

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-514**

**PHARMACOLOGY REVIEW(S)**



DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

**PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION**

NDA NUMBER: 21-514  
SERIAL NUMBER: N-000, BC (Chemistry Amendment, related to the full response to Not-Approvable Letter dated 4/25/03)  
DATE RECEIVED BY CENTER: 11/21/05  
PRODUCT: Daytrana<sup>®</sup> (methylphenidate) Transdermal System  
INTENDED CLINICAL POPULATION: Children (6-12 years old) with Attention Deficit Hyperactivity Disorder.  
SPONSOR: Noven Pharmaceuticals, Inc.  
DOCUMENTS REVIEWED: Vol. 14.1  
REVIEW DIVISION: Division of Psychiatry Drug Products (HFD-130)  
PHARM/TOX REVIEWER: Linda H. Fossom, Ph.D.  
PHARM/TOX SUPERVISOR: Barry N. Rosloff, Ph.D.  
DIVISION DIRECTOR: Thomas P. Laughren, M.D.  
PROJECT MANAGER: Richardae Taylor, Pharm.D.

Date of review submission to Division File System (DFS): 12/19/05.

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## 1 BACKGROUND

According to DSS, methylphenidate (as the hydrochloride) has been approved for treatment of Minimal Brain Dysfunction/Attention Deficit Hyperactivity Disorder as several oral formulations:

- immediate-release tablets (under NDA 10-187, as Ritalin, approved 12/5/1955, sponsored by Novartis),
- sustained/extended release tablets/capsules (NDA 18-029, as Ritalin SR, approved 3/30/1982, sponsored by Novartis; under NDA 21-842, as Ritalin LA, approved 6/5/2005, sponsored by Novartis; under NDA 21-121, as Concerta Extended-release Tablets, approved 8/1/2000, sponsored by Alza, marketed by McNeil Consumer); under NDA 21-259, as Metadate CD Extended-release Capsules, approved 4/3/2001, sponsored by UCB Pharma);
- immediate-release oral solution (under NDA 21-419, as Methylin Oral Solution, approved 12/19/2002, sponsored by Mallinckrodt Baker); and
- immediate-release chewable tablets (under NDA 21-475, as Methylin Chewable Tablets, approved 4/15/2003, sponsored by Mallinckrodt).

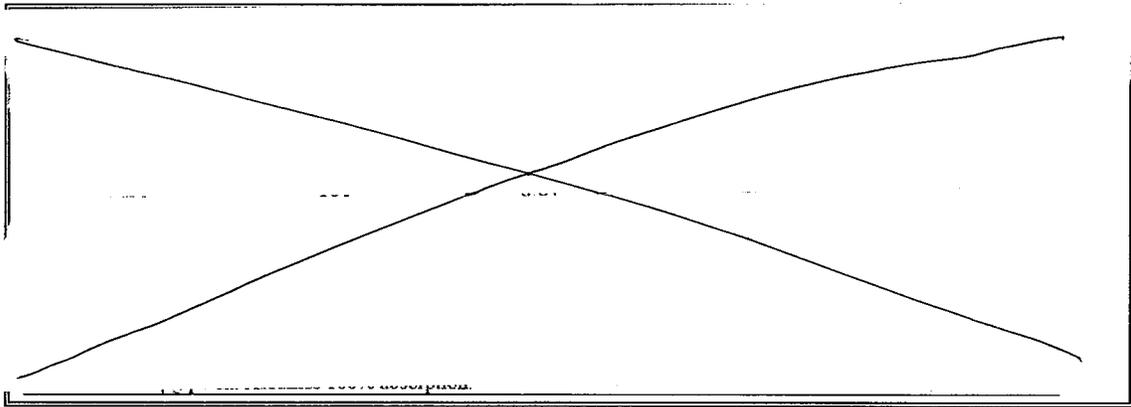
Methylphenidate has not yet been approved in this country for administration by any route other than oral. The maximum recommended human oral dose is 60 mg per day.

Under the current NDA, Noven is seeking approval of a transdermal formulation of methylphenidate hydrochloride for the treatment of Attention Deficit Hyperactivity Disorder in children aged 6-12 years. The initial submission of NDA 21-514 (6/27/02) was determined to be Not Approvable (letter issued 4/25/03), based on clinical and chemistry issues; there were no Pharmacology/Toxicology issues communicated in the letter. The Sponsor responded to the not approvable letter (N-000, AZ, received 6/28/05) and that response is currently under review.

During this review cycle the Chemistry Review Team (in a teleconference on 11/14/05) asked the Sponsor to provide information regarding the controls for residual \_\_\_\_\_ from the acrylic adhesive in their methylphenidate transdermal patch, namely what \_\_\_\_\_ are present, the amounts of those \_\_\_\_\_ and how the Sponsor determined that those levels are safe. The Sponsor's response to those questions (N-000, BZ, stamp-dated 11/21/05, letter-dated 11/18/05) was provided as a 6-page answer to the question "How are \_\_\_\_\_ controlled in the Methylphenidate Transdermal System?" which is reviewed below.

## 2 SPECIFICATIONS FOR RESIDUAL \_\_\_\_\_ THAT ARE PRESENT IN THE PATCH

The Sponsor has set specifications for the \_\_\_\_\_ used in the acrylic adhesive in the patch, namely, \_\_\_\_\_ and \_\_\_\_\_ (see the Sponsor's table, below).



The Sponsor also noted that testing of "clinical supplies" showed that the actual levels of \_\_\_\_\_ and \_\_\_\_\_ were each less than 50 ppm (at the highest dose, i.e., in the 37.5 cm<sup>2</sup> patch), substantially lower than the specifications of 100 and 200 ppm, respectively.

### 3 THE SPONSOR'S ANALYSIS OF THE TOXICITY CONCERNS FOR THESE \_\_\_\_\_

The maximum recommended human dose for this patch formulation is \_\_\_\_\_ mg methylphenidate per 37.5 cm<sup>2</sup> patch per day, which the Sponsor claims will deliver 30 mg over 12 hours (the patch will be applied for up to 9 hours per day and replaced daily). Based on the ICH Guidance Q3B(R) Impurities in New Drug Products (Revision 1, November 2003), the qualification threshold for a drug to be administered at a daily dose of 10 mg – 100 mg is 0.5% or 200 µg TDI (total daily intake), whichever is lower. The qualification threshold would be 150 µg based on a TDI of 30 mg (0.5% of 30 mg is 150 µg which is lower than the limit of 200 µg) or 200 µg based on a TDI of 83.5 mg (0.5% of 83.5 mg is 420 µg, which is higher than the limit of 200 µg).

The current specifications for \_\_\_\_\_ and \_\_\_\_\_ would result in maximum TDIs of 41 µg and 83 µg, respectively; each is well below the more conservative threshold of qualification of no more than 150 µg per day and would not require qualification. No further action would be necessary unless there was some particular concern for a toxicity that could not be adequately monitored in humans, such as carcinogenicity or reproductive toxicity.

#### 3.1 \_\_\_\_\_

The Sponsor stated that according to OSHA (Occupational Safety and Health Administration) and NIOSH (National Institute for Occupational Safety and Health, part of CDC, Center for Disease Control and Prevention) the recommended exposure limit (REL) for \_\_\_\_\_ is 10 ppm (35 mg/m<sup>3</sup>; by inhalation). The Sponsor calculated that the TDI

of — at the REL (based on 8 hr/day exposure and a human respiratory volume of 28,800 liters/day, which is for an adult) would be 336 mg; this is approximately 10,000-times the TDI of 41 µg for the methylphenidate patch, but over-estimates the safety margin for children because presumably they have a lower respiratory volume than adults.

The Sponsor cited a chronic toxicity and carcinogenicity study ( — ) and concluded that administration of — to rats by whole body inhalation for 2 years at concentrations up to 135 ppm (519 mg/m<sup>3</sup>) did not cause systemic toxicity, target organ toxicity or carcinogenicity (details of this study are discussed below). The Sponsor considered the highest dose tested to be a No Observed Effect Concentration (NOEC) for systemic and target organ toxicity, because the effects were limited to irritation-related changes in the olfactory epithelium and cornea. Based on this NOEC, the Sponsor calculated a permitted daily exposure (PDE) for — of 90 mg for a 50-kg human (based on the residual solvents guidance ICH Q3C, 1997; with correction factors of 5 for rats to humans, 10 for inter-individual variability, 1 because the 2-year study duration is at least half the life-time of mice, 1 because the Sponsor did not consider there to be any severe systemic toxicity, and 10 because a NOEL was not identified). This PDE of 90 mg is more than 2000 times the maximum TDI of 41 µg for the methylphenidate patch for a 50-kg adult and more than 800 times the TDI for a 20-kg child (the average weight for a 6-year-old child based on the CDC charts from 2000).

The Sponsor also cited studies from the literature demonstrating that — was not mutagenic in bacterial mutagenicity assays (Ames test; — ), but positive for in vitro and in vivo clastogenicity ( — ).

However, the Sponsor concluded that — was not carcinogenic, based on the chronic toxicity and carcinogenicity studies published by — and coworkers ( — ). [In the carcinogenicity study, male and female rats (86/sex/dose at autopsy) were (whole-body) exposed to — vapors, at concentrations up to 135 ppm (i.e., 475 mg/m<sup>3</sup>; the Sponsor says 519 mg/m<sup>3</sup>) for 6 hr per day, 5 days per week for 24 months. The authors of the study concluded that — was not carcinogenic, but caused irritation to eyes and nasal epithelium; skin was not listed as a tissue of origin in the table listing primary tumors, however, it is assumed that skin was analyzed and found negative, certainly for gross lesions.]

The Sponsor also cited an embryo-fetal developmental toxicity study ( — ) where rats were exposed to — at concentrations up to 100 ppm by whole-body inhalation for 6 hr/day on days 6-20 of gestation; developmental toxicity (reduced fetal weights) was seen at 100 ppm, with reduced maternal body weight gain and food consumption at 50 and 100 ppm.

[According to the EPA, National Center for Environmental Assessment, “ — has been determined to be a systemic toxicant. The daily exposure to the human population (including sensitive subgroups) that is likely to be without appreciable risk

during a lifetime, for \_\_\_\_\_ is 0.03 mg/kg/day for oral exposure.” (Quoted from Health and Environmental Effects Profile for \_\_\_\_\_ U.S. Environmental Protection Agency, Washington, D.C., \_\_\_\_\_ ; on the US EPA website.) This limit of 0.03 mg/kg/day would be 600 µg/day for a 20-kg child (using the mean weight for 6-year-old children from CDC charts from 2000), which is 15-times the TDI of 41 µg for the methylphenidate patch.]

### 3.2 \_\_\_\_\_

For systemic toxicity, the Sponsor cited dermal carcinogenicity studies that were conducted in 2 different strains of mice (discussed in detail below), where application to the skin of mice 3 times per week for 2 years at concentrations up to 86.5% did not affect mortality or body weight, suggesting minimal systemic toxicity (skin tumors are discussed below). Based on this NOAEL, the Sponsor estimated the PDE (for a 50-kg adult; with correction factors of 12 for mice to humans, 10 for inter-individual variability, 1 because the 2-year study duration is at least half the life-time of mice, 1 because the Sponsor did not consider there to be any severe systemic toxicity, and 10 because a NOEL was not identified) for \_\_\_\_\_ (as discussed above for \_\_\_\_\_, to be 28 mg/day, which is more than 300 times the maximum TDI of 83 µg for the methylphenidate patch for a 50-kg adult and more than 120 times the TDI for a 20-kg child (the average weight for a 6-year-old child based on the CDC charts from 2000).

The Sponsor concluded that genetic toxicity studies for \_\_\_\_\_ in the literature indicated equivocal or no mutagenic activity (summarized in \_\_\_\_\_ ; \_\_\_\_\_ ).

[\_\_\_\_\_ appears to be negative in Ames tests: an Ames test from the literature (\_\_\_\_\_, \_\_\_\_\_) and, according to their website, NTP determined \_\_\_\_\_ to be negative in Salmonella assays in 1982, using TA98, TA100, TA1535, TA1537; in 1984, using TA97, TA98, TA100, TA1535; both studies conducted without and with activation (induced rat and hamster S9), but without either TA102 or E. coli WP2 uvr A. Additionally, \_\_\_\_\_ did not produce mutations at the hprt locus in CHO cells (↑ \_\_\_\_\_ ).

Evidence in the published literature regarding in vitro clastogenicity was inconclusive: \_\_\_\_\_ was considered equivocal in mouse lymphoma cells when tested without activation only (unreliable and non-dose-related increase in aberrations (small colonies) and no increase in micronuclei; \_\_\_\_\_ ).

No in vivo clastogenicity studies were cited by the Sponsor and none were found in the published literature by this Reviewer.

Although the Sponsor stated that “\_\_\_\_\_ was not considered carcinogenic to skin in dermal carcinogenicity studies in mice” and cited \_\_\_\_\_ and

\_\_\_\_\_ they make this conclusion based on a) the negative findings in NMRI mice ( \_\_\_\_\_ ) and b) the skin tumors in C3H/HeJ mice that "occurred only at concentrations of \_\_\_\_\_ ( $\geq 21\%$ ) that produced chronic, severe skin irritation and damage ( \_\_\_\_\_ ). They also cited an earlier study ( \_\_\_\_\_ , \_\_\_\_\_ ) where skin tumors were also reported in C3H/HeJ mice.

\_\_\_\_\_ and coworkers ( \_\_\_\_\_ ) investigated the effects of \_\_\_\_\_ administered dermally to C3H/HeJ mice and concluded that "there is an association between severe skin-irritation symptoms and the occurrence of benign and malignant [skin] tumors." In this study, concentrations of \_\_\_\_\_ of 2.5, 21, and 86.5% were applied in a volume of 25  $\mu$ l of acetone 3 times per week to the clipped intrascapular skin of male mice (40 group) for their life-time (acetone- and untreated-controls were included); there were no skin tumors at the low dose (or in either control group), but increases in skin tumors at mid- and high-doses; especially papillomas (4 and 8, respectively), cornified squamous cell carcinomas (20 and 16, respectively), malignant melanomas (7 and 9, respectively), and fibrosarcomas (5 and 0, respectively). Additionally, in another group, given 43% \_\_\_\_\_ for 24 weeks, then continued without treatment to the end of the study, there were no skin tumors. It should be noted that based on macroscopic exams conducted throughout this study, all doses resulted in scabbing and scaling, however, this resolved after ~4-5 weeks of dosing at the low dose (2.5% \_\_\_\_\_) and ~7 weeks after cessation of dosing at 43%, but continued throughout dosing at 21% and 86.5%; and papillomas were noted at week 53 in the 21% dose group and at week 45 in the 86.5% dose group. Scabbing and scaling (followed by thickened skin) appeared to precede tumor formation and could be considered a premonitory sign. Additionally, assuming that the skin surface exposed to \_\_\_\_\_ is no more than a circle of 2-inch diameter (i.e., ~20  $\text{cm}^2$  area and probably a generous estimate for the dorsal skin of a 30-g mouse), the local dose at the NOAEL of 2.5% \_\_\_\_\_ (i.e., 625  $\mu\text{g}/25 \mu\text{l}$ ) would be at least 31  $\mu\text{g}$  per  $\text{cm}^2$  or ~1200  $\mu\text{g}$  for the 37.5  $\text{cm}^2$  methylphenidate patch. This is more than 14 times the maximum TDI of 83  $\mu\text{g}$  for the methylphenidate patch.

\_\_\_\_\_ and coworkers ( \_\_\_\_\_ ) investigated the effects of \_\_\_\_\_ administered dermally to NMRI mice, a strain determined to be more resistant to the irritant effects of \_\_\_\_\_. Male NMRI mice (40/group) were treated with concentrations of \_\_\_\_\_ of up to 85% (in acetone) administered dermally (25  $\mu$ l) for 2 years (with benzo(a)pyrene as positive control; acetone vehicle control). There were no skin tumors at any dose of \_\_\_\_\_ although there was considerable evidence of irritation at all doses (hyperkeratosis and hyperplasia); 31 mice in the positive control group showed squamous cell carcinomas.]

The Sponsor also cited an embryo-fetal developmental toxicity study \_\_\_\_\_, \_\_\_\_\_, where rats were exposed to \_\_\_\_\_ at concentrations up to 100 ppm by whole-body inhalation for 6 hr/day on days 6-20 of gestation; there was no developmental toxicity or teratogenicity at any concentration, but maternal body weight gain was reduced at 100 ppm.

### 3.3 The Sponsor's conclusions

The Sponsor concluded that both  $\text{C}_{12}\text{H}_{22}\text{O}_{11}$  and  $\text{C}_{12}\text{H}_{22}\text{O}_{11}$  are potent skin irritants, but would not be expected to produce significant irritation at the low levels ( $\leq 0.01\%$  and  $\leq 0.02\%$ , respectively) present in the Methylphenidate Transdermal System. They also noted that acrylic adhesives are used in a number of currently marketed transdermal pharmaceutical products and provided a list of 7 products that apparently have patch sizes and duration/frequency of use similar to the proposed methylphenidate patch (see Sponsor's table, below). However, the amounts of these  $\text{C}_{12}\text{H}_{22}\text{O}_{11}$  in these approved products were not provided by the Sponsor and are not readily available from other sources. [It should be noted that  $\text{C}_{12}\text{H}_{22}\text{O}_{11}$  is present in Nitrodur and  $\text{C}_{12}\text{H}_{22}\text{O}_{11}$  is present in Climara Pro, Oxytrol, Androderm, Alora, and Vivelle Dot (see table on page 19 of Dr. Klein's Chemistry Review of NDA 21-336/NDA 21-708, finalized in DFS 11/8/05).]

Product	Patch Sizes (cm <sup>2</sup> )	Duration/Frequency of Use
Nitrodur	5-40	24 hr.
Climara	6.5-25	7 days
Oxytrol	39	3-4 days
Androderm	37	Daily
Alora	18-36	3-4 days
Vivelle	7.25-29	3-4 days
Vivelle Dot	2.5-10	3-4 days
Methylphenidate Transdermal System	12.5 - 37.5	9 hours

Additionally, it should be noted that according to IARC,  $\text{C}_{12}\text{H}_{22}\text{O}_{11}$  and  $\text{C}_{12}\text{H}_{22}\text{O}_{11}$  are both currently categorized as Group 3, that is, not classifiable as to carcinogenicity in humans. This means that there is not enough information to classify them as probably not carcinogenic to humans (Group 4), but also not enough information to classify them as possibly (Group 2B), probably (Group 2A), or known to be (Group 1) carcinogenic to humans.

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#### 4 OVERALL SUMMARY AND CONCLUSIONS

Under the current NDA, Noven is seeking approval of a transdermal formulation of methylphenidate hydrochloride for the treatment of Attention Deficit Hyperactivity Disorder in children aged 6-12 years. [The maximum recommended human dose for this patch formulation is \_\_\_\_\_ mg methylphenidate per 37.5 cm<sup>2</sup> patch per day, which the Sponsor claims will deliver 30 mg over 12 hours (the patch will be applied for up to 9 hours per day and replaced daily).]

The initial submission of this NDA was determined to be Not Approvable, based on clinical and chemistry issues; there were no Pharmacology/Toxicology issues communicated in the letter. The Sponsor has responded to the Not Approvable letter and that response is currently under review. During this review cycle, the Chemistry Review Team asked the Sponsor to provide information regarding the controls for residual \_\_\_\_\_ from the acrylic adhesive in their methylphenidate transdermal patch, namely the \_\_\_\_\_ that are present, the amounts of those \_\_\_\_\_, and how the Sponsor determined that those levels are safe. The Sponsor's response regarding the safety of the \_\_\_\_\_ is the subject of the current review.

The Sponsor has set specifications for the \_\_\_\_\_ used in the acrylic adhesive in the patch, namely, \_\_\_\_\_ and \_\_\_\_\_. The current specifications for \_\_\_\_\_ and \_\_\_\_\_ would result in maximum TDIs of 41 µg and 83 µg, respectively; each is well below the threshold of qualification of no more than 150 µg per day and would not require qualification. No further action would be necessary unless there was some particular concern for a toxicity that could not be adequately monitored in humans, such as carcinogenicity or reproductive toxicity.

Based on carcinogenicity studies and embryo-fetal reproductive toxicology studies cited by the Sponsor from the published literature, the residual \_\_\_\_\_ impurities \_\_\_\_\_ and \_\_\_\_\_ do not appear to pose any particular safety concern that cannot be monitored for in humans and addressed in labeling (see below).

It should be noted that methylphenidate in the patch produced local dermal irritation at the site of application in clinical and animal studies and sensitization in humans. Both the acrylic \_\_\_\_\_ and \_\_\_\_\_ are also irritants. Additionally, \_\_\_\_\_ produced skin tumors at the site of application in one strain of mice, but not another, apparently through a non-genotoxic mechanism and probably related to severe, prolonged skin irritation (with scabbing and scaling) at the site of application. Based on the clinical and animal studies, patients should not continue to apply the patch if irritation occurs. Labeling for most other approved patches includes instruction that patches should not be applied to irritated skin. This labeling issue has been addressed by Dr. Brenda Carr, Medical Officer in Dermatology, in her review/consultation (#753) of a clinical study investigating contract sensitization with the methylphenidate patch (review finalized in DFS 10/26/05).

Finally, the Sponsor indicated that the amounts of \_\_\_\_\_ and \_\_\_\_\_ in the patch are considerably lower than the specifications; 50 ppm compared with specifications of 100 ppm and 200 ppm, respectively. It would seem prudent to ask the Sponsor to lower the specifications, since both \_\_\_\_\_, as well as the drug substance, are skin irritants (and the product is to be used in children). [NB Apparently the Sponsor has communicated their commitment to lower the levels of these \_\_\_\_\_ as much as possible (see Chemistry Review by Sherita McLamore, Ph.D., finalized in DFS 12/14/05).]

## 5 RECOMMENDATIONS

From a Pharmacology/Toxicology perspective, this NDA may be Approved, as always contingent upon acceptable labeling being negotiated.

Linda H. Fossom, Pharmacologist *{see appended electronic signature page}*  
Barry Rosloff, Supervisor *{see appended electronic signature page}*

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/s/

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Linda Fossom  
12/19/2005 06:58:35 AM  
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12/19/2005 12:37:25 PM  
PHARMACOLOGIST

April 8, 2003

Review and Evaluation of Pharmacology and Toxicology  
Original NDA Review

NDA: 21-514  
Sponsor: Noven Pharmaceuticals  
Miami, FI  
Received: 6/28/02  
Drug: Methylphenidate transdermal system (MethyPatch)  
Indication: ADHD  
Related IND: 54,732  
Background:

This NDA for a methylphenidate patch relies primarily on the methylphenidate literature for its preclinical information. A primary dermal irritation study in rabbits and a dermal sensitization study in guinea pigs were performed prior to initiation of clinical trials and have been reviewed previously (submission dated 8/17/98; Pharmacologist Review dated 9/8/98). Following negotiations between the Division and sponsor at EOP2, it was agreed that the only additional animal toxicology studies required prior to approval would be a 3-month dermal irritation/toxicity study, an *in vivo* genotox assay, and developmental toxicology studies (meeting minutes dated 2/4/00). In addition, toxicokinetics studies examining the exposures associated with the doses used in the NTP carcinogenicity studies were requested. The following new studies were submitted with the NDA and are reviewed below:

1. 13-week dermal toxicity in mice
2. 13-week dermal toxicity in rats
3. In vivo mouse micronucleus assay
4. Embryofetal development study in rats
5. Embryofetal development study in rabbits
6. Pre- and postnatal development study in rats

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

1. 13-week dermal toxicity study with methylphenidate in mice (study no. 6543-139; conducted by \_\_\_\_\_; report dated 4/26/01; GLP; Vol. 1.116)

Mice (CD-1; 10/sex/grp) received topical doses of 0 (petroleum jelly vehicle), 0.5, 1.5, 2.5, or 3.5 mg base/day (dose volume: 0.1 ml/day; 2 cm x 2 cm area) of methylphenidate for 13-weeks (corresponding dose levels of 20, 60, 100, and 140 mg/kg/day for assumed constant BW of 25 g). Endpoints included survival, clinical observations, dermal irritation, ophthalmoscopic findings, body weights, food consumption, limited clinical pathology (week 14), organ weights, gross pathology, and limited histopathology (only skin was examined microscopically). There were no treatment-related effects on survival, body weights, dermal irritation scores, ophthalmoscopic findings, hematology, or clinical chemistry. Hyperactivity was seen at all but the LD and food consumption was significantly increased in HD males. Adrenal weights were increased in treated females at all doses. Increased incidence and severity of acanthosis (graded minimal to moderate) in both treated and untreated skin was seen microscopically at doses of 2.5 mg or greater (Table 1). This was said to be consistent with a skin response to irritation, possibly due to excessive grooming related to the stimulant effect of the drug. No evidence of preneoplastic changes (cellular atypia, dysplasia, papillary hyperplasia, endophytic downgrowth) was reported. The only dermal plasma drug level data in mice are from a 2-week dose range-finding study in which doses of 0.15, 0.25, 0.35, and 0.45 mg/day were mistakenly given, ie, 1/10 the intended doses (Table 2).

Table 1.

Table 1  
Incidence and Mean Severity Grades of Acanthosis in Treated and Untreated Skin

Sex	Male					Female				
	1	2	3	4	5	1	2	3	4	5
Group	1	2	3	4	5	1	2	3	4	5
Dose (mg/day)	0	0.5	1.5	2.5	3.5	0	0.5	1.5	2.5	3.5
Treated Skin										
Minimal (+1)	0	0	1	0	3	1	0	1	2	5
Slight (+2)	0	1	0	0	0	0	0	0	0	2
Moderate (+3)	0	0	0	0	0	0	0	0	0	1
Mean Severity Grade	0.0	0.2	0.1	0.0	0.3	0.1	0.0	0.1	0.2	1.2
Untreated Skin										
Minimal (+1)	0	0	0	0	0	0	0	0	2	3
Slight (+2)	0	0	0	0	1	0	0	0	1	3
Moderate (+3)	0	0	0	0	0	0	0	0	1	1
Moderately Severe (+4)	0	0	0	0	0	0	0	0	1 <sup>a</sup>	0
Mean Severity Grade	0.0	0.0	0.0	0.0	0.2	0.0	0.0	0.0	1.1	1.2

<sup>a</sup> Group 4 female H93830 had a skin sore noted at necropsy and an epidermal erosion (ulcer) microscopically.

Table 2.

SUMMARY OF PLASMA DRUG LEVELS (NG/ML) - PHASE I  
15-DAY DERMAL RANGE-FINDING STUDY WITH METHYLPHENIDATE IN MICE

	d-Methylphenidate		l-Methylphenidate		d-Ritalinic Acid		l-Ritalinic Acid	
	Male	Female	Male	Female	Male	Female	Male	Female
0 mg/day	0.00 ± 0.00 n = 5	0.00 ± 0.00 n = 5	0.00 ± 0.00 n = 5	0.00 ± 0.00 n = 5				
0.15 mg/day	2.95 ± 0.86 n = 5	3.07 ± 1.87 n = 5	1.66 ± 0.51 n = 5	1.64 ± 1.68 n = 5	0.00 ± 0.00 n = 5	1.17 ± 2.62 n = 5	40.45 ± 11.58 n = 5	33.01 ± 11.03 n = 5
0.25 mg/day	5.48 ± 0.94 n = 4	5.95 ± 1.99 n = 5	3.27 ± 1.00 n = 4	3.48 ± 0.96 n = 5	2.40 ± 4.80 n = 4	4.72 ± 2.70 n = 5	66.34 ± 26.54 n = 4	53.81 ± 5.71 n = 5
0.35 mg/day	7.26 ± 1.54 n = 5	8.19 ± 3.69 n = 5	4.68 ± 1.71 n = 5	4.93 ± 2.38 n = 5	10.77 ± 3.78 n = 5	7.92 ± 5.51 n = 5	118.54 ± 28.12 n = 5	84.45 ± 32.95 n = 5
0.45 mg/day	8.85 ± 1.49 n = 5	8.77 ± 2.07 n = 5	5.79 ± 1.22 n = 5	5.74 ± 1.48 n = 5	12.45 ± 2.91 n = 5	9.30 ± 3.24 n = 5	140.61 ± 30.47 n = 5	95.81 ± 27.46 n = 5

Note: Individual values below the limits of quantitation were assigned a value of 0 for purposes of this summary presentation.

2. 13-week dermal toxicity study with methylphenidate in rats (C — study no. 6543-138; conducted by C — ; report dated 5/10/01; GLP; Vol. 1.118)

Methylphenidate was topically administered to rats (SD; 10/sex/grp) for 13 weeks at doses of 0 (petroleum jelly vehicle), 2.5, 5.0, 10.0, or 15.0 mg base/day (dose volume: 0.3 ml/day; 2.5 cm x 4.5 cm area) in males and 0, 1.75, 3.5, 7.0, and 10.5 mg base/day in females (corresponding to dose levels of 10, 20, 40, and 60 mg/kg/day at assumed constant BWs of 250 g for males and 175 g for females). Endpoints included survival, clinical observations, dermal irritation, ophthalmoscopic findings, body weights, food consumption, limited clinical pathology (week 14), organ weights, gross pathology, and limited histopathology (only skin was examined microscopically). One C male was found dead during Week 9 and 1 HD male was sacrificed during week 10 due to the severity of dermal lesions. There were no effects on food consumption or ophthalmoscopic findings. Hyperactivity was seen at the 2 highest doses in both sexes. Evidence of dermal irritation (erythema [slight to severe], atonia, desquamation/scaling, and fissuring) was observed at 10.0 mg or greater in males and females. At the end of the treatment period, BW gain was significantly decreased at the HD in both sexes. Skin sores were evident at necropsy in 4 HD males and 8 HD females. Microscopic findings included epidermal erosion, epidermal necrosis with surface exudate, hyperkeratosis, epidermal/dermal inflammation, and/or dermal fibroplasia in the treated skin of HD males and females and acanthosis and associated inflammation and fibroplasia in the treated skin at 10.0 mg or greater in males and 7.0 mg or greater in females (Table 3). There was said to be no evidence of preneoplastic changes (cellular atypia, dysplasia, papillary hyperplasia, or endophytic downgrowth). Plasma drug levels associated with dermal administration of 15, 15, 35, and 45 mg/day in a 2-week dose-rangefinding study are shown in Table 4. The LD was considered the MTD in this study based on dermal irritation and exaggerated pharmacological effects, which were more pronounced in females than males.

Table 3.

Mean Severity Grade of Microscopic Findings in Treated Skin

Sex Group	Male					Female				
	1	2	3	4	5	1	2	3	4	5
Dose (mg/day)	0	2.5	5	10	15	0	1.75	3.5	7	10.5
Epidermal Erosion	0	0	0	0	1.2	0	0	0	0	1.8
Epidermal Necrosis/Surface Exudate	0	0.1	0	0	1.0	0	0	0	0	2.1
Epidermal/Dermal Inflammation	0	0.2	0	0	2.1	0	0.2	0.1	0.3	2.9
Acanthosis	0.1	0.3	0.3	0.5	2.0	0	0.1	0	0.4	2.5
Dermal Fibroplasia	0	0	0	0	0.8	0	0	0	0	1.2

Table 4.

Summary of Plasma Drug Levels (Ng/ml)

15-Day Dermal Range-Finding Study with Methylphenidate in Rats

	d-Methylphenidate		l-Methylphenidate		d-Ritalinic Acid		l-Ritalinic Acid	
	Male	Female	Male	Female	Male	Female	Male	Female
0 mg/day	0.46 ± 0.43 n = 5	0.21 ± 2.90 n = 5	0.35 ± 0.48 n = 5	1.22 ± 0.69 n = 5	0.00 ± 0.00 n = 5	0.00 ± 0.00 n = 5	0.00 ± 0.00 n = 5	0.00 ± 0.00 n = 5
15 mg/day	200.18 ± 93.30 n = 5	1001.43 ± 311.90 n = 4	109.98 ± 54.34 n = 5	681.30 ± 252.85 n = 4	83.86 ± 52.47 n = 5	491.80 ± 156.71 n = 4	467.11 ± 318.08 n = 5	2479.75 ± 824.84 n = 4
25 mg/day	246.36 ± 102.66 n = 5	977.06 ± 417.69 n = 5	136.66 ± 59.29 n = 5	662.74 ± 275.74 n = 5	96.36 ± 40.90 n = 5	457.72 ± 195.05 n = 5	510.99 ± 205.43 n = 5	2383.40 ± 965.02 n = 5
35 mg/day	355.08 ± 143.17 n = 5	1244.33 ± 315.84 n = 4	226.30 ± 84.90 n = 5	818.90 ± 252.02 n = 4	102.18 ± 44.65 n = 5	601.20 ± 134.28 n = 4	596.84 ± 248.66 n = 5	2663.70 ± 926.22 n = 4
45 mg/day	556.34 ± 238.79 n = 5	1326.30 ± 631.94 n = 3	458.50 ± 279.42 n = 5	955.73 ± 473.93 n = 3	145.70 ± 72.15 n = 5	510.60 ± 235.75 n = 3	979.40 ± 646.52 n = 5	2240.15 ± 990.43 n = 3

Notes: Individual values below the limits of quantitation were assigned a value of 0 for purposes of this summary presentation.  
Doses of 0, 15, 25, 35, and 45 mg/day correspond to dose levels of 0, 60, 100, 140, and 180 mg/kg/day assuming a constant body weight of 250 g for both sexes.

3. Mouse micronucleus test (study no. 21481-0-455OECD; conducted by report dated 10/9/00; GLP; vol. 1.116)

In the dose range-finding test, 400 mg/kg was estimated to be the MTD based on mortality at single oral (gavage) doses of 500 mg/kg or greater. There were no apparent sex differences in toxicity. In the definitive assay, single oral doses of 0, 100, 200, or 400 mg/kg were administered to males only (6/timepoint/group) and animals were sacrificed after 24 or 48 hrs and bone marrow smears prepared for analysis of micronucleated immature erythrocyte (PCE) frequencies and proportions of immature erythrocytes (PCE/NCE ratio).

Signs of toxicity were observed at all doses (hyperactivity, chewing) and there were 5 deaths at the HD (3/6 in 24 hr and 2/6 in 48 hr groups; dead animals replaced from supplemental HD group). There was no evidence of cytotoxicity (ie, no statistically significant decrease in PCE:NCE ratio) and no increase in micronucleated PCEs at either sampling time in methylphenidate-treated mice (Table 5). Cyclophosphamide produced the expected increase in micronucleated PCEs but did not decrease the proportion of PCEs at 24 hr.

Table 5.

MICRONUCLEUS DATA SUMMARY TABLE

ASSAY: 21481		TEST ARTICLE: Methylphenidate HCl		
TREATMENT	DOSE	HARVEST TIME (HR)	% MICRONUCLEATED PCEs MEAN OF 2000 PER ANIMAL ± S.E. MALES	RATIO PCE:NCE MEAN ± S.E. MALES
CONTROLS				
VEHICLE	Saline	24 hr	0.07 ± 0.03	2.07 ± 0.43
		48 hr	0.10 ± 0.02	1.07 ± 0.12
POSITIVE	CP 80mg/kg	24 hr	2.68 ± 0.44*	1.82 ± 0.34
TEST ARTICLE	100mg/kg	24 hr	0.03 ± 0.01	2.64 ± 0.53
		200mg/kg	24 hr	0.10 ± 0.04
	400mg/kg	24 hr	0.06 ± 0.02	1.70 ± 0.20
		48 hr	0.05 ± 0.02	0.88 ± 0.04

\* Significantly greater than the corresponding vehicle control, p<0.01.  
 CP = Cyclophosphamide  
 PCE = Polychromatic erythrocyte  
 NCE = Normochromatic erythrocyte

4. Oral embryofetal development study in rats (study no. 6543-132; conducted by \_\_\_\_\_, \_\_\_\_\_, report dated 5/17/00; GLP; vol. 1.120)

A. Methods

Pregnant S-D rats (25/group) were administered 0, 20, 60, or 100 mg/kg/day methylphenidate HCl by oral gavage from Day 6 to Day 17 of gestation. Dams were sacrificed on Day 20 of gestation for examination of the uterine contents. Fetuses were examined for external, visceral, and skeletal abnormalities (1/2 fixed for Wilson's sectioning, 1/2 stained for skeletal examination).

Strain: CD (SD) BR

Lot No.: B05273

Dose Justification: Doses were based on the results of a dose range-finding study in which severe clinical signs (self-mutilation) and mortality were observed at doses of 140 mg/kg or above.

B. Results

a. F0 Effects

- i. There were 3 HD deaths, all considered T-R: 2 dams were found dead on GDs 8 and 9 and 1 dam was sacrificed on GD 8. Clinical signs in animals that died included hyperactivity, prostration, labored respiration, chromodacryorrhea, and self-mutilation.
- ii. T-R clinical signs in remaining dams consisted primarily of hyperactivity at all doses, and self-mutilation at the HD.
- iii. Significantly decreased BW gain was seen at the 2 highest doses, primarily during the first days to treatment (GDs 6-8). BW gain over GDs 6-18 was 27 and 35% below C and GD 20 BWs were 5 and 6% below C, in MD and HD dams, respectively.

b. Litter Effects

- i. There were no clear effects on cesarean section parameters or fetal weights, although resorptions were slightly increased and fetal weights slightly decreased at the MD and HD (none statistically significant).
- ii. There were no apparent effects of treatment on incidences of external, visceral, and skeletal malformations or on external and visceral variations. A possible effect on skeletal variations was seen, however: increased incidences of incomplete ossification of various skeletal elements were seen at all doses, although the effect was not always dose-related (Table 6). Fetal incidences of incomplete ossification of the hyoid body and skull were significantly increased at the MD and HD.

**Table 6** Incomplete ossification in rat embryofetal development study

Statistically Significant Fetal Skeletal Variations				
Finding	0 mg/kg/day	20 mg/kg/day	60 mg/kg/day	100 mg/kg/day
<b>Incomplete/Unossified Hyoid Body</b>				
Fetal incidence	40/165 (24%)	52/169 (31%)	63/164 (38%)**	60/149 (40%)**
Litter incidence	14/25 (56%)	21/25 (84%)*	19/25 (76%)	17/22 (77%)
<b>Incomplete Ossification of Skull</b>				
Fetal incidence	9/165 (5.5%)	15/169 (8.9%)	22/164 (13%)*	28/149 (19%)**
Litter incidence	7/25 (28%)	9/25 (36%)	8/25 (32%)	12/22 (55%)
<b>Incomplete Ossification of Vertebral Arch(es)</b>				
Fetal incidence	32/165 (19%)	33/169 (20%)	38/164 (23%)	33/149 (22%)
Litter incidence	10/25 (40%)	14/25 (56%)	16/25 (64%)	16/22 (73%)*
<b>Less than Four Caudal Vertebrae Ossified</b>				
Fetal incidence	55/165 (33%)	19/169 (11%)**	44/164 (27%)	58/149 (39%)
Litter incidence	14/25 (56%)	9/25 (36%)	18/25 (72%)	19/22 (86%)*
<b>5<sup>th</sup>/6<sup>th</sup> Sternebra(e) Incomplete Ossification</b>				
Fetal incidence	90/165 (55%)	63/169 (37%)**	88/164 (54%)	84/149 (56%)
Litter incidence	22/25 (88%)	21/25 (84%)	24/25 (96%)	21/22 (95%)
<b>5<sup>th</sup> Sternebra Unossified</b>				
Fetal incidence	50/165 (30%)	24/169 (14%)**	43/164 (26%)	43/149 (29%)
Litter incidence	16/25 (64%)	14/25 (56%)	18/25 (72%)	17/22 (77%)
<b>Other Sternebra(e) Incomplete Ossification</b>				
Fetal incidence	1/165 (0.6%)	4/169 (2.4%)	10/164 (6.1%)**	3/149 (2.0%)
Litter incidence	1/25 (4.0%)	3/25 (12%)	5/25 (20%)	3/22 (14%)
<b>14<sup>th</sup> Rudimentary Rib(s)</b>				
Fetal incidence	4/165 (2.4%)	3/169 (1.8%)	18/164 (11%)**	8/149 (5.4%)
Litter incidence	3/25 (12%)	1/25 (4.0%)	7/25 (28%)	6/22 (27%)
<b>Incomplete Ossification of Ischium (a)</b>				
Fetal incidence	2/165 (1.2%)	6/169 (3.6%)	9/164 (5.5%)*	5/149 (3.4%)
Litter incidence	2/25 (8.0%)	3/25 (12%)	4/25 (16%)	3/22 (14%)

Note: \* =  $p \leq 0.05$   
 \*\* =  $p \leq 0.01$

5. Oral embryofetal development study in rabbits (Study no. 6543-135; conducted by \_\_\_\_\_ report dated 2/27/01; GLP; vol. 1.122)

A. Methods

Presumed pregnant rabbits (20/group) were administered doses of 0, 50, 100, 150, or 200 mg/kg/day methylphenidate HCl from Day 7 to Day 20 of gestation. Dams were sacrificed on GD 29 for examination of the uterine contents, and fetuses were examined for external, visceral, and skeletal abnormalities (fresh dissection method followed by staining for skeletal examinations).

Strain: New Zealand White

Lot No.: B05273

Dose Justification: Doses were based on the results of a dose range-finding study in which doses up to 150 mg/kg/day produced no significant maternal or developmental toxicity.

B. Results

a. F0 Effects

- i. T-R deaths were seen at the 2 highest doses: 2 and 8 does died at 150 and 200 mg/kg, respectively. Clinical signs in these animals included hyperactivity, stereotypy, increased respiration, and increased respiration.
- ii. Clinical signs observed in the remaining animals consisted primarily of hyperactivity, repetitive movements, and increased respiration (D-R incidence and severity) at

≥ 100 mg/kg.

- iii. There was a D-R reduction in BW gain with a significant BW loss at the HD. BW changes from GD7-21 were 147.11, 120.75, 67.71, 66.62, and -69.42 gm in the C, LD, MLD, MHD, and HD groups, respectively.

b. Litter Effects

- i. There were no apparent effects on litter parameters. Resorptions, numbers of live fetuses, and fetal weights were similar across groups.
- ii. There were no apparent effects of treatment on incidences of major abnormalities with the possible exception of a finding of hydrocephaly in 2 fetuses from 1 HD litter (Table 7). This would not have been remarkable by itself, but in combination with the increase in dilatation of the lateral ventricles also seen in the HD group may be of significance.
- iii. An increase in the fetal (1.2, 0, 1.4, 2.4, and 5.8% in C, LD, MLD, MHD, and HD) and litter incidences (11, 0, 12, 13, and 33%) of dilatation of the lateral ventricles (considered a visceral variation) was seen at the HD (Table 8). This effect was considered (in the study report) "not an adverse fetal effect," which is unfounded. No additional T-R differences in incidences of fetal variations were seen.

Table 7. Major visceral malformations in rabbit embryofetal development study

SUMMARY OF FETAL SOFT TISSUE MALFORMATIONS						
RABBIT DEVELOPMENTAL TOXICITY STUDY WITH METHYLPHENIDATE HCL						
DOSE LEVEL		GROUP 1 0 MG/KG/DAY	GROUP 2 50 MG/KG/DAY	GROUP 3 100 MG/KG/DAY	GROUP 4 150 MG/KG/DAY	GROUP 5 200 MG/KG/DAY
LITTERS EVALUATED	N	18	16	17	16	12
FETUSES EVALUATED	N	164	130	139	125	86
LIVE	N	164	130	139	125	86
DEAD	N	0	0	0	0	0
INTERNAL HYDROCEPHALY						
FETAL INCIDENCE <sup>a</sup>	N	0	0	0	0	2
	%	0.0	0.0	0.0	0.0	2.2
LITTER INCIDENCE	N	0	0	0	0	1
	%	0.0	0.0	0.0	0.0	8.3
HEART AND/OR GREAT VESSEL MALFORMATIONS						
FETAL INCIDENCE	N	0	0	1	0	0
	%	0.0	0.0	0.7	0.0	0.0
LITTER INCIDENCE	N	0	0	1	0	0
	%	0.0	0.0	5.9	0.0	0.0
GALL BLADDER AGENESIS						
FETAL INCIDENCE	N	0	0	0	1	0
	%	0.0	0.0	0.0	0.8	0.0
LITTER INCIDENCE	N	0	0	0	1	0
	%	0.0	0.0	0.0	6.2	0.0
TOTAL FETAL SOFT TISSUE MALFORMATIONS						
FETAL INCIDENCE <sup>a</sup>	N	0	0	1	1	2
	%	0.0	0.0	0.7	0.8	2.3
LITTER INCIDENCE	N	0	0	1	1	1
	%	0.0	0.0	5.9	6.2	8.3

STATISTICAL ANALYSES WERE CONDUCTED. IF SIGNIFICANT DIFFERENCES OCCUR, THEY ARE DENOTED AS FOLLOWS: \* = P<0.05 \*\* = P<0.01.  
 N = NUMBER  
<sup>a</sup> SIGNIFICANT POSITIVE TREND

Table 8. Incidences of visceral variations in rabbit embryofetal development study

SUMMARY OF FETAL SOFT TISSUE VARIATIONS  
RABBIT DEVELOPMENTAL TOXICITY STUDY WITH METHYLPHENIDATE HCL

DOSE LEVEL		GROUP 1	GROUP 2	GROUP 3	GROUP 4	GROUP 5
		0 MG/KG/DAY	50 MG/KG/DAY	100 MG/KG/DAY	150 MG/KG/DAY	200 MG/KG/DAY
LITTERS EVALUATED	N	18	16	17	16	12
FETUSES EVALUATED	N	164	130	139	125	86
LIVE	N	164	130	139	125	86
DEAD	N	0	0	0	0	0
DILATATION OF LATERAL VENTRICLE(S)						
FETAL INCIDENCE <sup>a</sup>	N	2	0	2	3	5
	%	1.2	0.0	1.4	2.4	5.8*
LITTER INCIDENCE <sup>a</sup>	N	2	0	2	2	4
	%	11	0.0	12	13	33
VARIATIONS OF THE MAJOR VESSELS						
FETAL INCIDENCE	N	19	7	10	9	7
	%	12	5.4*	7.2	7.2	8.1
LITTER INCIDENCE	N	8	5	7	7	7
	%	44	31	41	44	58
INTERMEDIATE LOBE OF LUNG SMALL/MISSING						
FETAL INCIDENCE	N	8	2	3	7	2
	%	4.9	1.5	2.2	5.6	2.3
LITTER INCIDENCE	N	4	2	2	5	1
	%	22	13	12	31	8.3
GALL BLADDER SMALL						
FETAL INCIDENCE	N	0	0	1	1	0
	%	0.0	0.0	0.7	0.8	0.0
LITTER INCIDENCE	N	0	0	1	1	0
	%	0.0	0.0	5.9	6.2	0.0
TOTAL FETAL SOFT TISSUE VARIATIONS						
FETAL INCIDENCE	N	28	9	16	20	12
	%	17	6.9**	12	16	14
LITTER INCIDENCE	N	12	6	8	12	8
	%	67	38	53	75	67

STATISTICAL ANALYSES WERE CONDUCTED. IF SIGNIFICANT DIFFERENCES OCCUR, THEY ARE DENOTED AS FOLLOWS: \* - P<0.05 \*\* - P<0.01.  
N = NUMBER

<sup>a</sup> SIGNIFICANT POSITIVE TREND

6. Pre- and postnatal development study in rats (Study No. 6543-133; conducted by \_\_\_\_\_; report dated 4/2/01; GLP; vol. 1.121)

A. Methods

Pregnant S-D rats (25/group) were assigned to 4 dose groups to receive 0 (vehicle), 20, 40, or 60 mg/kg/day of d,l-methylphenidate (d,l-MPH) by oral gavage from Day 6 of gestation through Day 20 of lactation. Dams were allowed to deliver and nurse their litters before being sacrificed on PND 21. Reproductive outcome from F0 and F1 generations were monitored and F1 litters were monitored for growth and development, including assessment of maturational landmarks, open field activity, and learning and memory.

Strain: — CD (SD); BR  
Lot No.: B05273

B. Results

a. F0 Effects

- i. There were 2 deaths, 1 each in the MD and HD groups. No remarkable signs were noted prior to death. T-R clinical signs in all groups consisted primarily of hyperactivity and increased activity. Self-mutilation was seen in 2 HD dams.
- ii. Maternal BW gain was significantly decreased during the gestational treatment periods in the MD and HD groups. Maternal BW gain over GDs 6-20 was 13 and 20% below C in the MD and HD groups, respectively (both SS). Maternal BW gain was comparable among groups during the lactational treatment period.

b. Natural Delivery Observations

- i. There was a D-R decrease in pup survival in the d,l-MPH groups (viability and weaning indices were 78.8 and 91.9% of C, respectively, at the HD), with a significantly lower mean number of pups/litter at the HD (Table 9). The number of pups surviving to PND 21 was 81% of C in the HD group. Most of the pup loss occurred during the first 4 days after birth.
- ii. Offspring BWs were dose-dependently decreased at birth (~10% at HD) and throughout lactation, with statistically significant differences seen at the MD and HD (Table 10). These BW deficits remained during the postweaning phase, with significant differences in BW seen in the HD group throughout the first 3 weeks postweaning. The weight differences had been made up by the end of the observation period (7-14 weeks postweaning).
- iii. Delays in the attainment of most maturational landmarks were seen in HD group pups (statistically significant for pinna unfolding; Table 11). There were no clear treatment effects on measures of activity (photocell chamber at PND 22 and 5 weeks postweaning) or learning and memory (M maze testing at 3 weeks postweaning).
- iv. There were no apparent effects of treatment on offspring reproductive function (mating trials performed beginning on 7 weeks postweaning).
- v. There were no treatment-related differences in offspring necropsy observations.

Table 9.

NATURAL DELIVERY DATA AND LITTER DATA SUMMARY - F0 GENERATION					
STUDY FOR EFFECTS ON PRE- AND POSTNATAL DEVELOPMENT, INCLUDING MATERNAL FUNCTION, IN THE RAT					
DOSE LEVEL		GROUP 1 0 MG/KG/DAY	GROUP 2 20 MG/KG/DAY	GROUP 3 40 MG/KG/DAY	GROUP 4 60 MG/KG/DAY
<b>PUP SURVIVAL INDICES</b>					
LIVEBIRTH INDEX	MEAN%	99	99	99	99
(NUMBER BORN ALIVE/NUMBER BORN)					
VIABILITY INDEX	MEAN%	99	97	95	78
(NUMBER ALIVE DAY 4 PRECULL/ NUMBER LIVEBORN)					
WEANING INDEX	MEAN%	99	95	100	91
(NUMBER ALIVE AT WEANING/ NUMBER ALIVE AT DAY 4 POSTCULL)					
<b>PUP DISPOSITION</b>					
CULLED DAY 4	TOTAL	124	106	111	64
KILLED		0	0	0	0
DIED		1	3	9	40
CANNIBALIZED		0	0	0	6
MISSING		3	6	6	24
PUPS SURVIVING AT 21 DAYS	TOTAL	191	189	187	156
<b>PUPS DYING, KILLED, MISSING, AND/OR CANNIBALIZED</b>					
DAYS 0-4		3	8	15	66
DAYS 5-21		1	1	0	4
<b>ENTIRE LITTER DIED, KILLED, MISSING, AND/OR CANNIBALIZED</b>					
DAYS 0-4	N	0	0	0	1
DAYS 5-21	N	0	0	0	2

STATISTICAL ANALYSES WERE CONDUCTED. IF SIGNIFICANT DIFFERENCES OCCUR, THEY ARE DENOTED AS FOLLOWS: \* = P<0.05 \*\* = P<0.01.  
 N = NUMBER OF LITTERS.  
 TOTAL = NUMBER OF PUPS OR IMPLANTS.

Table 10.

NATURAL DELIVERY DATA AND LITTER DATA SUMMARY - F0 GENERATION

STUDY FOR EFFECTS ON PRE- AND POSTNATAL DEVELOPMENT, INCLUDING MATERNAL FUNCTION, IN THE RAT

DOSE LEVEL		GROUP 1 0 MG/KG/DAY	GROUP 2 20 MG/KG/DAY	GROUP 3 40 MG/KG/DAY	GROUP 4 60 MG/KG/DAY
DAY 0 MALES	MEAN	6.57	6.62	6.51	6.07
	S.D.	0.34	0.47	0.64	0.77
	N	24	24	24	24
COVARIATE ADJUSTED MEAN		6.63	6.60	6.54	5.95**
DAY 0 FEMALES	MEAN	6.32	6.23	6.09	5.77
	S.D.	0.46	0.42	0.58	0.75
	N	24	24	24	23
COVARIATE ADJUSTED MEAN		6.37	6.21	6.11	5.71**
DAY 4 MALES - PRECULL	MEAN	10.67	10.47	9.87	9.27
	S.D.	1.02	1.05	1.37	1.98
	N	24	24	24	23
COVARIATE ADJUSTED MEAN		10.62	10.46	9.85	9.36*
DAY 4 FEMALES - PRECULL	MEAN	10.29	10.16	9.50	9.08
	S.D.	0.97	1.07	1.41	1.78
	N	24	24	24	21
COVARIATE ADJUSTED MEAN		10.33	10.17	9.51	9.02**
DAY 4 MALES - POSTCULL	MEAN	10.69	10.48	9.91	9.34
	S.D.	1.10	1.07	1.41	1.98
	N	24	24	24	23
COVARIATE ADJUSTED MEAN		10.64	10.46	9.89	9.43*
DAY 4 FEMALES - POSTCULL	MEAN	10.30	10.21	9.64	9.09
	S.D.	1.03	1.06	1.45	1.77
	N	24	24	24	21
COVARIATE ADJUSTED MEAN		10.32	10.22	9.65	9.05**
DAY 7 MALES	MEAN	17.55	17.12	15.95	14.96
	S.D.	1.57	1.64	2.33	3.32
	N	24	24	24	22
COVARIATE ADJUSTED MEAN		17.20	16.88	15.86	15.70*

STATISTICAL ANALYSES WERE CONDUCTED. IF SIGNIFICANT DIFFERENCES OCCUR, THEY ARE DENOTED AS FOLLOWS: \* = P<0.05 \*\* = P<0.01.  
N = NUMBER OF LITTERS.

Table 11.

REFLEX AND DEVELOPMENT - MEAN AGE IN DAYS OF PUPS REACHING CRITERION - F1 GENERATION

STUDY FOR EFFECTS ON PRE- AND POSTNATAL DEVELOPMENT, INCLUDING MATERNAL FUNCTION, IN THE RAT

DOSE LEVEL		GROUP 1 0 MG/KG/DAY	GROUP 2 20 MG/KG/DAY	GROUP 3 40 MG/KG/DAY	GROUP 4 60 MG/KG/DAY
PREPULSIL SEPARATION	MEAN	41.58	41.58	41.79	42.71
	S.D.	1.67	1.35	1.69	1.62
	N	24	24	24	21
COVARIATE ADJUSTED MEAN		41.55	41.59	41.78	42.76
VAGINAL OPENING	MEAN	31.79	31.21	31.67	32.38
	S.D.	0.93	0.78	1.55	1.56
	N	24	24	24	21
COVARIATE ADJUSTED MEAN		31.81	31.20	31.67	32.36
EYE OPENING	MEAN	14.29	14.38	14.38	14.81
	S.D.	0.69	0.65	0.65	0.93
	N	24	24	24	21
COVARIATE ADJUSTED MEAN		14.30	14.38	14.38	14.80
HAIR GROWTH	MEAN	9.17	8.75	8.38	9.81
	S.D.	0.76	0.85	0.92	1.63
	N	24	24	24	21
COVARIATE ADJUSTED MEAN		9.20	8.77	8.37*	9.75
INCISOR ERUPTION	MEAN	12.00	11.67	11.79	12.33
	S.D.	1.06	0.96	1.14	1.24
	N	24	24	24	21
COVARIATE ADJUSTED MEAN		12.07	11.71	11.79	12.21
PINNA UNFOLDING	MEAN	2.67	2.71	3.08	3.65
	S.D.	0.56	0.46	0.63	1.03
	N	24	24	24	23
COVARIATE ADJUSTED MEAN		2.83	2.77	3.12	3.37*

STATISTICAL ANALYSES WERE CONDUCTED. IF SIGNIFICANT DIFFERENCES OCCUR, THEY ARE DENOTED AS FOLLOWS: \* = P<0.05 \*\* = P<0.01.

<sup>a</sup> STATISTICAL ANALYSIS NOT CONDUCTED.

N = NUMBER OF LITTERS

<sup>b</sup> PUPS REACHING CRITERION = TOTAL NUMBER OF PUPS WITH MEASURE PRESENT/TOTAL NUMBER TESTED ON FIRST DAY OF TEST.

SUMMARY AND EVALUATION

An extensive stereoselective presystemic metabolism has been observed after oral administration of racemic methylphenidate (d,l-MPH) to humans that results in plasma levels of d-methylphenidate (d-MPH) that are 8-10-fold higher than those of the l-isomer. This is bypassed with transdermal administration of d,l-MPH, which produces much higher exposures to l-MPH compared to oral dosing in humans. The ratio of d- to l-MPH is approximately 2:1 in the plasma of pediatric patients wearing a 50 Cm<sup>2</sup> patch (3.6 mg/hr) for 12 hrs. Thus, patients treated with transdermal MPH will be exposed to considerable amounts of l-MPH, which is pharmacologically active but variably less potent than the d-isomer. Pharmacology studies submitted by the sponsor compared the acute effects of d,l-, d-, and l-MPH on general activity and behavior following iv administration to rats and dogs. All three MPH entities produced qualitatively similar stimulant-type effects, which included increased activity, increased respiration, restlessness, stereotypic behavior, aggression, and convulsions. In both species the rank order of potency for producing these effects was d>d,l>l.

No repeated-dose studies comparing the toxicity of d- and l-MPH were submitted by the sponsor. However, in general and developmental toxicity studies of d-MPH conducted by Celgene for Focalin (NDA 21-278), positive control groups treated with d,l-MPH were included for comparison. At doses equimolar in d-MPH content (up to 50 mg/kg d-MPH and 100 mg/kg d,l-MPH for 3 months in rats), the incidence and/or severity of clinical signs (e.g., hyperactivity, stereotypic behavior, self-mutilation) and anorexia tended to be greater in the groups administered d,l-MPH as compared to the parallel dose groups given the d-isomer alone, although the observations were similar in nature between the d- and d,l-treated groups. The few developmental effects observed (delayed fetal skeletal ossification, decreased postweaning offspring BW gain) were also more pronounced in groups exposed to d,l-MPH. These results are not surprising given that the dose of the racemate was twice that of the d-enantiomer, and l-MPH is pharmacologically active. However, part of the basis for the greater toxicity of the racemate may come from a pharmacokinetic interaction between the two enantiomers. When equimolar doses of d-MPH were administered either as the pure enantiomer or as part of the racemate, exposures to d-MPH (based on plasma AUC) were consistently greater in animals given the racemate, presumably as a result of a metabolic interaction (this has been described previously in rats). In some cases the magnitude of this AUC difference (up to 3-fold) appeared to be greater than any quantitative differences in toxicity; however, C<sub>max</sub> values for d-MPH were more similar between d- and d,l-MPH-treated animals, so the degree to which this PK interaction is reflected in toxicity may depend on which parameter is more important for the toxic effect. In addition, of course, animals treated with the racemate were exposed to the pharmacological/toxicological effects of l-MPH, which is present in animals (rodents and dogs) at plasma levels similar to those of d-MPH following oral administration of the racemate. This may not always be additive with the actions of d-MPH, however. In a literature study comparing the pharmacological activity of MPH and its enantiomers in rats, the locomotor inducing activity of pure d-MPH was greater than that of an equimolar dose of the d-isomer given as part of the racemate, indicating that the l-isomer could be interfering with the effects of the d-isomer. Studies of the effects of MPH on motor hyperactivity induced by 6-OHDA in juvenile rats found that both d- and d,l-MPH inhibited activity in lesioned rats, while l-MPH did not. d-MPH was 3 times more potent than d,l-MPH in this model, and pretreatment of lesioned rats with l-MPH reduced the motor inhibiting effects of d-MPH. Thus, l-MPH appears to interact pharmacokinetically and pharmacodynamically to influence the activity of the d-enantiomer as well as contribute its own effects. There is no evidence in animals, however, that the presence of the l-enantiomer introduces any unique effects.

The genetic toxicology study performed by the sponsor with d,l-MPH (mouse micronucleus test) was negative, in agreement with other results reported for the racemate in the same test. However, in assays conducted by NTP, d,l-MPH reportedly increased sister chromatid exchanges and chromosome aberrations in CHO cells (NTP technical report 439). In carcinogenicity studies of d,l-MPH conducted by NTP, which are considered adequate for the NDA, rats (F344/N; 70/sex/grp) were fed diets containing 0, 100, 500, or 1000 ppm and mice (B6C3F1; 70/sex/grp) diets containing 0, 50, 250, or 500 ppm for 2 years (NTP Technical Report 439). These doses were based on the results of 13-week dose range-finding studies in which liver weights were increased at doses of 1000 ppm or greater in rats and 125 ppm or greater in mice, and centrilobular hypertrophy and hepatocellular degeneration or necrosis were seen at doses of 500 ppm or greater in male mice. In the 2-year studies, there were no significant differences in survival among groups of rats or mice. The only T-R clinical observation was increased fighting in HD male mice. At the LD, MD, and HD, final mean BWs were 102, 95, and 90% of C for male rats; 96, 89, and 78% for female rats; 97, 89, and 93% for male mice; and 98, 93, and

97% of C for female mice, respectively. The average amount of d,l-MPH consumed per day was estimated to be, respectively, 5, 25, and 50 mg/kg for LD, MD and HD rats; 6, 30, and 60 mg/kg for LD, MD, and HD male mice; and 8, 40, and 80 mg/kg for LD, MD, and HD female mice. There were no D-R increases in neoplasms in rats receiving d,l-MPH. In fact, administration of MPH was associated with decreased incidences of fibroadenomas of the mammary gland in female rats. In mice, however, administration of MPH was associated with increased incidences of eosinophilic foci and hepatocellular adenomas in HD males and females and hepatoblastomas in HD males. Incidences of hepatocellular carcinoma were similar among control and treated mice. It was concluded that, under the conditions of these studies, there was no evidence of carcinogenic activity in rats, but that there was some evidence of carcinogenic activity in male and female mice based on the occurrence of hepatocellular neoplasms. No plasma levels were obtained in the original studies, but TK studies were conducted by the sponsor at the same dietary doses of d,l-MPH and in the same mouse and rat strains as in the NTP studies. The results of these studies are compared to data collected in clinical studies in **Table 12**. The ratios of d- to l-MPH were approximately 1:1 in mice and rats at the highest doses tested, and exposures to each enantiomer were similar to or somewhat greater than those expected in children using the transdermal dosage form (at dose of approximately 3.6 mg/hr). This data supports the relevance of the oral rodent studies to the current application.

No evidence of teratogenic activity was identified in rat and rabbit embryofetal development studies conducted by the sponsor. There was evidence of developmental toxicity, however, both in the embryofetal and pre- and postnatal development studies. These findings agree with the results of previous studies submitted to the Agency and with the limited data reported in the literature for d,l-MPH. Doses that were at least minimally maternally toxic were evaluated in all three of the current studies. Recent data also indicate that early postnatal exposure to d,l-MPH can have long-term effects on behavioral parameters in rodent offspring (Ritalin LA, NDA 21-284 ), and this information should be added to the label.

In the 13-week mouse dermal toxicity studies, MPH (base) induced minimal to moderate changes of skin irritation characterized by acanthosis and inflammation; the NOEL for skin irritation was > 60 mg/kg/day. In rats, dermal MPH induced more severe changes of skin irritation, which were characterized by epidermal erosion/necrosis with exudate, acanthosis, parakeratosis and inflammation; the NOEL for skin irritation was 20 mg/kg/day. Hyperactivity occurred in both species; the NOEL for this effect was 20 mg/kg/day in mice, and 10 mg/kg/day in rats. Plasma levels measured at 2 hours after the last dose (day 15) in rats given the HD (approx. 60 mg/kg/day) are compared to levels in pediatric patients in **Table 13**.

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**Table 12.**

**Comparison of C<sub>max</sub> and AUC Values of Methylphenidate and Ritalinic Acid Isomers in Mice, Rats and Pediatric Patients**

	Mouse (500 ppm)	Rat (1000 ppm)	Pediatric Patients (Pooled Sexes)
<i>d</i> -methylphenidate			
C <sub>max</sub> (ng/mL)	M: 20.31 (~ 0.65*) F: 10.21 (~ 0.32)	M: 39.6 (~ 1.30) F: 67.7 (~ 2.20)	31.37 <sup>a</sup>
AUC (ng*h/mL)	M: 225.73 (~ 0.91) F: 160.30 (~ 0.64)	M: 510 (~ 2.05) F: 1097 (~ 4.40)	249.27 <sup>a</sup>
<i>l</i> -methylphenidate			
C <sub>max</sub> (ng/mL)	M: 23.67 (~ 1.30) F: 13.97 (~ 0.78)	M: 40.2 (~ 2.20) F: 51.5 (~ 2.90)	18.08 <sup>a</sup>
AUC (ng*h/mL)	M: 222.96 (~ 1.60) F: 205.98 (~ 1.46)	M: 632 (~ 4.50) F: 769 (~ 5.50)	140.53 <sup>a</sup>
<i>d</i> -ritalinic acid			
C <sub>max</sub> (ng/mL)	M: 48.31 (~ 0.28) F: 38.27 (~ 0.22)	M: 165 (~ 0.97) F: 159 (~ 0.94)	170.0 <sup>b</sup>
AUC (ng*h/mL)	M: 740.81 (~ 0.22) F: 518.17 (~ 0.16)	M: 2519 (~ 0.76) F: 3059 (~ 0.92)	3319.0 <sup>b</sup>
<i>l</i> -ritalinic acid			
C <sub>max</sub> (ng/mL)	M: 581.38 (~ 3.50) F: 469.88 (~ 2.80)	M: 1400 (~ 8.50) F: 1127 (~ 6.80)	164.9 <sup>b</sup>
AUC (ng*h/mL)	M: 8810.57 (~ 2.99) F: 7012.16 (~ 2.38)	M: 20377 (~ 6.90) F: 20328 (~ 6.90)	2948.0 <sup>b</sup>

\* Values in parentheses are multiples of the values in pediatric patients.

<sup>a</sup>N17-016, patch worn for 12 hours, AUC value obtained from 0 – 12 hours.

<sup>b</sup>N17-002, patch worn for 24 hours, AUC value obtained from 0 – 24 hours.

Table 13.

**Comparison of C<sub>max</sub> and AUC Values of Methylphenidate and Ritalinic Acid Isomers in Rats and Pediatric Patients**

	Rat [15 mg/day, (~ 60 mg/kg/day)]	Pediatric Patients (Pooled Sexes)
<i>d</i> -methylphenidate		
C <sub>max</sub> (ng/mL)	M: 200.18 (~ 6.38**) F: 1001.67 (~ 31.93)	31.37 <sup>a</sup>
<i>l</i> -methylphenidate		
C <sub>max</sub> (ng/mL)	M: 109.98 (~ 6.08) F: 681.30 (~ 37.68)	18.08 <sup>a</sup>
<i>d</i> -ritalinic acid		
C <sub>max</sub> (ng/mL)	M: 83.86 (~ 0.50x) F: 491.80 (~ 2.90x)	170.00 <sup>b</sup>
<i>l</i> -ritalinic acid		
C <sub>max</sub> (ng/mL)	M: 476.11 (~ 2.80x) F: 2497.75 (~ 15.10x)	164.90 <sup>b</sup>

<sup>a</sup>Plasma samples were collected at 2 hours after dosing on the last day (day 15), however it is unknown when C<sub>max</sub> levels were reached.

\*\* Values in parentheses are multiples of the values in pediatric patients.

<sup>a</sup>N17-016, 50 cm<sup>2</sup> MTS worn for 12 hours.

<sup>b</sup>N17-002, 2 x 10 cm<sup>2</sup> MTS worn for 24 hours.

RECOMMENDED LABELING:

2 Page(s) Withheld

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

       ✓ § 552(b)(4) Draft Labeling

       § 552(b)(5) Deliberative Process

The NDA is approvable with respect to the pharmacology/toxicology portion. Recommendations concerning the proposed labeling are made in the Summary and Evaluation section of the review.

J.E. Fisher, Ph.D.

cc:  
NDA (21-514)  
Div File  
HFD-120/BRosloff/AMHomonnayWeikel/EFisher

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/s/

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