CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-726

PHARMACOLOGY REVIEW(S)

Memo

IND/NDA numbers:	I63,934 / N21-726
Review number:	2
Sequence number/date/type of submission:	000/July 14th 2004/commercial IND/NDA serial#s 002-007 December 15 and 23 2004
Information to sponsor:	Yes (x) No ()
Sponsor and/or agent:	Schwarz Pharma
Manufacturer for drug substance :	
Reviewer name:	Aisar Atrakchi, Ph.D.
Division name:	Neuropharmacological Drug Products/HFD-120
Review completion date:	January 6, 2005
Drug:	
Trade name:	Niravam®
Generic name (list alphabetically):	Alprazolam

Subject:

This is follow up information on the safety of and its monomers. is used in alprazolam oral disintegrating tablets . As stated in the original Pharmacology/Toxicology review dated August 12th 2004, the amount of proposed in the tablet monomers exceeds amounts present in other approved drugs. Information on chemistry and manufacturing controls as well as safety/toxicology of are reported in DMF . Additional safety information were obtained from the published literature as well as from a consult for ANDA prepared by Dr. Terry Peters, HFD-520. The following are Approved NDAs with

ANDA#

(the last 4 are prescription drugs).

Background:

is a copolymer

are soluble in the gastric juice.

for tablets, capsules, pellets, polymers are used as excipients in pharmaceutical preparations and have been in use world wide

are accepted excipients in many pharmaceuticals approved by the Japanese and European countries.

Evaluation:

polymers in general when ingested, are not absorbed or degraded, they are excreted unchanged, no known systemic toxicity have been identified except for where local and systemic effects have been seen following long term use of high doses

Based on the available safety information and a single

radiolabelled distribution study, — is not absorbed systemically following oral ingestion and is excreted within 5 days of administration almost exclusively in feces. The — has low acute lethal dose via oral, i.p., or s.c., it is not a skin or eye irritant and does not cause skin sensitization in animal models. *In vitro* data do not suggest phototoxicity. Daily oral administration of — to rats for 6 months was well tolerated without mortality or any drug related toxicities up to 2000mg/kg/d dose. **Based on the NOAEL of 2000mg/kg/d in the 6 month rat oral toxicity study and a safety factor of 100, daily intake of 20mg/kg/d of — is considered safe. The calculated amount of — — in alprazolam at the maximum daily dose of 10mg is — or — ng/kg/d for a 60kg person a value well below the calculated maximum safe dose of 20mg/kg/d.**

The following toxicology studies have been conducted using —

Acute Toxicity studies:

Rat (— suspended in 1% methylcellulose administered by oral gavage to 5/sex up to 15,000mg/kg with 1 month observation period. No drug related deaths, clinical signs, or necropsy findings; LD50 was >15,000mg/kg

Rat & Mice (—

Oral LD50:	mice > 15,000mg/kg	Rat >3000mg/kg
S.C. LD50:	mice > 5000mg/kg	Rat > 2000mg/kg
I.P. LD50:	mice > 5000mg/kg	Rat > 1000mg/kg

Rabbit — oral suspension administered by gavage to 4 rabbits did not cause any drug related effects when tested at doses between 170-320mg/kg up to the observation drug-free period of 8days.

— . LC50 of — to Poecilia reticulate was 4.81mg/l

Repeat Dose Toxicity Studies:

1 month oral toxicity study in beagle dogs with — Doses tested were 100, 300, and 750mg/kg/d in gel caps administered to 3/sex/group for 28d; the control group received empty gel caps. High dosed females vomited and histopath exam showed focal superficial mucosal congestion in the duodenum. The high dose was reduced to 750mg/kg/d due to vomiting at 1000mg/kg/d dose.

6 month oral toxicity study —): Rats (20/sex) were administered 0, 500, or 2000mg/kg/d of — admixed in the diet for 6 months. Parameters assessed include: clinical signs, B.wt, food intake, Clinical chemistry, hematology, urinalysis, ophthalmoscopy, gross morphology, organ wts, and histopath exam of 29 tissues from high dose and controls. There was no drug related deaths and no drug related toxicities on any of the parameters measured. The NOAEL was therefore, 2000mg/kg/d (unclear to this reviewer why 2000mg/kg/d is not a NOEL).

Absorption and Excretion of — radiolabelled ^{14}C — was administered as a single oral dose to rats at 40mg (5.6uCi of ^{14}C-per rat). Almost all radioactivity (mean 93.3%, 88.8-95.7%) was recovered in feces by 5d after dose with majority recovered within 48hr; <0.02% was detected in urine. Also, 92% was recoveried when ^{14}C- — was added to control feces. There was no difference in radioactivity label between drug and control in liver, kidneys, spleen, blood, and mesenteric lymph nodes when analyzed on days 1, 3, 7, or 14 after dose. Both small and large intestines at 24hr postdose, showed higher radioactivity than the corresponding tissue control, levels were comparable to control within 3 days. This was contributed to contamination of intestinal content rather

than a direct drug effect. Results in this study showed that — is well absorbed after oral administration to the rat and is rapidly eliminated via feces; there was no evidence of accumulation of radioactivity in tissues.

Genetic Toxicity:

Bacterial Ames gene mutation assay (—
— ; study was GLP and followed OECD guideline 471): the mutagenic potential of —
—was examined using TA100, TA98, TA1535, TA1537, and TA1538 were tested in -/+S9 at 5 concentrations between 10-5000ug/plate; the positive controls Na azide, 2AA, and 4-Nitro-o-phenylendiamine were used and anticipated results obtained. The **was not mutagenic in any of the strains tested up to 5000ug/plate.**

In vitro cytotoxicity assay: Cell growth analysis using BCA staining with an extract of —
— was incubated for 24hr with culture medium and the extract was added to mouse connective tissue cell line L929 for 72hr. This assay measures the protein content in cell culture, the higher the level the more cytotoxicity. — **did not produce leachable products that were cytotoxic in this assay**. It is noted that the extract was not characterized or analyzed for content.

Mammalian gene mutation assay using *in vitro* mouse lymphoma $TK^{+/-}$ locus (this information is obtained from a review by Dr. Terry Peters, HFD-520 for ANDA —): this assay was conducted at — , with completion date of March 2000 and was conducted under GLP/QA. — , was tested at 5 concentrations up to 31.3ug/ml in -/+ S9 in duplicate cultures. The was highly cytotoxic at ≥15.6ug/ml in Experiment 1 in presence and absence of S9, and at 31.0ug/ml in experiment 2 and in both experiments, clear precipitate was seen at ≥7.8ug/ml. — , **did not increase mutant frequencies up to the concentrations tested in either -/+ S9.**

In vivo bone marrow micronucleus in CD-1 mice: this information was also obtained from Dr. Terry Peters's review of ANDA — this study was conducted by — ith completion date of May 2000. CD-1 mice (5/sex/dose except 10/sex in high dose and controls), were administered — at 500, 1000, or 2000mg/kg i.p. clinical signs were seen in males as hunched posture and ataxia, bone marrow toxicity was seen only in females dosed 2000mg/kg and in all drug male groups. 2000 polychromatic erythrocytes were analyzed per animal and MMC at 2mg/kg served as the positive control. — **did not cause a significant increase in MNPC erythrocytes up to 2000mg/kg dose compared to vehicle (saline), control mice.**

Genetic Toxicology Conclusion:
A full battery of genetic toxicology assays was conducted with —
— and neither —was found to be mutagenic in any of these assays including the *in vivo* mouse bone marrow micronucleus up to 2000mg/kg i.p.

Teratogenicity:

—was administered in the diet at 1000mg/kg to 20 female rats between gd6-16; control group received the diet alone. There were no drug related effects on food intake, B.wt or clinical signs. On gd20 fetuses were removed and examined, no drug related effects on fetal parameters.

Skin and Eye Irritation:

Rabbit (— /; study was GLP and followed OECD guideline #404): 500mg aliquot of — was applied to shaved/prepared skin of 3 rabbits for 4hrs, skin irritation was assessed 1, 24, 48, and 72hr postdose. There was no drug related findings.

Guinea Pig — study was GLP and followed OECD guideline #406): the potential of — to induce delayed dermal sensitization was evaluated by the Buehler skin sensitization test. At the induction phase, guinea pigs were treated 1x per week for 3 weeks with — , after 14d latency period, animals were challenged with — on the other flank. The skin reaction was graded and compared to the control. — did not show any signs of allergic reaction.

Acute eye irritation in the rabbit (— udy was GLP and followed OECD guideline #405): 100mg — was instilled into the ey of a total of 3 rabbits; the other eye served as the control. Response was assessed at 1, 24, 48, and 72hr postdose. Slight redness was seen at 1hr in all 3 rabbits and in 1 out of the 3 at 24h postdose. Complete recovery occurred by 48hr.

Phototoxicity:

— , Study was GLP and followed OECD guidelines # 2000/33 EC B41): — was dissolved in DMSO and dilutd 1:100 ratio in Earls balance solution, Balb/c 3T3 cells were treated for 1hr at 37 degrees with additional 50min in presence and absence of non-toxic dose of UVA respectively. response was assessed 24hr later and cytotoxicity determined as reduction of neutral red reuptake and compared to the controls. — was not phototoxic under these conditions.

Other:

— , was used in formulations for NDAs — epresenting — M.S. Holloman's review (HFD-530, dated —), under Safety Concerns, it stated that toxicology data sheets from the manufacturer of — ndicate that high doses >200mg/kg/d can affect food intake, food absorption, as well as water and electrolyte balance. In her review, levels of — were going to range between — **mg/kg/d** depending on — dose and therefore, would pose a safety risk to the proposed young patient population (ages 2-12years). The sponsor consequently decided to discontinue development of this formulation. It was unclear to this reviewer if — formulation was tested in any of the clinical trials with —

Based on the above information —. specifically, there are no safety concerns for the use of — in alprazolam oral tablets. **The safety concerns however, are for the — monomers that make up — . According to — manufacturer of — monomers is present at — ppm in — comprising a total of — The amount of — present in 10mg maximum daily dose of alprazolam will be — Therefore, the daily intake of — calculated based on (— specifications will be —** This amount is higher than that present in approved and marketed drugs (table generated by Dr. C. Tele, reviewing Chemist):

Summary of Daily Intake of — ...sed in Approved NDAs

NDA#			21-726
Product (ODT)			**Niravam**
Applicant			Schwarz
Active Ingredient			Alprazolam
Indication			Antianxiety agent
Approval Date			**Approvable**
Strengths			0.25, 0.5, 1, 2 mg
Maximum Daily Dose			10 mg
Daily Intake of —			
Daily Intake of —			
(Calculated on the basis of — mers specification)			
Daily Intake of —			

From these values, it can be argued that although the amount of total as well as — in alprazolam tabs is higher than any found in these 3 marketed drugs, the amount of — in alprazolam tab of — is relatively close enough to — present in — Also, based on the following information obtained from the published literature, DMF, and USP monographs, it can be concluded that the presence of these — at the calculated level per daily dose, does not pose a safety risk.

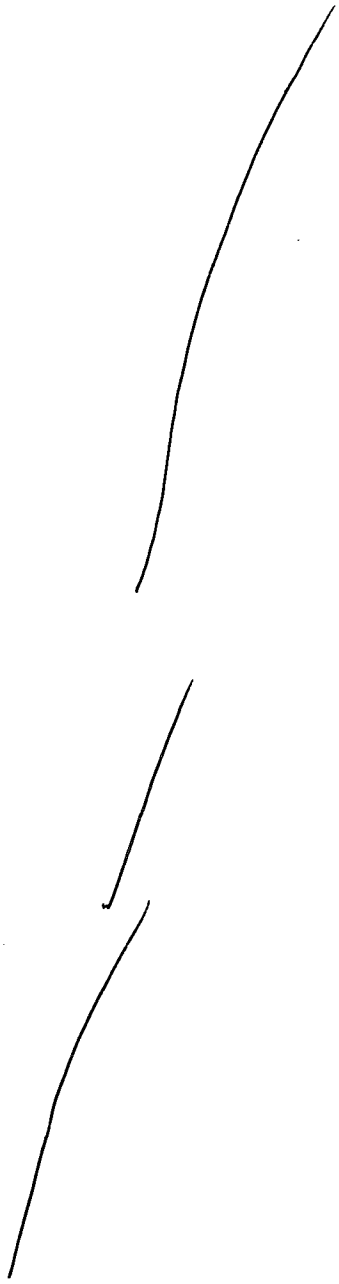
Extensive literature search was done for each monomer, most of the information is founf for the — some on — and no or very little information was found on the —. The following summarizes the available information:

4 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling



Evaluation and Conclusions:

Based on the available information presented here, there are no safety concerns regarding the use of [redacted] at the proposed daily amount of [redacted] present in alprazolam maximum daily dose. [redacted] are not absorbed systemically, eliminated unchanged

and , tested negative for mutagenicity and clastogenicity potential using the ICH recommended battery for genetic toxicity tests.

The Division expressed safety concerns regarding the monomers in because:

- of the relatively large amounts present in per maximum daily intake of alprazolam, a value that is higher than any found in approved drugs and,
- the lack of safety information on

Dr. C. Tele, the reviewing Chemist, recently obtained information on the limits of The current specs for is not more than in the The revised limit appears to be **based on manufacturer's analytical methodology i.e. product quality rather than safety concerns** (emails from , Dec 3rd, 2004).

The following summarizes some of the currently available information on the monomers . This information *may* justify accepting the current specs of

1. have been used worldwide for over 50 years in in the manufacturing of pharmaceutical dosage forms No toxicities or adverse effects have been reported.

2. There are European, Japanese, and US monographs

3. The single dose LD50 values in animals for each monomer provide large safety margin (in g/kg in one or more of these species: rats, mice, and rabbits).

4. The published literature though relatively old, provide non-clinical data on acute, subchronic, chronic/carcinogenicity studies, genetic toxicity, reproductive/developmental and neurotoxicity. The genetic toxicity data are conflicting with being positive in some assays but negative in others, however, an NTP 2 year rat and mouse carcinogenicity studies via inhalation showed to be devoid of tumorigenic activity.

5.

6. The information on the reproductive/developmental effects for — seem to indicate absence of malformation. Only 2 reports were found for —, one did not show any effect whereas the 2nd found gross and skeletal malformations and fetal death following i.p. injection of — at 1/10, 1/5, or 1/3 the LD50 dose. No information could be located for — Definitive conclusions can not be based on single reports.

7. Although information was sparse for — the — — oased on the available information — — is less than that of — and, based on single dose LD50 values, similar to there seem to be large safety margins for — On the other hand, and similar to — the genetic toxicity data are conflicting.

8. The revised limit of — — appears to be based on product quality (improvement in analytical method), not on safety concerns. If we are to calculate the amount of monomers present in 10mg alprazolam daily dose based on the — limit, then this comes up to — —, an amount of no or minimal safety concern.

9. The only epidemiology study that showed a correlation between long term occupational exposure to — and colon/rectal cancer incidence, when re-analyzed recently, did not find such correlation.

10. Comparison of the daily intake per dose for each monomer in alprazolam to those found in 3 other recently approved drugs show the value of — in alprazolam vs. — found in — a relatively close values. Although of note that the amount of — — is highest in alprazolam compared to the other drugs (comparison table on page 5).

11. — s, is found in several OTC marketed drugs including — as well as in —

In conclusion, there seem to be relatively adequate safety data — that allows us to accept the current specs of — The recent limit of — — eems to be based on quality issues rather than safety data. Although the safety data for the — are small and inadequate, their presence may be justifiable if we are to assume that the functional backbone and hence toxicity profiles of — are comparable to that of — based on chemical structural similarity — Therefore, the specs of — are acceptable and may not pose a significant clinical safety risk. Moreover, the calculated amount of — per the maximum daily dose of alprazolam may be acceptable without safety concerns since it is close to the —found for — an approved drug.

A final note, this reviewer strongly recommends to the manufacturer of [redacted] to attempt to reduce to a minimum the amount of [redacted] in the final products.

Memo

IND/NDA number:	63,934/21726
Drug:	Alprazolam/Xanax®
Sponsor and/or agent:	Schwarz Pharma
Reviewer name:	Aisar Atrakchi, Ph.D.
Supervisor name:	Barry Rosloff, Ph.D.
Division name:	Neuropharmacological Drug Products/HFD-120
Date:	October 4th 2004

The following are non-clinical information on — monomers —

monomers, — are used . Collectively, — monomers are present as impurities at specification level of NMT — Although the safety profile is known for — , it is not for monomers. — was not carcinogenic in either rats or mice in NTP *inhalation* carcinogenicity studies up to 1000ppm (500ppm in female rats), it was negative in the Ames bacterial mutation assay, the V79/HPRT mammalian *in vitro* gene mutation assay, and in one peripheral blood SCE assay in factory workers. However, — was clastogenic in the mouse lymphoma and CHO mammalian chromosomal aberration assays in -/+S9 and in a peripheral blood lymphocyte SCE assay in factory workers. Information was scarce on — except in one reference this monomer was found not to be cytotoxic and did not induce chromosomal aberration in rat bone marrow cells. No information was available on —

Because of the unusually high level of — and the limited safety information on the individual monomers except for some for — this reviewer recommends reducing the specification levels of these monomers to minimal.

Information to sponsor:
The total specification level of the — is — This level is high and the sponsor should attempt to reduce it to minimal. The safety profile for these monomers is unknown except for — here it was shown not be a carcinogen up to 1000ppm in rats and mice via inhalation but mutagenicity information is inconsistent with some showing it to be a clastogen whereas it was negative in other mutagenicity assays.

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/s/

Aisar Atrakchi
10/14/04 08:55:54 AM
PHARMACOLOGIST

Barry Rosloff
10/15/04 06:01:50 PM
PHARMACOLOGIST