CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-259

PHARMACOLOGY REVIEW(S)

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11/30/00

Cited in DFS
1/30/01

Pharmacologist Review of NDA 21-259
Original Summary

SPONSOR: Medeva Pharmaceuticals, Inc.
755 Jefferson Road
Rochester, New York 14603

DRUG: methylphenidate hydrochloride modified release capsules

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

RELATED APPLICATIONS:

1) ——— (precursor to present NDA)

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

3) ——— / NDA 21-121 (for the marketed product Concerta)

INTRODUCTION:

This formulation contains both immediate-release (IR) and extended-release (ER) beads such that 30% of the dose is provided by the IR component and 70% by the ER component.

Methylphenidate has been marketed in this country for several decades. Since an adequate animal reproduction battery had never been performed with methylphenidate, we requested that the sponsor perform a segment II study. It was agreed that a pre- and post-natal rat study conducted under the sponsor's IND for d-methylphenidate ——— could be used; this study used 3 dose levels of d-methylphenidate and a single dose level of the racemate, and is reviewed below.

We also requested that the sponsor address the question of the effects of methylphenidate on developing organisms, either by showing that adequate studies had already been done, or by performing a study (post-marketing if desired). The sponsor performed a literature search which is discussed below.

Other relevant animal studies have been performed by (or under contract from) NTP; these include a continuous breeding study in mice (reviewed in detail in my review of NDA 21-121 of

4/12/00), 2 year carcinogenicity studies in rats and mice (reviews of 7/6/95, and 8/22/95, filed in division files of NDAs 10-187 and 18-029), carcinogenicity studies in P53 and TG-AC mice (review of 11/29/96, filed in division files of NDAs 10-187 and 18-029) and genotoxicity assays. The results of these studies have been incorporated into the Concerta labeling and are currently proposed to be incorporated into the Ritalin labeling; the wording describing these studies should be identical for the labeling of the present product.

PRE- AND POST- NATAL DEVELOPMENTAL TOXICITY STUDY IN RATS

A) Methods

Mated F were randomized into the following groups; N=48 each.

I) control
II) d -methylphenidate 2.5 mg/kg/day
III) d-methylphenidate 8 mg/kg/day
IV) d-methylphenidate 25 mg/kg/day
V) dl-methylphenidate 50 mg/kg/day

Doses expressed as free base. Mode of administration was by gavage.

Twenty-four Fo/group were dosed from days 1-17 of gestation and were sacrificed on day 20 of gestation. Fetuses were examined externally. Approximately ½ of fetuses examined for soft tissue abnormalities and variants by free-hand serial sectioning. Remaining fetuses were examined for visceral abnormalities by open dissection, followed by skeletal exam (Alizarin Red S).

The remaining Fo were allowed to litter normally, and were dosed from day 1 of gestation through the lactation period. Pup survival, growth, development , and reproductive performance were assessed.

Strain: Sprague-Dawley (Charles River UK, outbred albino)

Drug batch #: 1) 1231 (d isomer)
2) M81 ORO1 (dl isomer)

Lab: [redacted]

Volumes: 1.12-1.13

B) Results

1) Observed signs in Fo

Groups IV and V had excessive rearing, hyperactivity, "erratic movement", and agitation; incidence similar between groups. A low incidence of salivation and mydriasis was seen in group V and to a lesser extent in group IV. One group V rat had a "very marked reaction" on day 2 of gestation and was sacrificed.

Group III had excessive rearing, hyperactivity, "erratic movement", and a low incidence of agitation.

Group II had excessive rearing and a low incidence of erratic movement and agitation.

2) Fo bodyweight

Decreased gain in groups IV and V and slight/equivocal decrease in group III. Weight at end of gestation and lactation periods in groups IV and V were 90-93% of control; initial weights in these groups were 97-98% of control.

3) Fo food consumption

Decreased in group IV and to a slightly greater degree in group V. Overall consumption ~ 90% of control.

4) Reproductive data for Fo sacrificed day 20 of gestation

No drug effects. (See sponsor's table 5, attached).

5) Fetal Exams

Results shown in sponsor's Tables 6-8, attached.

There were no clear drug effects. A small number of major abnormalities was seen in all drug groups with most occurring in group V. (Table 6). The most prevalent finding was kinked ribs, the incidences of which were said to be within the "recent background range." The other scattered major abnormalities seen were said "to have been seen in recent studies." The incidence of supernumerary ribs was slightly greater in all drug groups compared to control, but this was not dose-related and was said to be "within the expected background frequency."

6) Reproductive data for Fo allowed to deliver

Results shown in sponsor's Tables 13-15, attached. There were no clear drug effects on stillborn pups; however pup survival was subsequently decreased in groups III-V, with the greatest effect in group V. Overall (through day 21 PP) % pup survival (mean of individual litter %s) was 75%, 68%, 51%, 56% and 19% in groups I-V, resp; most of the excess deaths occurred by day 4 PP. Numbers of litters with total litter loss (not shown in attached tables) were 1, 4, 6, 5, and 15 in groups I-V, resp; this occurred by day 4 or shortly thereafter. It is not clear if necropsies were

performed in any of the above deaths; "occasional" pups may have been necropsied but it is not clear from the presentation of the results what the findings were.

Pup weights (Table 15) were decreased in group V; effects apparent by day 1 PP; mean on day 21 ~ 88% of control. (Weights remained below controls through the post-weaning period).

7) F_1 postnatal development

- Parameters measured :

- Preweaning: time to pinna detachment, incisor eruption, and eye opening; auditory and visual function; negative geotaxis.

-Postweaning: bodyweight gain; open field behavior; rotarod performance; multiple Y-water maze learning and recall; time of vaginal opening and balano-preputial separation; reproductive performance (F_1 dams sacrificed day 14-16 of gestation).

- There were no clear/pronounced drug effects. However, note that in some cases it would be difficult to detect modest effects due to small sample size (group V in pre- weaning tests) or large inter-animal variation (open field, rotarod, and Y-maze tests). The following slight/equivocal effects were seen: decreased weight gain in group V males (but not females), although weight as % of control at 14 weeks PP was the same as at week 4; age at preputial separation in group V males; increased pre- implantation loss in groups IV and V (4%, 3%, 4%, 9%, and 8% in groups I-V, respectively).

8) Plasma drug levels

Levels of parent drug and the metabolite ritalinic acid were measured in a rangefinding study in which rats were given d-methylphenidate at 0, 5, 10, 20, and 30 mg/kg, and dl-methylphenidate at 60 mg/kg, during days 1-17 of gestation. Samples were taken on days 1 and 17, at 0.5, 1, 2, 4, 6, and 8 hr. post-dose (N=3/time point). Results for parent drug are attached. Results for ritalinic acid are not shown since it was determined that degradation had occurred and it was concluded that the data "cannot be considered definitive."

d-MPH/dl-MPH
Pre- and Post-Natal Developmental Toxicity Study in Rats
Teratology Phase
Pregnancy Performance and Foetal Weight

Table 5

	Group/Dose Level (mg.kg^{-1}.day^{-1})				
	1 (0)	2 (*d*-MPH 2.5)	3 (*d*-MPH 8)	4 (*d*-MPH 25)	5 (*dl*-MPH 50)
Number of animals mated	24	24	24	24	24
Number pregnant at day 20 necropsy	21	22	22	20	23
Number of premature decedents	0	0	0	0	1[a]
Pregnancy frequency as %	88	92	92	83	100
Total corpora lutea graviditatis	339	344	332[b]	324	358
Total number of implants	318	316	303[b]	313	326
Pre-implantation loss as %	6	8	9[b]	3	9
Total live implants (%)	310 (97)	308 (97)	310 (97)	291 (93)	312 (96)
Total dead implants (%)	8 (3)	8 (3)	9 (3)	22 (7)	14 (4)
Total early embryonic deaths (%)	8 (3)	6 (2)	9 (3)	22 (7)	13 (4)
Total late embryonic deaths (%)	0	1 (0.3)	0	0	1 (0.3)
Total foetal deaths (%)	0	1 (0.3)	0	0	0
Mean corpora lutea graviditatis	16.1 ± 2.2	15.6 ± 2.9	15.8 ± 3.0	16.2 ± 1.9	15.6 ± 2.4
Mean implants	15.1 ± 2.4	14.4 ± 2.8	14.5 ± 3.0	15.7 ± 1.9	14.2 ± 3.0
Mean live implants	14.8 ± 2.4	14.0 ± 2.8	14.1 ± 3.2	14.6 ± 2.4	13.6 ± 3.2
Mean dead implants	0.4 ± 0.9	0.4 ± 0.6	0.4 ± 0.6	1.1 ± 1.2	0.6 ± 1.1
Mean early embryonic deaths	0.4 ± 0.9	0.3 ± 0.6	0.4 ± 0.6	1.1 ± 1.2	0.6 ± 1.1
Mean late embryonic deaths	0	0.05 ± 0.2	0	0	0.04 ± 0.2
Mean foetal deaths	0	0.05 ± 0.2	0	0	0
Total live male foetuses (%)	147 (47)	148 (48)	143 (46)	155 (53)	152 (49)
Total live female foetuses (%)	163 (53)	160 (52)	167 (54)	136 (47)	161 (51)
Live foetal sex ratio (♂♀)	1:1.11	1:1.08	1:1.17	1:0.88	1:1.06
Mean total uterus weight (g)	86 ± 12	83 ± 14	85 ± 17	84 ± 10	81 ± 17
Mean litter mean foetal weight (g)†	3.59 ± 0.25	3.68 ± 0.25	3.76 ± 0.27	3.57 ± 0.38	3.75 ± 0.30
Mean litter mean placental weight (g)†	0.55 ± 0.07	0.58 ± 0.06	0.55 ± 0.06	0.55 ± 0.07	0.58 ± 0.06
Mean amniotic fluid weight per foetus(g)†	1.31 ± 0.18	1.28 ± 0.19	1.32 ± 0.22	1.27 ± 0.24	1.25 ±0.18

Means are given ± Standard Deviation
Note: Premature decedents excluded below double line
a = Animal killed prematurely on Day 2 of gestation
b = Excludes Animal 110
† = Analysed statistically

d-MPH/dl-MPH
Pre- and Post-Natal Developmental Toxicity Study in Rats

Table 6 ***Group Incidence of Major Foetal Abnormalities***

Abnormality	Group/Dose Level (mg.kg^{-1}.day^{-1})				
	1 (0)	2 (*d*-MPH 2.5)	3 (*d*-MPH 8)	4 (*d*-MPH 25)	5 (*dl*-MPH 50)
	Incidence of Foetuses (Litters)				
Kinked ribs	0	3 (2)	1 (1)	3 (1)	3 (3)
Incomplete ossification of ribs	0	0	1 (1)	1 (1)	1 (1)
Termination of vertebral column (includes anury)	0	0	0	0	2 (2)
Interrupted vertebral column with multiple vertebral/rib irregularities	0	0	0	0	1 (1)
Craniorachischisis, shortened trunk, with partial duplication of vertebral column; kinked scapula; bilateral microphthalmia; suspected absence of tracheal cartilages; thymus and heart ventricles enlarged; fused intermediate to right caudal lung lobe, with enlarged right lobe; dorsal aorta displaced to left; left subclavian artery narrowed; spleen small, pale and dorsally displaced; absent bladder	0	0	0	0	1 (1)
Partially duplicated inferior vena cava	0	0	0	0	1 (1)
Number with major abnormality	0	3 (2)	2 (2)	3 (1)	7 (6)
Total number examined	310 (21)	308 (22)	310 (22)	291 (20)	312 (23)

d-MPH/dl-MPH
Pre- and Post-Natal Developmental Toxicity Study in Rats

Table 7 *Group Incidence of Minor Abnormalities and Variants*

Abnormality/Variant	Group/dose Level (mg.kg^{-1}.day^{-1})				
	1 (0)	2 (*d*-MPH 2.5)	3 (*d*-MPH 8)	4 (*d*-MPH 25)	5 (*dl*-MPH 50)
	Incidence of Foetuses (Litters)				
Visceral					
Haemorrhage within eye	0	1 (1)	1 (1)	1 (1)	0
Haemorrhage within brain ventricle	0	1 (1)	0	1 (1)	1 (1)
Subdural haemorrhage	0	0	0	1 (1)	0
Minimal dilation of brain ventricle(s)	1 (1)	0	0	0	1 (1)
Reduced thyroid	1 (1)	1 (1)	1 (1)	0	0
Enlarged right side of thymus	0	0	1 (1)	0	0
Haemorrhage dorsal fat pad region	1 (1)	2 (2)	0	1 (1)	4 (4)
Small additional vessel cervical region	1 (1)	0	0	0	0
Intra thoracic haemorrhage	0	3 (1)	0	0	0
Small interventricular septal defect	0	0	1 (1)	0	3 (2)
Minimal caudal displacement of origin of azygous vein	0	0	1 (1)	0	0
Anterior displaced origin of left vena cava	0	0	0	0	1 (1)
Additional lobe of liver	0	3 (3)	2 (2)	0	1 (1)
Protrusion of median liver lobe with thinning of diaphragm	14 (7)	10 (8)	3 (2)	8 (6)	11 (6)
Hepatic haemorrhage	1 (1)	3 (3)	0	0	0
Intra abdominal haemorrhage	1 (1)	1 (1)	1 (1)	3 (3)	1 (1)
Displaced testis(es)	5 (5)	9 (4)	3 (3)	5 (5)	7 (7)
Dilated renal pelvis	0	3 (2)	0	2 (2)	3 (3)
Dilated ureter(s)	2 (2)	6 (5)	0	3 (3)	3 (2)
Left umbilical artery	0	1 (1)	0	0	0
Subcutaneous haemorrhage affecting					
Cranium	11 (5)	7 (5)	13 (7)	8 (4)	8 (5)
Trunk	2 (1)	4 (4)	3 (2)	2 (2)	0
Limbs	1 (1)	0	0	0	0
Number with minor visceral abnormality	36 (16)	32 (13)	27 (14)	32 (14)	32 (15)
Total number examined	310 (21)	308 (22)	310 (22)	291 (20)	312 (23)

Table 7
(continued) ***Group Incidence of Minor Abnormalities and Variants***

Parameter	Group/Dose Level (mg.kg^{-1}.day^{-1})				
	1 (0)	2 (*d*-MPH 2.5)	3 (*d*-MPH 8)	4 (*d*-MPH 25)	5 (*dl*-MPH 50)
	Incidence of Foetuses (Litters)				
Skeletal					
Area of ossification between parietal and interparietal	0	0	1 (1)	1 (1)	1 (1)
Cervical rib	0	0	1 (1)	0	0
Slightly kinked ribs	0	4 (2)	0	4 (2)	1 (1)
Additional area of ossification arising from 6th sternebra	0	0	1 (1)	2 (2)	2 (1)
Hemicentric thoracic vertebra	0	0	1 (1)	0	0
One extra pre-sacral vertebra	0	2 (2)	0	0	0
Number with minor skeletal abnormality	0	6 (4)	4 (4)	7 (5)	4 (2)
Number of ribs:					
13th reduced rib(s)	1 (1)	0	0	0	0
13 Complete rib(s)	144 (21)	119 (22)	133 (22)	111 (20)	127 (22)
Vestigial supernumerary rib(s) on 14th thoracic vertebra	10 (8)	37 (14)	21 (10)	32 (13)	28 (13)
Reduced supernumerary rib(s) on 14th thoracic vertebra	0	0	1 (1)	0	0
10 complete rib(s)	0	0	0	0	1 (1)
Total number examined	155 (21)	156 (22)	155 (22)	143 (20)	156 (23)

d-MPH/dl-MPH
Pre- and Post-Natal Developmental Toxicity Study in Rats

Table 8 *Group Incidence of Foetal Skeletal Ossification Parameters*

Abnormality	Group/Dose Level ($mg.kg^{-1}.day^{-1}$)				
	1 (0)	2 (*d*-MPH 2.5)	3 (*d*-MPH 8)	4 (*d*-MPH 25)	5 (*dl*-MPH 50)
	Incidence of Foetuses (Litters)				
Incomplete ossification affecting:					
≥4 skull bones	8 (5)	6 (3)	7 (5)	10 (6)	11 (6)
≤3 skull bones	37 (17)	33 (13)	30 (14)	39 (13)	38 (16)
Cervical vertebral arch(es)	4 (4)	2 (2)	3 (3)	0	1 (1)
Thoracic centrum(a)	13 (8)	13 (8)	7 (5)	8 (6)	5 (5)
Pubis/es	5 (3)	2 (2)	8 (4)	13 (10)	14 (8)
Ischium/a	2 (2)	1 (1)	2 (2)	3 (3)	4 (2)
Lumbar vertebral arches	0	0	0	0	1 (1)
Sacral vertebral arch(es)	18 (10)	12 (8)	14 (17)	16 (9)	10 (5)
2nd and/or 4th metacarpal(s)	1 (1)	3 (2)	1 (1)	4 (2)	8 (5)
Unossified:					
5th metacarpal(s)	68 (17)	48 (16)	54 (16)	74 (16)	53 (18)
5th metatarsal(s)	1 (1)	1 (1)	0	1 (1)	2 (2)
Ossified:					
Anterior arch of atlas ossified	38 (14)	39 (20)	38 (17)	46 (15)	43 (18)
>2 cervical vertebral centra ossified	5 (3)	10 (4)	27 (11)	7 (4)	8 (4)
Phalangeal elements ossified	20 (5)	27 (11)	22 (11)	13 (5)	18 (9)
Number of sternebrae retarded					
0	31 (13)	65 (18)	53 (16)	43 (16)	51 (18)
1	66 (21)	51 (20)	68 (20)	55 (19)	67 (20)
2	56 (19)	35 (14)	31 (12)	38 (13)	35 (18)
3	1 (1)	3 (3)	1 (1)	7 (4)	0
>3	1 (1)	2 (2)	2 (1)	0	3 (2)
Total number examined	155 (21)	156 (22)	155 (22)	143 (20)	156 (23)

For Tables 13 and 14

$$\text{Pregnancy Index} = \frac{\text{Number pregnant}}{\text{Number mated}}$$

$$\text{Gestation Index} = \frac{\text{Number bearing live pups}}{\text{Number pregnant}}$$

For each litter and group:

$$\text{Birth Index} = \frac{\text{Total number of pups born (live and dead)}}{\text{Number of implantation scars}}$$

$$\text{Live Birth Index} = \frac{\text{Number of pups live on Day 0 of lactation}}{\text{Total number born (live and dead)}}$$

$$\text{Viability Index} = \frac{\text{Number of pups live on Day 4 of lactation}}{\text{Number live on Day 0}}$$

$$\text{Lactation Index} = \frac{\text{Number of pups live on Day 21 of lactation}}{\text{Number live on Day 4}}$$

$$\text{Overall Survival Index} = \frac{\text{Number of pups live on Day 21 of lactation}}{\text{Total number of pups born}}$$

d-MPH/dl-MPH
Pre- and Post-Natal Developmental Toxicity Study in Rats
Littering Phase

Table 13 *F_0 Generation*
Duration of Gestation and Overall Litter Performance

	Group/Dose Level ($mg.kg^{-1}.day^{-1}$)				
	1 (0)	2 (*d*-MPH 2.5)	3 (*d*-MPH 8)	4 (*d*-MPH 25)	5 (*dl*-MPH 50)
Number Mated	24	24	24	24	23[b]
Number Pregnant	22	22	23	21	22
Pregnancy Index as %	92	92	96	88	92
Duration of Gestation (Days)					
21	8	5	1	0	6
22	13	16	19	20	16
23	1	1	3	0	0
Mean Duration	21.7	21.7	22.1	22.0	21.8
Number of females producing a live litter	22	21	22	19	20
Gestation index as %	100	95	96	90	91
Mean number of implant sites[a] per pregnancy ± standard deviation	15.0 ± 4.2	15.4 ± 1.9	16.0 ± 1.8	14.9 ± 1.6	15.0 ± 1.4
Mean total number of pups[a] born†	14.6 ± 2.5	14.6 ± 1.9	14.6 ± 1.5	13.1 ± 2.7	14.3 ± 1.1
Mean number of live pups[a] per litter ± standard deviation:					
Day 0 of lactation	14.1 ± 2.4	14.2 ± 2.2	13.6 ± 2.0	12.8 ± 2.8	14.3 ± 1.1
Day 1 of lactation	13.3 ± 2.4	13.4 ± 3.3	12.3 ± 2.7	11.2 ± 3.5	11.9 ± 3.4
Day 4 of lactation	11.4 ± 3.2	12.4 ± 3.3	10.3 ± 3.4	9.7 ± 3.8	9.1 ± 3.4
Day 7 of lactation	11.1 ± 3.2	12.3 ± 3.3	10.3 ± 3.4	9.7 ± 3.8	8.9 ± 3.4
Day 14 of lactation	11.2 ± 3.2	12.2 ± 3.2	10.6 ± 3.6	9.6 ± 3.8	8.7 ± 3.4
Day 21 of lactation†	11.1 ± 3.2	12.2 ± 3.2	10.3 ± 3.5	9.6 ± 3.8	8.6 ± 3.4

a = Excludes litters where all pups died
b = Excludes Animal 232
† = Analysed statistically
Significantly different from the Control: *P<0.05, ** P<0.01, ***P<0.001

d-MPH/dl-MPH
Pre- and Post-Natal Developmental Toxicity Study in Rats
Littering Phase

Table 14 *F_1 Generation*
Survival Indices

		Group/Dose Level ($mg.kg^{-1}.day^{-1}$)				
		1 (0)	2 (*d*-MPH 2.5)	3 (*d*-MPH 8)	4 (*d*-MPH 25)	5 (*dl*-MPH 50)
Birth Index	Mean Litter Index (%)	88	96	89	87	93
	Number Losing >2 pups	4	1	5	7	3
	Number of Litters	22	22	22	20	22
Live Birth Index	Mean Litter Index (%)	97	90	88	89	88
	Number Losing >1 pup	2	4	8	5	4
	Number of Litters	22	22	22	20	22
Viability Index Days 0-4	Mean Litter Index (%)	79	75	58	61	24
	Number Losing >3 pups	6	6	11	10	18
	Number of Litters	22	21	21	19	20
Lactation Index Days 4-21	Mean Litter Index (%)	98	98	93	99	73
	Number Losing >1 pup	1	1	0	0	3
	Number of Litters	21	18	17	15	9
Overall Survival Index Birth-21	Mean Litter Index (%)	75	68	51	56	19
	Number Losing >4 pups	6	7	13	10	20
	Number of Litters	22	22	22	20	22

d-MPH/dl-MPH
Pre- and Post-Natal Developmental Toxicity Study in Rats
Littering Phase

Table 15 *F_1 Generation*
Group Mean Litter and Pup Weight (g) ± Standard Deviation

Day of Lactation	Group/Dose Level ($mg.kg^{-1}.day^{-1}$)				
	1 (0)	2 (*d*-MPH 2.5)	3 (*d*-MPH 8)	4 (*d*-MPH 25)	5 (*dl*-MPH 50)
LITTER					
Day 1	79 ± 15	80 ± 18	71 ± 16	64 ± 19	63 ± 18
Day 4	95 ± 29	107 ± 30	88 ± 32	79 ± 34	68 ± 30
Day 7	138 ± 40	153 ± 41	129 ± 44	116 ± 49	95 ± 43
Day 14	282 ± 71	295 ± 80	261 ± 82	236 ± 86	193 ± 83
Day 21†	445 ± 103	475 ± 112	421 ± 127	373 ± 129	312** ± 122
Mean of Litter Mean Pup Weight					
MALES					
Day 1	6.3 ± 1.4	6.2 ± 0.8	5.9 ± 0.7	6.1 ± 0.7	5.4 ± 0.5
Day 4	8.5 ± 0.9	8.8 ± 1.4	8.8 ± 1.1	8.4 ± 1.3	7.7 ± 1.9
Day 7	12.7 ± 1.4	12.8 ± 1.9	13.0 ± 1.5	12.3 ± 2.1	10.8 ± 3.1
Day 14	26.4 ± 3.2	25.2 ± 4.6	26.6 ± 2.6	25.8 ± 3.2	21.9 ± 5.5
Day 21†	42.2 ± 6.2	40.5 ± 5.1	43.0 ± 5.0	40.9 ± 5.3	36.8 ± 6.7
FEMALES					
Day 1	5.6 ± 0.7	5.9 ± 0.7	5.4 ± 0.7	5.6 ± 0.7	5.2 ± 0.3
Day 4	8.0 ± 1.1	8.4 ± 1.3	8.1 ± 1.2	7.5 ± 1.3	7.2 ± 1.5
Day 7	11.9 ± 1.6	12.2 ± 1.7	12.0 ± 1.9	11.4 ± 1.8	10.3 ± 2.5
Day 14	25.1 ± 3.3	24.1 ± 4.7	25.0 ± 3.1	24.1 ± 2.5	21.4 ± 4.4
Day 21†	40.2 ± 5.9	38.7 ± 5.3	40.5 ± 5.1	38.8 ± 4.4	35.9 ± 5.2

Means exclude litters where all pups died
† = Analysed statistically
Significantly different from the Control: *P<0.05, ** P<0.01, ***P<0.001

Plasma levels (rangefinding study)

Table 5. Pharmacokinetic analyses of MPH in mated female rats given gavage doses of *d*-MPH or racemate.

Dose* (mg/kg)	Day 1				Day 17			
	C_{max} (ng/ml)	T_{max} (h)	AUC (ng.h/ml)	$T_{1/2}$ (h)	C_{max} (ng/ml)	T_{max} (h)	AUC≠ (ng.h/ml)	$T_{1/2}$ (h)
5.8 *d*-MPH	11.7	0.5	18.2	1.3	24.2	0.5	39.5	1.0
12 *d*-MPH	70.7	0.5	97.8	1.4	102	0.5	164	1.1
23 d-MPH	88.9	0.5	266	1.3	154	0.5	625	2.7
35 *d*-MPH	217	0.5	925	2.6	497	0.5	1284	2.2
69 *d,l*-MPH	315	0.5	1573	2.1	268	2.0	1593	1.8
+	213	0.5	788	1.6	165	2.0	717	1.5

Results are for *d*-MPH except where marked + which are for *l*-MPH
The doses are expressed as the hydrochloride salt

* Doses expressed as HCl salt. Doses as free base = 5, 10, 20, 30, and 60, respectively

≠ $AUC_{0-\infty}$

EFFECTS ON DEVELOPING ANIMALS

We had requested (IND 52,318, letter of 4/1/99) that the sponsor address the question of the effects of methylphenidate on neurobehavioral development when given to young animals, either by providing adequate data from the literature or by performing (post-marketing if desired) an animal study. The sponsor has provided a brief discussion of animal studies from the literature; as discussed in my review of NDA 21-121 (4/12/00), these studies have not adequately addressed the problem of concern. An adequate study should involve drug exposure during the entire relevant period of development (considering the age range the intended population), 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. It is recommended that the sponsor perform (phase IV) a study in juvenile animals which aims to fulfill these criteria.

(The sponsor also argues that the pre- and post – natal rat study included in the present NDA provides useful developmental information. Dams were dosed [3 dose levels of the d-isomer, 1 of the racemate] from day 1 of gestation through day 21PP, and various pre-and post- weaning behavioral parameters were examined in the pups. The sponsor notes that many of these parameters would normally be included in a developmental toxicity study. However, the study performed cannot adequately substitute for a valid developmental study since the pups were not directly dosed [it is possible that some drug exposure occurred via the milk but this was not measured], and at any rate there was no drug exposure beyond the end of the lactation period, whereas exposure beyond this time is necessary to correspond to the age of the intended human population).

SUMMARY AND EVALUATION:

The sponsor's pre- and post-natal rat study used daily doses (free base) of 2.5, 8, and 25 mg/kg of d-methylphenidate, and 50 mg/kg of dl methylphenidate. The doses were adequate in that the higher doses caused maternal toxic signs and decreased food consumption and body weight gain. (These effects were generally similar between groups receiving 25 mg/kg of the d isomer and 50 mg/kg of the dl isomer, although a few effects were slightly more pronounced in the latter, suggesting some contribution of the l isomer). There were no clear drug effects on fetal exams; a slightly increased incidence of major abnormalities was seen in the group receiving the racemate although these were generally scattered in type and said to be WNL. Among dams allowed to deliver, pup survival was decreased at 8 and 25 mg/kg of the d isomer and 50 mg/kg of dl, with the greatest effect in the latter group; pup weights were also decreased in the latter group (again suggesting some contribution of the l isomer). There were no clear/pronounced effects on postnatal development, although in some cases it would have been difficult to detect modest effects due to small sample sizes or large inter-animal variation.

(Note that the results with the racemate of the segment II portion of this study are qualitatively similar to those in the segment II rat study submitted to the Concerta NDA 21-121 [review of 4/12/00]. [Note that the dose of the racemate in the present study was about twice that of the HD of the previous study]. This similarity includes the finding of a very slightly higher incidence of scattered malformations at HD. These could not clearly be ascribed to drug in these studies; however it will be instructive to see if this pattern continues in future studies [which are being performed for additional formulations and routes of administration of methylphenidate]. [The types of malformations seen in the two studies generally did not overlap, with the possible exception of vertebral and rib abnormalities; these should be looked for in future studies]. On the other hand, the results of the postnatal portion of the present study differ from those found in a pre- and post-natal study submitted to the Concerta IND ——— on 9/6/00. In the latter, the HD, which was ~ ½ that used in the present study, produced no decrease in pup survival, and a decrease in pup weights which was less than that seen in the present study. [There was also a smaller decrease in maternal weight gain, and no decrease in maternal food consumption, at the HD in the Concerta study]. However, in a rangefinding study submitted to the Concerta NDA, a higher dose was used, which was approximately equal to the dose of the racemate in the present [Medeva] study, and at this dose a decrease in pup survival was seen [along with decreased maternal food consumption and weight gain]).

Genotoxicity assays (Ames Test, chromosomal aberrations in human lymphocytes in vitro, rat liver in vivo/in vitro UDS, mouse micronucleus) were performed with the d enantiomer only, and are therefore not reviewed in the present review. The drug was positive in the chromosomal aberration assay; this is in agreement with studies showing that the racemate was clastogenic in CHO cells; the latter is currently included in the labeling of marketed methylphenidate products.

The sponsor, based on a previous review of the literature and their conduct of a pre- and post-natal rat study, concluded that a developmental study in juvenile animals is not necessary. However, as discussed above, it is felt by this reviewer that the existing data do not adequately address the areas of concern. It is thus recommended that an adequate study be performed during phase IV.

LABELING:

It is proposed that the preclinical sections of the labeling be identical to those approved for the Concerta labeling (and currently proposed for the Ritalin labeling), with the exception that the second paragraph of the Pregnancy section describe the results of the rat pre- and post- natal study preformed by the present sponsor (in place of the descriptions of the studies performed by the other sponsors). (Note that the situation regarding this section has become quite complicated. Since adequate reproduction studies with methylphenidate had never been performed, we have been requiring sponsors of new methylphenidate products to perform such studies, e.g. a recently performed rat segment II study is described in the recently approved Concerta labeling. Numerous additional rat studies are being performed under various INDs for modified oral formulations, transdermal formulations, and formulations for the d enantiomer. One solution would be to include all studies in the labeling of all products, which would involve modifying the labeling of already marketed products as each new product comes to market. This would allow for the most comprehensive summary of findings in labeling. However, we have been advised that it may not be possible to do this for legal reasons, with the exception that statements in the labeling of the reference listed drug [Ritalin in this case], as well as adverse effects, can be put in the labeling of all products. This approach has the disadvantage of having different studies described in the labeling of each product, including the listing of different animal- to- human ratios [mg/kg, mg/m^2, AUC] if different doses were used. [This problem is already apparent: the rat study in the present application used a dose twice as high as the HD in the rat study described in the Concerta labeling, despite the fact that in both cases the doses were adequately chosen by standard MTD criteria. The AUC of parent compound at the dose used in the present study was also about twice as high as that at the HD of the Concerta study])

The rat- to- human AUC ratio for the pre- and post-natal study should not be included in the present labeling, since plasma levels of the metabolite ritalinic acid could not be accurately measured. Levels of ritalinic acid are much greater than those of parent drug, and we have used (in the Concerta labeling), and intend to use, the sum of parent and metabolite to calculate this ratio.

Suggested wording for the second paragraph of the pregnancy section is as follows. (Note that doses are expressed as the HCl salt. For rat- to- human ratios, an MRHD of 2 mg/kg is used. A mg/kg- to - mg/m^2 multiplier of 31 [for a 40 kg 12 year old female] is used for humans):

A reproduction study in rats revealed no evidence of teratogenicity at an oral dose of 58 mg/kg/day. However, this dose, which caused some maternal toxicity, resulted in decreased postnatal pup weights and survival when given to the dams from day one of gestation through the lactation period. This dose is approximately 30 fold and 6 fold the maximum recommended human dose of Metadate on a mg/kg and mg/m^2 basis, respectively.

RECOMMENDATIONS:

This NDA is approvable. Proposed labeling is given above. It is recommended that the finding of decreased pup weights and survival seen in the rat pre- and post-natal study be added to the labeling of other marketed methylphenidate products.

It is recommended that the sponsor perform (phase IV) a study in juvenile animals to examine the effects of methylphenidate on developing systems, with particular emphasis on neurobehavioral and reproductive parameters. A proposed protocol for such a study may be submitted for our comments.

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