CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-121

PHARMACOLOGY REVIEW(S)

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4/12/2000

Pharmacologist Review of NDA 21-121
Original Summary

SPONSOR: Alza Corporation
1900 Charleston Road
P.O. Box 7210
Mountain View, CA 94039-7210

DRUG: OROS methylphenidate . HCl

CATEGORY: CNS stimulant, used in attention deficit hyperactivity disorder (ADHD) and narcolepsy

RELATED APPLICATIONS:

1 [redacted] .. present NDA)

2. NDAs 10-187 and 18-029 (for immediate and sustained release formulations, respectively, of the marketed product Ritalin).

INTRODUCTION:

OROS methylphenidate is designed to release a portion of the dose immediately, and the remainder at an ascending rate over 8-9 hours. It is to be taken once daily. Methylphenidate has been marketed for several decades. Since an adequate reproduction battery and an in vivo genotoxicity study had never been performed with methylphenidate, it was requested that the sponsor perform additional studies. It was also requested that the sponsor address the question of possible adverse effects on developing juvenile organisms; it was agreed that this could be done post-marketing, although the sponsor has submitted a literature review in the present NDA.

TABLE OF CONTENTS

CONTINUOUS BREEDING REPRODUCTION STUDY (RACB) IN MICE

A) Methods

40/sex at 0, and 20/sex at 120, 500, or 1000 ppm in diet. (Estimated daily mg/kg doses were 18, 76, and 160 for M and 18, 76, and 150 for F).

Dosing was from 1 week before cohabitation, throughout a 14 week cohabitation period, and for 3 weeks following cohabitation.

Mice were cohabited 1:1. On average 5 litters were produced with the first 4 being immediately removed. The last litter born was reared by the dam until weaning. At weaning, F_1 animals from control and HD groups were treated at the same doses at the parents (i.e. 0 and 1000 ppm, resp.) to assess F_1 fertility. Study sponsored by National Toxicology Program and performed by

[redacted]

Drug Lot # [redacted]

Mouse strain: VAF Crl: Swiss CD-1 (ICR) BR

B) Results

1) Observed signs / mortality

Text states no drug-related signs; specific methods and results not given. Nine deaths occurred scattered across all groups.

2) F_0 bodyweights

Very slight decreases seen in HD M weeks 2-14. (Mean weights 94-98% of control). No consistent effect in F.

3) F_0 food consumption

No drug effect; note that at most times consumption could not be evaluated separately in M and F.

4) Reproductive parameters

There were no drug effects on any of the reproductive parameters measured, which included the following:

a) Fo

1) fertility index and time to litter

2) number of live pups born

3) live pup weights and pup sex ratio

4) pup survival and bodyweights through day 21 PP

5) measurements made at necropsy (N=10/sex in control and HD):

   a) sperm morphology, motility, and density

   b) estrous cycle length and relative frequency of estrus stages (measured for 12 days prior to necropsy, although it is not clear how this could be done since, according to the sponsor's diagram of the conduct of this study, dams were sacrificed at the end of the lactation period).

   c) Organ weights showed no drug effect except for slight increases in absolute and relative liver weights (relative weight 1.2x above control). Ovary weights were slightly increased but not statistically significant. Other organs weighed: kidney and male reproductive organs.

b) F_1

(Parameters measured essentially same as above except cohabitation period was 7 days and only 1 litter produced, which was not followed after birth. Only controls and HD were used).

Results were the same as above (including the slight increase in liver and ovary weight) except that seminal vesicle weight was slightly decreased. Note that there were no statistically significant effects on bodyweight in F_1 although, as in the case with F_0, weights in HD males were very slightly (2-4 %) below controls.

SEGMENT II REPRODUCTION IN RATS

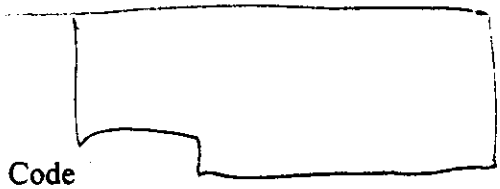
A) Methods

25 F at 0, 5, 12.5, or 30 mg/kg/day, by gavage, days 6-17 of gestation. (Day of evidence of mating= day 0 of gestation).

The above total daily doses were given in 2 equally divided doses approximately 4 hours apart.

Dams were sacrificed day 20 of gestation. All fetuses examined externally and viscerally (fresh dissection technique) and skeletally (Alizarin staining). Heads from ~ 1/2 fetuses per litter were examined by Wilson sectioning technique; heads from remaining fetuses examined by mid-coronal slicing.

The study was performed at



Drug Code

Rat Strain: Crl: CD (SD) 1GS BR

(This study was submitted 2/15/00, and is located in volumes 7.4-7.5)

B) Results

1) Observed signs

a) Exophthalmos seen at MD and HD, D-R; also seen sporadically in a few LD.

a) Hyperactivity/ stereotyped behavior / hypersensitive to handling seen at HD and sporadically in a few MD.

2) Mortality

None

3) Dam bodyweights

Very slight weight loss at MD and HD during first few days of treatment, followed by a slightly decreased weight gain in these groups. Weights at end of

treatment period 98% and 96% of control in MD and HD, respectively. Gain slightly increased at HD after end of treatment period.

4) Dam food consumption

Decreased at MD and HD (85-95% and 80-90% of control, respectively). Slightly increased at MD and HD after end of treatment period.

5) Reproductive data

No drug effects on resorptions, live or dead fetuses, post-implantation loss, or fetal weights.

6) Fetal exams

(Summary table attached)

a) Malformations

Malformations were seen in the following numbers of fetuses (litters): controls 1 (1), LD 3 (3), MD 0 (0), and HD 7 (3).

As indicated in the table, the types of malformations were generally scattered. Four HD fetuses, from a single litter, had localized edema in the neck and/or thorax. An additional HD fetus, from a different litter, had gastroschisis (all lobes of liver, stomach, pancreas, and spleen and entire length of the intestine protruded through an opening in the ventral midline), and another HD fetus, from yet a different litter, had an umbilical hernia (several loops of the intestine protruded through an opening in the umbilicus). The HD fetus with gastroschisis also had, upon skeletal exam, a skull anomaly consisting of fused nasal bones (medial portion), sternoschisis (with sternal bands not fused), and a vertebral and associated rib anomaly (thoracic centra nos. 1-3 absent, right rib nos. 3 and 4 fused [medial and distal portions], right costal cartiliges nos. 3 and 4 were fused and joined the sternum in the normal no. 3 position and all other right costal cartileges joined the sternum one position lower than normal). An additional fetus from the same litter had a vertebral anomaly (left half of lumbar centrum no. 2 was absent and the right half was smaller than normal; the left half of lumbar arch and centrum no. 2 was located more posterior than normal, and the left half of lumbar arch and centrum no. 3 was located more anterior than normal). Scattered types of malformations seen in the other groups are shown in the summary table.

b) Variations

As indicated in the attached table, the fetal incidence of ossified cervical centrum no. 1 was increased at LD and HD but not clearly at MD; the litter

incidence was not clearly increased at HD. It was stated that "Since ossification of cervical centrum no. 1 indicates normal fetal development, [this increase] was not considered to be an adverse effect of treatment." Values were within the historical control range.

7) Plasma levels of drug and metabolite

Although not measured in this study, levels were measured in a (non-GLP) rangefinding study in which pregnant rats were given 5, 15, 30, or 60 mg/kg/day (in 2 equally divided doses approximately 4 hours apart) days 6-17 of gestation. Sampling was on days 6 and 17, at times shown in the attached tables of results. AUC of parent drug increased somewhat greater than in proportion to dose; AUC of the metabolite PPA increased roughly in proportion to dose. AUC of both parent and metabolite were 1.5-2x greater on day 17 than on day 6. AUCs of parent were ~ 10-15% those of the metabolite. (Note that in some cases plasma levels at the last time point measured [4 hours after the last dose] were still relatively high, in which cases AUC $_{0\text{-infinity}}$ or AUC $_{0\text{-}24}$ were substantially greater than AUC $_{0\text{-}8}$).

TABLE 16

STUDY OF METHYLPHENIDATE HCL ON EMBRYO/FETAL DEV. IN RATS

NUMBER OF FETUSES AND LITTERS WITH MALFORMATIONS - SUMMARY

DAY 20

SPONSOR:ALZA CORPORATION
SPONSOR NO.:TR-99-5607-017

DOSE GROUP:	FETUSES 1	2	3	4	LITTERS 1	2	3	4
NUMBER EXAMINED EXTERNALLY	407	367	316	374	25	24	22	24
FETAL ANASARCA	0	2	0	0	0	2	0	0
GASTROSCHISIS	0	0	0	1	0	0	0	1
UMBILICAL HERNIATION OF INTESTINE	0	0	0	1	0	0	0	1
LOCALIZED FETAL EDEMA	0	0	0	4	0	0	0	1
HYDROCEPHALY WITH OR WITHOUT DOME HEAD	1	0	0	0	1	0	0	0
VERTEBRAL AGENESIS	0	1	0	0	0	1	0	0
NUMBER EXAMINED VISCERALLY	407	367	316	374	25	24	22	24
KIDNEY(S)- FUSED	0	1	0	0	0	1	0	0
NUMBER EXAMINED SKELETALLY	407	367	316	374	25	24	22	24
VERTEBRAL ANOMALY WITH OR WITHOUT ASSOCIATED RIB ANOMALY	0	0	0	2	0	0	0	1
RIB ANOMALY	0	1	0	0	0	1	0	0
SKULL ANOMALY	0	0	0	1	0	0	0	1
STERNOSCHISIS	0	0	0	1	0	0	0	1
VERTEBRAL CENTRA ANOMALY	0	1	0	0	0	1	0	0
TOTAL NUMBER WITH MALFORMATIONS	1	2	0	6	1	2	0	3
EXTERNAL :	0	1	0	0	0	1	0	0
SOFT TISSUE:	0	2	0	2	0	2	0	1
SKELETAL :								
COMBINED :	1	3	0	7	1	3	0	3

1- 0 MG/KG/DAY 2- 5 MG/KG/DAY 3- 12.5 MG/KG/DAY 4- 30 MG/KG/DAY

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TABLE 18
STUDY OF METHYLPHENIDATE HCL ON EMBRYO/FETAL DEV. IN RATS
NUMBER OF FETUSES AND LITTERS WITH VARIATIONS - SUMMARY

DAY 20

SPONSOR:ALZA CORPORATION
SPONSOR NO.:TR-99-5607-017

DOSE GROUP:	FETUSES 1	2	3	4	LITTERS 1	2	3	4
NUMBER EXAMINED EXTERNALLY	407	367	316	374	25	24	22	24
NUMBER WITH FINDINGS	0	0	0	0	0	0	0	0
NUMBER EXAMINED VISCERALLY	407	367	316	374	25	24	22	24
IRIS-HEMORRHAGIC	0	0	1	0	0	0	1	0
KIDNEY(S)- SMALL	0	1	0	0	0	1	0	0
NUMBER EXAMINED SKELETALLY	407	367	316	374	25	24	22	24
27 PRESACRAL VERTEBRAE	2	1	0	2	2	1	0	1
STERNEBRA(E) #5 AND/OR #6 UNOSSIFIED	24	26	28	33	11	10	9	9
CERVICAL CENTRUM #1 OSSIFIED	30	63	44	68	14	22	14	16
14TH RUDIMENTARY RIB(S)	19	14	8	28	9	9	6	12
7TH CERVICAL RIB(S)	1	2	2	3	1	2	1	3
HYOID UNOSSIFIED	1	4	9	7	1	1	5	4
25 PRESACRAL VERTEBRAE	1	0	0	0	1	0	0	0
REDUCED OSSIFICATION OF THE 13TH RIB(S)	0	0	6	1	0	0	2	1
BENT RIB(S)	1	0	2	0	1	0	2	0
14TH FULL RIB(S)	1	1	0	0	1	1	0	0
UNCO-OSSIFIED VERTEBRAL CENTRA	0	0	0	1	0	0	0	1
ENTIRE STERNUM UNOSSIFIED	0	0	1	0	0	0	1	0
ISCHIUM UNOSSIFIED	0	1	0	0	0	1	0	0
PUBIS UNOSSIFIED	0	0	0	1	0	0	0	1
STERNEBRA(E) #1,#2,#3 AND/OR #4 UNOSSIFIED	0	1	0	0	0	1	0	0

1- 0 MG/KG/DAY 2- 5 MG/KG/DAY 3- 12.5 MG/KG/DAY 4- 30 MG/KG/DAY

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ALZA Corporation
ALZA Study No.: BIO-98-B017-5607

TABLE 1

Mean Methylphenidate Concentrations in Plasma of Pregnant Rats and Toxicokinetic Parameters for Gestation Day 6

Group Summary				
Group	2	3	4	5
Dose (mg/kg/day)*	5	15	30	60
Sex	F	F	F	F
Mean (±SD) Plasma Concentrations (ng/mL)**				
0 hr	0.06 (0.11)	0.12 (0.10)	0.00 (0.00)	0.06 (0.11)
20 min	12.21 (6.75)	55.05 (15.39)	122.82 (7.74)	237.02 (48.43)
1 hr	12.33 (3.94)	39.82 (14.26)	106.69 (31.53)	282.02 (132.85)
2 hr	9.65 (2.47)	26.67 (7.92)	53.70 (20.27)	175.50 (85.14)
4 hr	1.51 (0.84)	10.44 (8.19)	25.37 (6.56)	158.20 (38.22)
4 hr, 20 min	12.17 (4.11)	69.05 (8.37)	170.38 (81.92)	369.26 (50.88)
5 hr	22.71 (1.96)	67.19 (30.25)	117.44 (29.63)	313.73 (46.44)
6 hr	8.52 (3.56)	41.86 (10.38)	104.17 (8.46)	271.27 (138.09)
8 hr	2.02 (1.59)	16.30 (4.07)	53.52 (8.26)	161.32 (47.96)
Linear Regression of log Plasma Concentrations vs. Time***				
Slope	-0.3446	-0.1806	-0.1292	-0.09684
Y-Intercept (ng/mL)	1114	477	583	980
Coefficient of Determination (r^2)	0.993	0.972	0.970	0.990
Toxicokinetic Parameters				
Cmax (ng/mL)	22.7	69.1	170	369
Tmax (hr)	5	4.3	4.3	4.3
AUC 0-8 (ng–hr/mL)	72.4	283	653	1816
AUC 0-∞ (ng–hr/mL)	75.0	322	833	2539
Kel (1/hr)	0.794	0.416	0.298	0.223
Half-life (hr)	0.87	1.7	2.3	3.1
Cl (L/hr/kg)	66.7	46.6	36.0	23.6
Vd (L/kg)	84.0	112	121	106

* Administered as two equal doses approximately 4 hr apart.

** Data [illegible] eport. Individual values are presented in Tables 6–9. Individual values below the quantitation limit were set equal to zero. N=3, except N=2 for Group 5 at 20 min, 4 hr, 4 hr 20 min, and 6 hr.

*** From Tmax (after 2nd dose) to last value.

Appendix 4F

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TABLE 2

Mean Methylphenidate Concentrations in Plasma of Pregnant Rats and Toxicokinetic Parameters for Gestation Day 17

Group Summary				
Group	2	3	4	5
Dose (mg/kg/day)*	5	15	30	60
Sex	F	F	F	F
Mean (±SD) Plasma Concentrations (ng/mL)**				
0 hr	0.00 (0.00)	0.11 (0.19)	0.25 (0.22)	2.05 (1.31)
20 min	15.24 (4.31)	113.11 (55.78)	183.76 (87.20)	250.87 (138.59)
1 hr	17.48 (8.75)	80.94 (6.27)	157.80 (35.09)	296.35 (65.88)
2 hr	11.61 (2.66)	50.65 (29.85)	135.01 (40.22)	356.60 (182.08)
4 hr	1.63 (0.20)	17.58 (7.48)	74.09 (35.23)	425.10 (106.84)
4 hr, 20 min	29.58 (7.45)	83.38 (32.42)	269.41 (89.33)	614.83 (239.41)
5 hr	32.46 (7.25)	111.53 (64.36)	264.89 (114.45)	606.58 (384.98)
6 hr	15.00 (2.73)	39.94 (29.47)	171.85 (40.57)	514.63 (13.65)
8 hr	13.03 (16.33)	23.02 (6.37)	49.54 (11.69)	221.63 (39.77)
Linear Regression of log Plasma Concentrations vs. Time***				
Slope	-0.1176	-0.2129	-0.2113	-0.12627
Y-Intercept (ng/mL)	103	1043	2682	2476
Coefficient of Determination (r^2)	0.709	0.874	0.953	0.918
Toxicokinetic Parameters				
Cmax (ng/mL)	32.5	113	269	615
Tmax (hr)	5	0.3	4.3	4.3
AUC 0-8 (ng–hr/mL)	119	438	1175	3210
AUC 0-24 (ng–hr/mL)	166	485	1277	3965
Kel (1/hr)	0.271	0.490	0.487	0.291
Half-life (hr)	2.6	1.4	1.4	2.4
Cl (L/hr/kg)	30.1	30.9	23.5	15.1
Vd (L/kg)	111	63.1	48.3	52.0

* Administered as two equal doses approximately 4 hr apart.

** Data were [illegible] dividual values are presented in Tables 6–9. Individual values below the quantitation limit were set equal to zero. N=3, except N=2 for Group 5 at 20 min, 4 hr, and 6 hr.

*** From Tmax (after 2nd dose) to last value.

Appendix 4F

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ALZA Study No.: BIO-98-B017-5607

TABLE 3

Mean PPA Concentrations in Plasma of Pregnant Rats and Toxicokinetic Parameters for Gestation Day 6

Group Summary				
Group	2	3	4	5
Dose (mg/kg/day)*	5	15	30	60
Sex	F	F	F	F
Mean (±SD) Plasma Concentrations (ng/mL)**				
0 hr	0.44 (0.77)	0.98 (1.34)	0.45 (0.40)	0.40 (0.69)
20 min	77.23 (33.09)	429.77 (109.16)	698.36 (156.33)	1072.27 (441.45)
1 hr	167.45 (38.20)	503.05 (235.18)	1029.16 (248.65)	2221.28 (1042.11)
2 hr	76.58 (14.13)	279.12 (57.42)	440.85 (40.65)	1257.38 (209.71)
4 hr	24.30 (9.27)	100.38 (45.55)	294.30 (39.15)	961.56 (419.51)
4 hr, 20 min	175.32 (73.50)	668.07 (49.26)	1357.67 (713.12)	3070.19 (413.72)
5 hr	198.53 (20.40)	596.95 (23.01)	1035.86 (23.65)	2123.16 (498.91)
6 hr	89.08 (21.00)	351.56 (68.57)	943.67 (165.37)	1450.65 (626.07)
8 hr	51.02 (27.67)	231.93 (39.84)	557.99 (104.90)	1049.21 (597.17)
Linear Regression of log Plasma Concentrations vs. Time***				
Slope	-0.1859	-0.1306	-0.09980	-0.1214
Y-Intercept (ng/mL)	1454	2454	3544	9070
Coefficient of Determination (r^2)	0.916	0.959	0.973	0.923
Toxicokinetic Parameters				
Cmax (ng/mL)	199	668	1358	3070
Tmax (hr)	5	4.3	4.3	4.3
AUC 0-8 (ng–hr/mL)	759	2761	5727	11925
AUC 0-∞ (ng–hr/mL)	878	3532	8155	15676
Kel (1/hr)	0.428	0.301	0.230	0.280
Half-life (hr)	1.6	2.3	3.0	2.5
Cl (L/hr/kg)	5.69	4.25	3.68	3.83
Vd (L/kg)	13.3	14.1	16.0	13.7

* Administered as two equal doses approximately 4 hr apart.

** Data were derived [redacted] ort. Individual values are presented in Tables 6–9. Individual values below the quantitation limit were set equal to zero. N=3, except N=2 for Group 5 at 20 min, 4 hr, 4 hr 20 min, and 6 hr.

*** From Tmax (after 2nd dose) to last value.

[redacted]

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ALZA Study No.: BIO-98-B017-5607

TABLE 4

Mean PPA Concentrations in Plasma of Pregnant Rats and Toxicokinetic Parameters for Gestation Day 17

Group Summary				
Group	2	3	4	5
Dose (mg/kg/day)*	5	15	30	60
Sex	F	F	F	F
Mean (±SD) Plasma Concentrations (ng/mL)**				
0 hr	0.75 (0.18)	4.09 (1.12)	7.89 (2.80)	28.87 (7.07)
20 min	151.50 (44.97)	810.97 (131.53)	952.47 (563.33)	843.97 (91.13)
1 hr	295.48 (97.26)	1063.54 (73.14)	1792.73 (523.29)	2542.97 (457.87)
2 hr	125.97 (8.09)	476.91 (98.40)	1271.13 (217.66)	2366.32 (485.16)
4 hr	38.11 (7.74)	295.22 (215.15)	582.79 (138.22)	2422.54 (479.45)
4 hr, 20 min	353.18 (120.14)	1038.87 (315.95)	1879.38 (521.24)	3669.40 (309.05)
5 hr	351.37 (46.30)	1078.84 (258.15)	2486.41 (522.39)	3712.67 (404.45)
6 hr	147.92 (42.55)	440.00 (284.18)	1561.16 (267.15)	2740.74 (705.37)
8 hr	81.42 (15.63)	272.11 (78.23)	550.28 (96.63)	1774.36 (145.13)
Linear Regression of log Plasma Concentrations vs. Time***				
Slope	-0.1881	-0.1858	-0.2195	-0.1051
Y-Intercept (ng/mL)	2459	7596	31620	12148
Coefficient of Determination (r^2)	0.935	0.874	0.999	0.992
Toxicokinetic Parameters				
Cmax (ng/mL)	353	1079	2486	3713
Tmax (hr)	4.3	5	5	5
AUC 0-8 (ng–hr/mL)	1328	4703	10462	19736
AUC 0-24 (ng–hr/mL)	1516	5338	11550	26914
Kel (1/hr)	0.433	0.428	0.505	0.242
Half-life (hr)	1.6	1.6	1.4	2.9
Cl (L/hr/kg)	3.30	2.81	2.60	2.23
Vd (L/kg)	7.61	6.57	5.14	9.21

* Administered as two equal doses approximately 4 hr apart.

** Data were derived ——— Individual values are presented in Tables 6–9. Individual values below the quantitation limit were set equal to zero. N=3, except N=2 for Group 5 at 20 min, 4 hr. and 6 hr.

*** From Tmax (after 2nd dose) to last value.

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MOUSE MICRONUCLEUS ASSAY

A micronucleus assay was done in CD-1 mice. Single gavage doses were given as follows: M - 87.5, 175, and 350 mg/kg; F - 75, 150, and 300 mg/kg. (N=5/sex sacrificed at 24 and 48 hr. post-dose). Positive control was cyclophosphamide (80 mg/kg p.o.; sacrifice at 24 hr. only). Methylphenidate code #/control # = 0007690 / MV9800118. Study performed by [redacted]

One HD M died within 1 hour of dosing. Toxic signs included hyperactivity (all doses) and stereotyped behavior (primarily at HD). (In rangefinding studies, mortality was seen at 350 mg/kg and above).

Methylphenidate did not increase micronuclei in bone marrow PCEs. (At least 2000 PCEs per animal were scored). The positive control was active.

SUMMARY

A) Reproduction Studies

Two reproduction studies were submitted : (1) A continuous breeding study in mice (performed under contract from NTP) and (2) a segment II study in rats.

In the mouse study, drug was given in diet at concentrations of 120, 500, or 1000 ppm (~ 18, 76, 155 mg/kg). Both males and females were treated beginning one week prior to cohabitation, which was for 14 weeks during which time an average of 5 litters were produced. The last litter was reared by the dam (with drug treatment continuing) through day 21 PP, after which F_1 from controls and HD groups were raised through sexual maturity (with treatment at 0 and 1000 ppm, respectively) for evaluation of fertility. Many of the parameters ordinarily measured in the standard segment I and III studies were assessed (e.g. fertility, pup weight and survival) although the usual neurobehavioral milestones were not assessed in the offspring. There were no adverse drug effects on any of the measured reproductive parameters. The adequacy of the doses used may be questioned in that no observed signs were produced, no effects on bodyweight were seen in F, and only a very slight decrease in weight gain was seen in HD M (which was statistically significant for treated Fo but not for treated F_1). Rangefinding studies were not performed specifically for this study; data from 2- and 13- week NTP- sponsored dietary studies were used. As discussed in my review of these studies as well as of the NTP- sponsored dietary carcinogenicity study in mice (review of 7/6/95, filed in division files of NDAs 10-187 and 18-029), effects on bodyweight gain were variable and sometimes not reproducible across studies. Final bodyweights in these studies were generally clearly decreased (compared to controls) at 250 ppm and above in males and at 2000 ppm and above in females. (The magnitude of decrease in HD M in the present study is less than expected based on the previous studies). (The previous studies also indicated a greater effect on males vs females on parameters other than bodyweight, e.g. hyperactivity and lethality were seen in M only, at 4000 ppm). A potential role of poor palatability in causing decreases in weight gain might be considered; however this was not fully evaluated in the rangefinding studies (and in the present study food consumption could not be separately evaluated in M and F). However, it is noted that whereas the high doses used in the 2 week study caused decreases in both bodyweight gain and food consumption, the medium and high doses used in the carcinogenicity study (250 and 500 ppm) caused a decrease in weight gain only (in M only; no effects in F). Also note that increases in liver weights were seen in the present study in both M and F; this effect was also seen in previous studies and while by itself is not adequate to define an MTD, does indicate exposure to drug. Overall, it is concluded that the doses used in the present study were adequate, although the use of a dose twice as high (2000 ppm) in females would have been preferable.

In the rat segment II study, daily doses were 5, 12.5, and 30 mg/kg given by gavage (in 2 equally divided doses ~ 4 hr. apart) days 6-17 of gestation. Observed signs in dams were seen primarily at MD and HD and included exophthalmos, hyperactivity, hypersensitivity to handling, and stereotyped behavior. (In rangefinding studies, a dose

twice as high as HD produced a more pronounced effect on signs; a dose 4 times as high was not tolerated). Very slight initial weight loss / decreased weight gain was seen at MD and HD; weights at the end of the treatment period were 98% and 96% of control in MD and HD, respectively. Food consumption was decreased in these groups. There were no clear drug effects on reproductive parameters or fetal exams; the number of malformed fetuses was higher at HD than in controls but the few malformations noted either were scattered in type, occurred in a single litter, or were WNL. Plasma levels of parent compound and the metabolite PPA were measured in a rangefinding study in pregnant rats which used doses spanning the range used in the main study.

An additional study in rats, primarily to examine effects of an neurobehavioral development (treatment of dams from implantation to weaning) is currently underway and will be submitted post-marketing.

B) Mouse Micronucleus Assay

Methylphenidate was negative in this study (HD=350 and 300 mg/kg by gavage in males and females, respectively). The study was performed in conformity with current guidelines.

C) Literature Review of Developmental Studies

The sponsor has included (volume 1.30, p. 163-248) a review of the published literature on the behavioral and developmental effects of methylphenidate in animals and humans. (This was in response to our previous request that the sponsor address the issue of potential effects of methylphenidate on developing organisms).

According to the included review, there is no evidence for adverse developmental effects due to methylphenidate in humans, aside from a possible slight decrease in height and weight gain which was reversible after drug discontinuation. However, in general the human studies do not appear adequate to answer the question of concern; for example many did not involve long-term followup (particularly after cessation of drug treatment) and comparison with untreated ADHD controls. Many of the studies only used outcome measures known to be positively affected by methylphenidate.

The animal studies reviewed also do not adequately answer the question of concern. Of the few studies which used juvenile animals, the following contain data of some relevance: (1) Pizzi, et. al., Developmental Pharmacology and Therapeutics 9 : 361-368 (1986); (2) Pizzi, et. al., Neurotoxicology and Teratology 9: 107-111 (1987); (3) Greeley and Kizer, JPET 215: 545-551 (1980); and (4) Greeley, et. al., Endocrinology 106: 898-904 (1980). In the studies of Pizzi et. al., male rats given 35

mg/kg b.i.d. subcutaneously from days 5-24 of age had, on day 25, reduced bodyweight, femur length, and absolute weight of several organs compared to controls. Bodyweights returned to control by 6 days after cessation of treatment, and necropsies performed at 30 days after cessation of treatment showed all parameters had returned to control level. (Although this implies reversibility, the author notes that the growth rebound occurred during a period of rapid growth following drug treatment during the neonatal period, and that had drug treatment continued throughout this rapid growth period, it is possible the rebound would have not been seen). An additional study done in female rats suggested that older rats (treatment on days 35-54 of age) were not affected by the same dose (35 mg/kg/day s.c.) which reduced growth in younger rats; however it is not clear if using the same mg/kg dose is appropriate for this comparison.

The paper of Greeley and Kizer also showed a decrease in bodyweight gain and skeletal growth (naso-anal and length) in rats given methylphenidate (35 and 100 mg/kg, b.i.d., given s.c. to male and female rats of 5-7 days of age for 21 days and to male rats of 18-21 days of age for 18 days). It was stated that 12 months after cessation of treatment of the younger rats, bodyweights and lengths were similar to controls, although no data were shown. (Reversibility apparently not studied in the older rats). An additional experiment with the older rats showed that pair fed rats had similar decreases with the exception of skeletal growth at HD, which was more affected in the drug treated than in the pair fed rats, suggesting that at least in this instance the effect of drug was not totally explainable by its anorexigenic properties. Other finding in these studies included, in female rats treated from days 5-7 of age for 21 days at 35 or 100 mg/kg/day b.i.d. s.c., delayed vaginal opening and, during the 30 days after cessation of treatment, decreased number of estrous cycles. In older females (21-23 days of age treated for 30 days at 35 mg/kg b.i.d.) vaginal opening was delayed to a similar degree as in the younger rats although this was not statistically significant; the number of estrous cycles was decreased during, but not after cessation of treatment. Reproductive performance was not evaluated. (Note that the reliability of this paper may be questioned in that not all data were shown, there were various discrepancies noted [e.g. between statements in the methods and results sections and results and discussion sections], and one figure appears to be incorrectly labeled). In the paper of Greeley et. al., various parameters of thyroid function were measured at various times in juvenile rats of various ages; it was concluded that serum TSH was decreased in male (but not female) rats 12-18 months after cessation of treatment (35 or 100 mg/kg b.i.d. s.c. given to rats 5-7 days of age for 21 days). However, the validity of this conclusion may be questioned in view of the large number of measurements which were made, without apparent adjustment of the alpha level.

D) 30 Day Dog Study

This study, discussed in my review of 12/11/97 of [redacted] was primarily of value for assessing the local G.I effects of the OROS formulation. (The formulation used differed somewhat from the proposed human formulation, but was said to have the same degree of cumulative methylphenidate release). Four dogs/sex received 1,2, 3, or

4 OROS systems (with each containing 18mg methylphenidate) per day; i.e. the high dose was 72 mg (6-9 mg/kg) per day. Although the doses of methylphenidate were probably inadequate to assess systematic toxicity, it was shown that dogs can tolerate up to 4 methylphenidate-containing OROS systems per day for 30 days without producing local G. I. histopathology.

EVALUATION:

The requested preclinical studies have been submitted, and this NDA is approvable. As previously agreed on, an additional reproduction study in rats, primarily to examine effects on neurobehavioral development (with drug treatment of dams from implantation to weaning) is underway and will be submitted post-marketing.

We previously requested that the sponsor address the question of potential effects of methylphenidate on developing organisms, either by performing a study in juvenile animals or by submitting pertinent animal or human data from the published literature. It was agreed that this could be done post-marketing. The sponsor has included a review of literature. It appears that the studies which have been performed in animals and humans have not adequately addressed the problem of concern. An adequate study should involve drug exposure during development with subsequent evaluations at times when development of the various systems would be expected to have been completed. (Ideally, the evaluations should be made after discontinuation of drug exposure, to avoid confounding by transient drug effects). Evaluation should encompass as broad an array of systems and functions as possible. Few if any of the studies discussed were adequate by these standards. The human studies have the further problem of often not having a control group of untreated ADHD patients. It is recommended that the sponsor perform (phase IV) a study in juvenile animals which aims to fulfill the criteria noted above. Similar studies have been recommended for drugs in development which will be used extensively in children; endpoints to be measured include neurobehavioral and reproductive parameters.

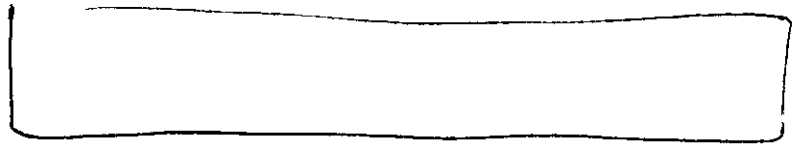
LABELING :

A) Carcinogenesis, Mutagenesis, Impairment of Fertility.

1) In the description of the NTP carcinogenicity studies in mice and rats, the animal/ human safety factors based on mg/kg dose are stated as 20 x and 15 x, respectively. This is based on a maximum recommended human daily dose of 54 mg given to an 18 kg patient, i.e. 3 mg/kg. However, based on the more standard upper human dose of 2 mg/kg, these factors should be changed to 30x and 22x, respectively (which are the factors used in the Ritalin labeling). The safety factors based on mg/m^2, using a multiplier of the mg/kg dose of 25 for humans (which is the appropriate factor for children), should be 3.6 x and 5.4 x for mice and rats, respectively. (Note that these mg/m^2 safety factors are slightly different from those in the Ritalin labeling. The litter presumably used a multiplier of 37, which is correct for adult humans. The Ritalin labeling should probably be modified to give mg/m^2 safety factors resulting from use of a multiplier of 25 to be more correct and to allow consistency across labelings).

   The phrases "(54 mg/qd)" and "(assuming an 18 kg patient)" should be removed from the first 2 paragraphs.

2) The safety factors given in the description of the Continuous Breeding study in mice (last paragraph of this section) should be changed to reflect a maximum human daily dose of 2 mg/kg (the sponsor used 1.54 mg/kg) and a mg/kg-to-mg/m^2 multiplier of 31 for a 12 year old 40 kg female human. The mg/kg and mg/m^2 safety factors should be 80x and 8x, respectively. The phrases "(54 mg qd)" and "(assuming a 35 kg patient)" should be removed.

3) 

4) In the fourth paragraph of this section (describing the genotoxicity studies), the second sentence should begin with "Sister chromatid exchanges and chromosome aberrations were increased, indicative of a weak..." (as it does in the Ritalin labeling). The next to the last sentence, which mentions and unscheduled DNA synthesis assay, should be removed since only a brief

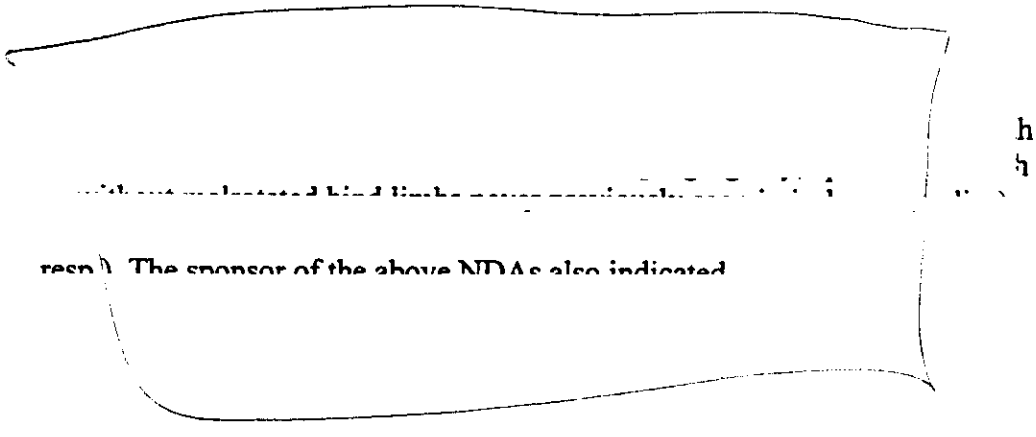
abstract of this study was submitted. The last sentence should end with the word "assay."

B) Pregnancy: Teratogenic Effects

1) In the first sentence, "Reproduction studies" should be in the singular since only a single rat study was performed. The words "impaired fertility or" should be removed since fertility was not assessed in this study.

2) The stated safety factors should be changed to reflect a maximum human daily dose of 2 mg/kg (the sponsor used 1.54 mg/kg) and a human multiplier of 31 (as above). The mg/kg and mg/m^2 safety factors should be 15 x and 3x, respectively. The phrases "(54 mg/qd)" and "(assuming a 35 kg patient)" should be removed from the first sentence.

3) Regarding relative AUC values (2nd sentence), it is not clear what the human values were which were used for comparison; this should be requested from the sponsor. The human values should be $AUC_{0\text{-}24\ hours}$ at steady state with the maximum recommended daily dose. Analogous values for the metabolite PPA should also be given; levels of this metabolite are much greater than those of parent drug in rats and humans; for comparison between these species the sum of the 2 compounds should be used. (The animal values are included under the findings of the segment II rat study earlier in this review).



C) Clinical Pharmacology section

It is stated that "the l-isomer has no pharmacologic activity." I believe this statement is too strong; there are some studies showing activity of the l

isomer, although it is less potent than the d isomer. Furthermore, most studies have focused on actions thought to be related to efficacy in ADHD, e.g. interactions with monoamine neurotransmitters. It is not clear that the relative lack of activity of the l isomer can be extrapolated to other areas.

RECOMMENDATIONS

This NDA is approvable.

[redacted]

The sponsor should be requested to provide human plasma AUC for both parent drug and PPA which can be used for comparison with those in pregnant rats. The human values should be obtained with dosing at the maximum recommended dose, should reflect steady state values, and should be $AUC_{0\text{-}24\ hours}$.

A study in juvenile animals should be performed (phase IV) to examine the effects of methylphenidate on developing systems, with particular emphasis on neurobehavioral and reproductive parameters.

Barry N. Rosloff, Ph.D.

Cc: NDA 21-121, original + division file
Fitzgerald, Homonnay

N:Rosloff/NDA 21-121
DT:04/20/00/ab