more than 75% rat pups died at 60 mg/kg PO of midazolam syrup. Some of these deaths were probably caused by effects of the vehicle, because there was 50% mortality due to dehydration in the placebo syrup treated pups. However, 25% deaths in the rat pups could be attributed to midazolam effects. In comparison, the LD50 in adult rats given IV midazolam in another study was 29-50 mg/kg, approximately equivalent to 116-200 mg/kg PO based on a calculation of 25% bioavailability, further suggesting increased sensitivity to midazolam lethality in juvenile compared to adult animals.

The following changes to the proposed package insert are recommended:

To the Sponsor:

Copy under Recommendations.

/S/

Kathleen A. Haberny, Ph.D. *5/22/98*

/S/

Team Leader: Dou H. Jean, Ph.D. *May 22, 1998*

cc: NDA 20-942 Arch
HFD 170/Division File
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