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## STUDY SYNOPSIS

<b>Protocol number:</b> SPD485-409	<b>Study drug:</b> Daytrana™, SPD485, <i>d,l</i> -( <i>threo</i> )-methylphenidate, Methylphenidate Transdermal System (MTS)
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**Title of the study:**

A Phase IIIb, Randomized, Double-Blind, Multi-Center, Parallel-Group, Placebo-Controlled, Dose Optimization Study, Designed to Evaluate the Safety and Efficacy of Daytrana™ Methylphenidate Transdermal System (MTS) in Adolescent Patients aged 13-17 years with Attention-Deficit/Hyperactivity Disorder (ADHD).

**Investigators:**

Multi-center study to be conducted in the United States only.

**Study centers:**

Approximately 20 study centers planned.

**Study period (planned):**  
April 2007 to February 2008

**Clinical Phase:**  
IIIb

**Objectives:**

**Primary**

- The primary objective of this study is to evaluate the efficacy of Daytrana™ compared to placebo, as determined by the change in the clinician completed ADHD-RS-IV, in the symptomatic treatment of adolescents (aged 13-17 years) diagnosed with Attention-Deficit/Hyperactivity Disorder (ADHD) by DSM-IV-TR criteria.

**Secondary**

- To assess the safety and tolerability of Daytrana™ compared with placebo based on occurrence of treatment-emergent adverse events (AEs), laboratory tests, vital signs, physical examinations, ECGs and weight.
- To assess the efficacy of Daytrana™ compared to placebo in the home environment as rated by the parent using the Conners' Parent Rating Scale-Revised: Short Form (CPRS-R) administered weekly, on one weekend day in the morning and afternoon.
- To assess global impressions of ADHD severity and improvement of Daytrana™ compared to placebo from the clinician and parent in response to treatment from Clinical Global Impressions (CGI-S and CGI-I) and Parent Global Assessments (PGA).
- To assess skin tolerance to Daytrana™ /Placebo Transdermal System (PTS), from the dermal response scale.
- To assess the relationship between plasma exposure and the safety and efficacy measures of Daytrana™ via sparse sampling.

**Methodology:**

This is a phase IIIb, randomized, double-blind, multi-center, parallel-group, placebo-controlled, dose optimization study designed to evaluate the safety and efficacy of Daytrana™ (10mg/9 hr, 15mg/9 hr, 20mg/9 hr, and 30mg/9 hr doses) compared to placebo in adolescent subjects (aged 13-17 years) diagnosed with ADHD. Subjects will visit the study site nine times during the course of approximately 14 weeks. The study will consist of three periods detailed below:

**Screening & Washout Period (1-6 weeks)**

Subjects will be screened for approximately 2 weeks prior to washout. Washout will be up to 30 days depending upon the half-life of the subject's current medication.

**Double-Blind Dose Optimization/Maintenance Period (7 weeks)**

Eligible subjects will be randomized in a 2:1 ratio to Daytrana™ or matching PTS and enter the double-blind stepwise dose optimization period. The objective of this period is to ensure subjects are titrated to at least an acceptable dose (see "acceptable condition" below) of Daytrana™ (using 10mg/9 hr, 15mg/9 hr, 20mg/9 hr, and 30mg/9 hr doses) based upon investigator review of parent rating forms, treatment emergent AEs, and clinical judgment (using the ADHD-RS-IV). The duration of this period is five weeks to allow for titration

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up to the highest dose and one titration down to a prior dose level, if necessary. No further titration up or down is permitted once subjects have been titrated down.

**Optimization Period (5 weeks)**

The duration of Daytrana™ /PTS patch wear will be nine hours per day; a new patch will be applied each morning. All subjects will be initiated on the Daytrana™ /PTS 10 mg dose and will be evaluated after one week (7 ± 3 days) for tolerability and effectiveness. Subjects may be titrated to the next patch size/dosage strength after a minimum of one week (± 3 days) on the previous size/dose based on the overall response of the subject. Additionally, subjects may be titrated back down to the previous patch size/dosage strength (once) during the Optimization Period (Visits 3, 4, 5, and 6) to optimize tolerability and effectiveness. Subject response will be categorized by the investigator into 1 of 3 conditions and associated actions:

1. **Intolerable condition:** (i.e., unacceptable safety profile) Requires the subject to be tapered to a lower Daytrana™ patch size. However, if the adjusted patch size/dose strength produces an intolerable effect as well, the subject should be discontinued from the study.
2. **Ineffective condition:** (i.e., < 25% change in ADHD-RS score from baseline with acceptable safety profile) Requires increasing the Daytrana™ patch size to the next available dose strength followed by weekly evaluation.
3. **Acceptable condition:** A response is defined as acceptable if it shows a significant reduction in ADHD symptoms with minimal side effects. Investigators should refer to the subject's baseline ADHD-RS-IV score to aid in dose adjustments. Subjects who have at least a 25% reduction from baseline in ADHD symptom scores at a given dose, as determined by the ADHD-RS-IV are considered to be at an acceptable dose. Subjects categorized as "acceptable" may be maintained at their current dose for the remainder of the study (through Visit 9). Alternatively, the subject's dose can be increased to the next larger patch size/dosage size, if the current dose is well tolerated, and in the Investigator's opinion the subject would potentially receive further symptom reduction through titration to the next patch size/dosage size. Visit 6 will be the last visit at which titration can occur. No further titration will be permitted after Visit 6.

Subjects who have **not** reached at least an acceptable dose (i.e. "Acceptable condition") by Visit 7, will be withdrawn from the study.

**Maintenance Period (2 weeks)**

Following successful titration to at least an acceptable dose of Daytrana™ / PTS by Visit 7, subjects will maintain the dose through the maintenance period. Double-blind assessment of the safety and efficacy of Daytrana™ / PTS will proceed for two weeks.

**Follow-Up Period (30 days)**

Subjects will receive a follow-up phone call 30 days (± 3 days) following their last dose of study drug (Visit 9/Early Termination) to collect information on any new or ongoing SAEs and/or AEs, as well as concomitant medications. Additionally, subjects that are discontinued due to an application site reaction may be contacted up to a year after the last dose of study medication to determine subsequent ADHD therapy and tolerability.

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**Number of subjects (total and for each treatment arm):**

Approximately 210 subjects will be randomized in a 2:1 ratio to receive either Daytrana™ (140 subjects) or Placebo (70 subjects).

It is expected that an effect size of 0.5 will be observed in this study. In order to achieve 85% power at a significance level of 0.05 (two-sided), a total sample size of 165 subjects (110 for Daytrana™ and 55 for Placebo) will be required. Assuming a dropout rate of 20%, approximately 210 subjects will be required in this study.

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**Diagnosis and main criteria for admission:**

Inclusion Criteria

- Subject must meet Diagnostic and Statistical Manual of Mental Disorders, 4<sup>th</sup> ed. – Text Revision (DSM-IV-TR) criteria for a primary diagnosis of ADHD based on a detailed psychiatric evaluation.
  - Subject must have a total score of ≥ 26 on the ADHD-RS-IV at the Baseline Visit (Visit 2).
  - Subject must have a minimum level of intellectual functioning, as determined by an IQ (based on KBIT) score of 80 or above.
  - Subject has blood pressure measurements within the 95th percentile for age, gender, and height at
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Screening and Baseline.

- Subject's ECG results are within the normal range or not clinically significant at Screening and Baseline as judged by the Investigator in conjunction with the central reader.
- Subject is a male or female aged 13-17 years inclusive at the time of consent.
- Females of Child-bearing Potential (FOCP) must have a negative serum beta Human Chorionic Gonadotropin (HCG) pregnancy test at Screening and a negative urine pregnancy test at Baseline and agree to use acceptable contraceptives throughout the study period and for 30 days after the last dose of investigational product.
- Subject has no comorbid illness that could affect safety or tolerability or in any way interfere with the subject's participation in the study.
- Subject and parent or legally authorized representative (LAR) are willing and able to comply with all the requirements defined in this protocol.
- Subject's parent or LAR must provide signature of informed consent, and there must be documentation of assent by the subject indicating that the subject is aware of the investigational nature of the study and the required procedures and restrictions.

Exclusion Criteria

- Subject has a current, controlled (requiring a restricted medication) or uncontrolled, comorbid psychiatric diagnosis (except ODD) with significant symptoms such as any severe comorbid Axis II disorders or severe Axis I disorders (such as Post Traumatic Stress Disorder (PTSD), psychosis, bipolar illness, pervasive developmental disorder, severe obsessive compulsive disorder, severe depressive or severe anxiety disorder) or other symptomatic manifestations that, in the opinion of the examining physician, will contraindicate Daytrana™ treatment or confound efficacy or safety assessments. Comorbid psychiatric diagnosis will be established with the screening interview of the K-SADS-Present and Lifetime – Diagnostic Interview (K-SADS-PL) and additional modules if warranted by the results of the initial interview.
  - Believed by the Investigator to be acutely at risk for suicidal or violent behavior towards him/herself or others, or a history of a suicide attempt requiring medical intervention.
  - Subject has a history of a structural cardiac abnormality, cardiomyopathy, cardiac rhythm abnormalities or other serious cardiac problems.
  - Subject is a known non-responder to psychostimulant treatment, operationally defined as no clinical improvement following separate trials of two psychostimulant medications, taken for ADHD at appropriate doses for at least 4 weeks each.
  - Subject, in the opinion of the Physician Investigator, is overweight (Body Mass Index (BMI)-for-age >90th percentile) per CDC BMI-for-age gender-specific charts.
  - Subject has a history of seizures during the last 2 years (exclusive of infantile febrile seizures), a tic disorder, a current diagnosis and/or family history of Tourette's Disorder.
  - Subject has Conduct Disorder.
  - Subject has a positive urine drug or alcohol result at Screening or at Baseline (with the exception of subject's current stimulant therapy, if any).
  - History of alcohol or other substance abuse or dependence as defined by DSM-IV (except caffeine or nicotine) within the last 6 months.
  - Subject has taken an investigational drug within 30 days prior to Screening.
  - Subject has any abnormal thyroid function that is not adequately treated in the opinion of the Physician Investigator.
  - Subject has any clinically significant laboratory abnormalities at Screening, in the opinion of the Physician Investigator.
  - Subject has a concurrent chronic or acute illness (such as severe allergic rhinitis or an infectious process requiring antibiotics), disability, or other condition that might confound the results of safety assessments administered in the study or that might increase risk to the subject. Similarly, the subject will be excluded if he or she has any additional condition(s) that in the Investigator's opinion would prohibit the subject from completing the study or would not be in the best interest of the subject. This would include any significant illness or unstable medical condition that could lead to difficulty complying
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with the protocol. Mild, stable asthma is not exclusionary.

- Subject has had treatment with any known hepatic and/or P450 enzyme altering agents (barbiturates, phenothiazines, cimetidine, etc.) within 30 days prior to Screening.
- Subject is taking any medication that is excluded. A history of previous or current use of Daytrana™ excludes the subject from participating in the study.
- Subject is taking other medications that have CNS effects or affect performance, such as sedating antihistamines and decongestant sympathomimetics. (Bronchodilators are not exclusionary.)
- The female subject is pregnant or lactating.
- Subject has any skin disease, or history of any chronic skin disease, skin cancer (with the exception of localized basal cell carcinoma of the skin which has been fully treated), skin manifestations of allergic disease, or other dermatologic conditions which would interfere with trial assessments or compromise subject safety (e.g. dermatitis, eczema or psoriasis).
- Subject has sensitive-skin syndrome (definition: subjects who often develop nonspecific skin irritancy reactions to bland materials) or has sensitivities to the ingredients in soaps, lotions, cosmetics or adhesives.
- Subject has clinical signs and symptoms of skin irritation (i.e., pruritus, burning, erythema) or hyper/hypopigmentation at the potential application sites (i.e., scars or tattoos).
- Subject has a documented allergy, hypersensitivity or "clinically significant" intolerance to Methylphenidate (MPH) or any components found in Daytrana™.

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**Test product, dose, and mode of administration:**

Daytrana™ (10mg/9 hr, 15mg/9 hr, 20mg/9 hr, and 30mg/9 hr doses) is designed to deliver *d,l* (*threo*)-methylphenidate transdermally at a continuous rate upon application to intact skin. Daytrana™ should be applied to a clean, dry, non-oily and non-irritated site on the hip of each subject. Initial placement on the left or right side will be up to the subject or caregiver. Subsequent applications should be alternated to the opposite side so that the same site is not used for 2 consecutive applications. The target wear time for Daytrana™ is 9 hours.

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**Duration of treatment:**

- Screening period: approximately 2 weeks
- Washout period (if applicable): 1 to 4 weeks
- Treatment period: 5 weeks optimization plus 2 weeks maintenance
- Follow-up: 30 days ( $\pm$  3 days)

Eligible subjects will visit the clinic 9 times over the course of approximately 14 weeks. At 30 days ( $\pm$  3 days) post-discontinuation or completion of study drug, a follow-up telephone contact will occur to collect information on any new or ongoing SAEs and/or AEs, as well as concomitant medications. Additionally, subjects that are discontinued due to an application site reaction may be contacted up to a year after the last dose of study medication.

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**Reference therapy, dose and mode of administration:**

Placebo will be provided as matching transdermal patches (PTS).

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**Criteria for evaluation:**

The primary outcome measure of the study will be the ADHD-RS, Version IV (DuPaul et al., 1998). The ADHD-RS consists of 18 items designed to reflect current symptomatology of ADHD. Each item is scored on a 4-point scale ranging from 0 (no symptoms) to 3 (severe symptoms), with the total score for the rating scale ranging from 0 to 54. The scale may be sub-divided into two sub-scales of 9 items each: hyperactivity/impulsivity and inattentiveness.

Secondary outcome measures will include the Conners' Parent Rating Scale- Revised: Short Form (CPRS-R), Clinical Global Impressions of Improvement (CGI-I), Parent Global Assessment (PGA), and the application skin site evaluation (Dermal Response Scale and Experience of Discomfort and Pruritus).

Adverse events (AEs), laboratory tests, physical examinations, weight, vital signs, and ECGs will assess the safety and tolerability of MTS compared to PTS.

Relationships will be explored between plasma concentrations of Daytrana™ and the response measures listed above.

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**Statistical methods:**

The primary efficacy variable is the ADHD-RS-IV total score change at the endpoint from Baseline. The primary efficacy analysis will be performed on the ITT population with last observation carried forward (LOCF) approach. The ITT population will include all randomized subjects who receive at least one dose of study medication, and have one baseline and at least one post baseline assessment of the ADHD-RS-IV. The primary efficacy variable will be assessed using analysis of covariance (ANCOVA) with treatment and center as factors and baseline ADHD-RS-IV score as a covariate. The null hypothesis is that there is no difference between MTS and placebo. The treatment comparisons will be tested at the significance level of 0.05. Homogeneity of treatment effect across centers will be assessed graphically. The same ANCOVA model will be used to analyze the primary efficacy variable at Visits 3, 4, 5, 6, 7, 8 and 9 for the observed case. To address incomplete data that results from either early termination (subjects withdrawn prior to Visit 9) or unavailability, a sensitivity analysis will be performed by a mixed-effects model repeated measures (MMRM) on ADHD-RS-IV total score change from baseline based on observed data. Subject will be used as a random effect. The unstructured covariance matrix will be utilized, and the model will include treatment, center and time (post baseline visit) as factors and baseline score as a covariate.

Additional statistical analyses of the primary efficacy variable, and analyses of secondary efficacy variables, are considered supportive. The CPRS-R will be analyzed using the same ANCOVA model described above to examine the treatment effects in the change in score at endpoint from baseline for the ITT population.

The CGI-I and PGA will be analyzed by a Cochran Mantel-Haenszel (CMH) test stratified by centers. Prior to the analysis, this variable will be dichotomized to two categories, with 'very much improved' and 'much improved' into one category and the remaining levels into the other.

Dermal evaluations will be assessed by treatment group. Continuous variables will be summarized using number of observations, mean, standard deviation (SD), median, minimum, and maximum values for each treatment group. Categorical values will be summarized using number of observations and percentages.

Adverse events will be coded using the MedDRA (version 7.0) adverse event dictionary. Frequency of treatment-emergent adverse events will be calculated for each body system, by preferred term, by treatment group, for number of subjects and percentage reporting the event. Withdrawals due to adverse events will be summarized for each system organ class and preferred term by treatment group. Adverse events will also be summarized by gender, age category (13-14 years vs. 15-17 years) and ethnic origin.

At applicable visits, descriptive statistics (number of observations, mean, SD, minimum, median and maximum values) will be presented for clinical laboratory tests (hematology and serum chemistry, urinalysis) and ECG; categorical values will be summarized using number of observations and percentages (urinalysis). Changes from Baseline and shift tables (for Baseline versus each applicable visit) will also be presented.

Vital signs (oral temperature, systolic and diastolic blood pressure, pulse, and respiratory rate), physical examination, and weight will be summarized by treatment group using appropriate descriptive statistics. Continuous variables will be summarized using a number of observations, mean, SD, minimum, median and maximum values. Categorical values will be summarized using number of observations and percentages.

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**Pharmacokinetic methods:**

The plasma *d*-MPH and *l*-MPH concentrations, collected at end-of wear-time (i.e. approximately 9.0 hours after application) during the dose maintenance and end of study visits, will be used as the measure of systemic exposure. Regression analyses conducted as part of Study SPD485-302 have previously demonstrated that the concentrations at this sampling time is highly correlated with area under the plasma concentration-time curve (AUC) in pediatric patients. The relationships between any treatment-related changes in relevant efficacy parameters (ADHD-RS-IV and CPRS-R ratings) and systemic exposure will be explored.

Relationships between relevant safety parameters (e.g. change in systolic BP, diastolic BP or pulse; treatment-emergent AEs including weight loss or sleep changes) and systemic exposure will be explored if appropriate.

## STUDY SCHEDULE

Visit	Screening ∇	Wash-out Call	Baseline	Double-Blind Treatment Period							Follow-up Call*
	1	No Visit	2	Dose Optimization					Dose Maintenance		No Visit
				3	4	5	6	7	8	9 EOS/ ET	
Week	-3 to -1	-1 <sup>^</sup>	0	1	2	3	4	5	6	7	11
Informed Consent/Assent	✓										
Psychiatric Evaluation α	✓		✓								
KBIT (IQ Test)	✓										
Inclusion/Exclusion Criteria	✓	✓	✓								
Demographics	✓										
Randomization			✓								
Medical and Medication Hx	✓										
Physical Examination Σ	✓										✓
Vital Signs β	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓
Height (calibrated stadiometer)	✓										✓
Weight (calibrated scale)	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓
IVRS			✓	✓	✓	✓	✓	✓	✓	✓	
Clinical Laboratory Tests φ	✓										✓
12-lead ECG ψ	✓		✓					✓			✓
Pregnancy Test (FOCP)**	✓		✓								✓
Urine Drug and Alcohol Test	✓		✓								
PI Dose Assessment ω				✓	✓	✓	✓	✓			
ADHD-RS-IV	✓		✓	✓	✓	✓	✓	✓	✓	✓	
CPRS-R δ			✓	✓	✓	✓	✓	✓	✓	✓	
CGI-S	✓		✓								
CGI-I				✓	✓	✓	✓	✓	✓	✓	
PGA			✓	✓	✓	✓	✓	✓	✓	✓	
PK Blood Draws ~								✓	✓	✓	
Study Medication Distribution π			✓	✓	✓	✓	✓	✓			
Study Medication Return/Accountability π				✓	✓	✓	✓	✓	✓	✓	
Dermal Evaluations λ				✓	✓	✓	✓	✓	✓	✓	
Concomitant Medications	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Adverse Events ∅∅	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

- ∇ If Screening and Baseline are greater than 28 days apart, subject will need to repeat clinical laboratory tests and conduct an abbreviated physical exam.
- <sup>^</sup> The washout period is one to four weeks in duration. This schedule was prepared to track a one-week washout.
- \* A visit window of 30 ±3 days will be permitted for the follow-up call.
- α Psychiatric evaluation at the Screening Visit includes the K-SADS-PL Screen Interview (and other modules if necessary) and an interview based on DSM-IV criteria. The K-SADS-PL will not be done at Baseline.
- β Includes oral temperature, blood pressure, pulse, and respiratory rate (Sealed - after 5 minutes of rest).
- φ Clinical Laboratory Tests will include hematology (CBC), serum chemistry, and urinalysis (and microscopic examination if protein and/or blood are detected during urinalysis).
- \*\* Includes Serum at Screening, Urine at Baseline, and a Serum at End of Study/Early Termination.
- ω PI Dose Assessment of tolerability and effectiveness of current study dose.
- δ Parent/caregiver to complete on last weekend day prior to each visit starting with the Baseline Visit at approximately 11:00AM and 3:00PM.
- ~ PK Blood Draws will occur at each of the last three visits; Visits 7, 8, and 9 (a single sample at the end of the wear-time, 9 hours after application, in each case).
- π Study medication includes the Daytrana<sup>SM</sup>.
- λ Refer to Appendix XX for specific dermal evaluation procedures.
- ∅∅ Spontaneously reported AEs will be collected throughout, non-directed questioning will occur.
- Σ Physical Examination includes an examination of the skin at the potential application sites.
- ψ ECG (average of three for baseline) will be obtained after the subject has rested for five minutes in the supine position.



**Proposed Pediatric Study Request (PPSR)  
Division of Psychiatry Products**

**Daytrana™  
(Methylphenidate Transdermal System)**

**IND 54,732  
NDA 21-514**

**Shire Development Inc.**

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**Attachment I Protocol No. SPD485-409: A Phase IIIb, Randomized, Double-Blind, Multi-Center, Parallel-Group, Placebo-Controlled, Dose Optimization Study, Designed to Evaluate the Safety and Efficacy of Daytrana™ Methylphenidate Transdermal System (MTS) in Adolescent Patients aged 13-17 years with Attention-Deficit/Hyperactivity Disorder (ADHD).**

## **1. TYPE AND OBJECTIVE OF STUDIES TO BE PERFORMED**

### **1.1 Study Objectives**

#### **1.1.1 Primary**

The primary objective of this study is to evaluate the efficacy of Daytrana™ compared to placebo, as determined by the change in the clinician completed ADHD-Rating Scale-IV (ADHD-RS-IV), in the symptomatic treatment of adolescents (aged 13-17 years) diagnosed with Attention Deficit Hyperactivity Disorder (ADHD) by DSM-IV-TR criteria.

#### **1.1.2 Secondary**

The secondary objectives are:

- To assess the safety and tolerability of Daytrana™ compared with placebo based on occurrence of treatment-emergent adverse events (AEs), laboratory tests, vital signs, physical examinations, ECGs and weight.
- To assess the efficacy of Daytrana™ compared to placebo in the home environment as rated by the parent using the Conners' Parent Rating Scale-Revised: Short Form (CPRS-R) administered weekly, on one weekend day in the morning and afternoon.
- To assess global impressions of ADHD severity and improvement of Daytrana™ compared to placebo from the clinician and parent in response to treatment using Clinical Global Impressions (CGI-S and CGI-I) and Parent Global Assessments (PGA).
- To assess skin tolerance to Daytrana™/Placebo Transdermal System (PTS), from the dermal response scale.
- To assess the relationship between plasma exposure and the safety and efficacy measures of Daytrana™ via sparse sampling.

### **1.2 Study Design**

See the Methodology section of the Study Synopsis (Attachment I)

## **2. INDICATION TO BE STUDIED**

The indication to be studied is ADHD.

### **3. NUMBER OF PATIENTS TO BE STUDIED**

Approximately 210 subjects will be randomized in a 2:1 ratio (Daytrana™: Placebo) to receive either Daytrana™ (140 subjects) or placebo (70 subjects).

### **4. AGE GROUPS IN WHICH THE STUDIES WILL BE PERFORMED**

The age group to be studied is male or female adolescents aged 13 to 17 inclusive.

### **5. STUDY ENDPOINTS**

#### **5.1 Primary Efficacy Endpoint**

The primary efficacy variable is the ADHD-RS-IV total score change at the endpoint from Baseline. The primary efficacy analysis will be performed on the Intent-To-Treat (ITT) population with last observation carried forward (LOCF) approach. The ITT population will include all randomized subjects who receive at least one dose of study medication, and have one baseline and at least one post baseline assessment of the ADHD-RS-IV.

#### **5.2 Secondary Efficacy Endpoints**

- The Conners' Parent Rating Scale- Revised: Short Form (CPRS-R) will be analyzed to examine the treatment effects in the change in score at endpoint from baseline for the ITT population.
- The Clinical Global Impressions of Improvement (CGI-I) and Parent Global Assessment (PGA) will be analyzed by a Cochran Mantel-Haenszel (CMH) test to assess global impressions of ADHD severity and improvement of Daytrana™ compared to placebo.
- Dermal evaluations will be assessed by treatment group using the application skin site evaluation (Dermal Response Scale and Experience of Discomfort and Pruritus).
- Adverse events (AEs), laboratory tests, physical examinations, weight, vital signs, and ECGs will assess the safety and tolerability of MTS compared to PTS.
- Relationships will be explored between plasma concentrations of Daytrana™ and the response measures listed above.

## **6. TIMING OF ASSESSMENTS**

### **6.1 Study Schedule of Assessments – Tabular Summary**

The procedures to be performed throughout the study are outlined in the schedule of Assessments shown in Table 1 of the attached Study Synopsis.

## **7. ENTRY CRITERIA**

### **7.1 Inclusion Criteria**

See the Inclusion Criteria section of the Study Synopsis (Attachment I)

### **7.2 Exclusion Criteria**

See the Exclusion Criteria section of the Study Synopsis (Attachment I)

## **8. DRUG INFORMATION**

### **8.1 Dosage Form**

Daytrana™ (provided as 10mg/12.5cm<sup>2</sup>, 15mg/18.75cm<sup>2</sup>, 20mg/25cm<sup>2</sup>, and 30mg/37.5cm<sup>2</sup> patch sizes) is designed to deliver *d,l* (*threo*)-methylphenidate transdermally at a continuous rate upon application to intact skin.

### **8.2 Route of Administration**

Daytrana™ is administered transdermally.

### **8.3 Regimen**

Daytrana™ should be applied to a clean, dry, non-oily and non-irritated site on the hip of each subject. Initial placement on the left or right side will be up to the subject or caregiver. Subsequent applications should be alternated to the opposite side so that the same site is not used for 2 consecutive applications. The target wear time for Daytrana™ is 9 hours.

**9. DRUG-SPECIFIC SAFETY CONCERNS TO BE MONITORED OR ASSESSED**

Safety will be assessed at each visit by analyzing the results of physical examinations, vital signs, AEs, ECG or laboratory evaluations as described in the schedule of assessments (Table 1 of Study Synopsis).

**10. STATISTICAL INFORMATION, INCLUDING POWER OF STUDY AND STATISTICAL ASSESSMENTS**

See the Statistical Methods section of the Study Synopsis (Attachment I).

**11. LABELING THAT MAY RESULT FROM THE STUDY**

Shire plans to submit a labeling supplement based upon the results of this study. This labeling supplement will be submitted to the Agency prior to the expiration of our exclusivity on April 6, 2009. This labeling change supplement will propose to amend the Clinical Trials section of the package insert to include the results of this double-blind, placebo controlled safety and efficacy study of Daytrana™ in adolescents aged 13 to 17.

**12. FORMAT OF THE REPORT TO BE SUBMITTED TO THE AGENCY**

A full clinical study report will be submitted to the Agency prior to expiration of our exclusivity on April 6, 2009. The clinical study report will be in accordance with all applicable regulations and guidances. The final report for this study will be submitted to the Agency as part of a labeling supplement to update the Clinical Trials section of the package insert for Daytrana™.

**13. TIMEFRAME FOR SUBMITTING REPORTS OF THE STUDIES**

The final report for this study will be submitted prior to the expiration of our exclusivity on April 6, 2009. Shire understands the pediatric exclusivity, if granted, will attach to all existing patents and exclusivity for this active moiety at the time this report is submitted.

## REQUEST FOR CONSULTATION

TO (Office/Division): OSE/Division of Surveillance, Research, and Communication Support (DSRCS), ATTN: Jeanine Best, WO22, RM 4472

FROM (Name, Office/Division, and Phone Number of Requestor): LT Felecia Curtis, DPP, 6-0877

DATE  
9/8/06

IND NO.

NDA NO.  
11-522, 21-303,  
21-514, 17,078,  
21-278, 21-802,  
21-259, 21-419,  
21-475, 10-187,  
18-029, 21-284,  
21-411

TYPE OF DOCUMENT  
Medication Guide for  
CNS Stimulant

DATE OF DOCUMENT  
N/A

NAME OF DRUG  
Daytrana, Adderall, Adderal  
XR, Concerta, Dexedrine,  
Focalin, Focalin XR,  
Metadate CD, Methylin  
Solution, Methylin chewable  
tablets, Ritalin, Ritalin SR,  
Ritain LA, Strattera

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG  
ADHD

DESIRED COMPLETION DATE  
10/30/06

NAME OF FIRM: Various

### REASON FOR REQUEST

#### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING        |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input checked="" type="checkbox"/> LABELING REVISION  |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE   |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW            |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input type="checkbox"/> OTHER (SPECIFY BELOW):        |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

#### II. BIOMETRICS

- |   |   |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |   |

#### III. BIOPHARMACEUTICS

- |  |  |
|--|--|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES         | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

#### IV. DRUG SAFETY

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: This consult is in follow-up to your 8-24-06 response to our consult on a medication guide for Concerta. We feel this is an excellent template to use for the other stimulant products, and we ask that you now help us to create medication guides for these products as well. You will note that several of these products

already have PPIs. We have attached draft labeling for 13 ADHD products for review. We have included Strattera since we have now reached agreement with Lilly on similar language for this product. Lilly, intends to bundle in the "agreed upon" changes pertaining to priapism, seizures, and aggressive behavior/hostility with the ADHD class labeling revisions. Some of these changes may warrant mention in the Strattera medguide as well. Please note that Strattera already has a MG pertaining to suicidality. We will be happy to meet with you to discuss this project as needed.

I will send the labels as Word files via email. If you have any questions, call me at 301-796-0877.

Thanks

SIGNATURE OF REQUESTOR LT Felecia Curtis, RN, RPM	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DFS <input type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/

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Thomas Laughren  
9/11/2006 09:46:52 AM



**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-514

Noven Pharmaceuticals, Incorporated  
Co-Development Partner Shire Pharmaceuticals  
Attention: Harris Rotman, Ph.D.  
Senior Manager, Regulatory Affairs  
725 Chesterbrook Boulevard  
Wayne, PA 19087

Dear Dr. Rotman:

Please refer to your new drug application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Daytrana (methylphenidate) Transdermal System.

Based upon the recommendations made by the members of two different advisory committees (i.e., the Drug Safety and Risk Management Advisory Committee on February 9, 2006 and the Pediatric Advisory Committee on March 22, 2006), we believe that additional labeling changes are warranted in order to adequately warn practitioners and patients about the use of CNS stimulant products to treat Attention-Deficit Hyperactivity Disorder (ADHD).

Therefore, we are requesting the following changes to product labeling. Please note that this same request is being sent to the manufacturers of all CNS stimulant products approved for the treatment of ADHD.

Please delete the current **WARNINGS** section of Daytrana product labeling and replace it with the following language under the **WARNINGS** section of labeling:

**WARNINGS**

**Serious Cardiovascular Events**

Sudden Death and Pre-existing Structural Cardiac Abnormalities or Other Serious Heart Problems

Children and Adolescents

Sudden death has been reported in association with CNS stimulant treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems.

Although some serious heart problems alone carry an increased risk of sudden death, stimulant products generally should not be used in children or adolescents with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of a stimulant drug.

### Adults

Sudden deaths, stroke, and myocardial infarction have been reported in adults taking stimulant drugs at usual doses for ADHD. Although the role of stimulants in these adult cases is also unknown, adults have a greater likelihood than children of having serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems. Adults with such abnormalities should also generally not be treated with stimulant drugs.

### Hypertension and other Cardiovascular Conditions

Stimulant medications cause a modest increase in average blood pressure (about 2-4 mmHg) and average heart rate (about 3-6 bpm) [see Adverse Events], and individuals may have larger increases. While the mean changes alone would not be expected to have short-term consequences, all patients should be monitored for larger changes in heart rate and blood pressure. Caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate, e.g., those with pre-existing hypertension, heart failure, recent myocardial infarction, or ventricular arrhythmia.

### Assessing Cardiovascular Status in Patients being Treated with Stimulant Medications

Children, adolescents, or adults who are being considered for treatment with stimulant medications should have a careful history (including assessment for a family history of sudden death or ventricular arrhythmia) and physical exam to assess for the presence of cardiac disease, and should receive further cardiac evaluation if findings suggest such disease (e.g., electrocardiogram and echocardiogram). Patients who develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease during stimulant treatment should undergo a prompt cardiac evaluation.

### **Contact Sensitization**

Use of Daytrana may lead to contact sensitization. Daytrana should be discontinued if contact sensitization is suspected. Erythema is commonly seen with use of Daytrana and is not by itself an indication of sensitization. However, sensitization should be suspected if erythema is accompanied by evidence of a more intense local reaction (edema, papules, vesicles) that does not significantly improve within 48 hours or spreads beyond the patch site. Diagnosis of allergic contact dermatitis should be corroborated by appropriate diagnostic testing.

Patients sensitized from use of Daytrana, as evidenced by development of an allergic contact dermatitis, may develop systemic sensitization or other systemic reactions if methylphenidate containing products are taken via other routes, e.g., orally. Manifestations of systemic sensitization may include a flare-up of previous dermatitis or of prior positive patch-test sites, or generalized skin eruptions in previously unaffected skin. Other systemic reactions may include headache, fever, malaise, arthralgia, diarrhea, or vomiting.

Patients who develop contact sensitization to Daytrana and require oral treatment with methylphenidate should be initiated on oral medication under close medical supervision. It is possible that some patients sensitized to methylphenidate by exposure to Daytrana may not be able to take methylphenidate in any form.

A study designed to provoke skin sensitization revealed a signal for Daytrana to be an irritant and also a contact sensitizer. This study involved an induction phase consisting of continuous exposure to the same skin site for 3 weeks, followed by a 2 week rest period, and then challenge/rechallenge. Under conditions of the study, Daytrana was more irritating than both the placebo patch control and the negative control (saline). Of 133 subjects who participated in the challenge phase of the sensitization study, at least 18 (13.5%) were confirmed to have been sensitized to Daytrana based on the results of the challenge and/or re-challenge phases of the study.

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## **Psychiatric Adverse Events**

### Pre-Existing Psychosis

Administration of stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a pre-existing psychotic disorder.

### Bipolar Illness

Particular care should be taken in using stimulants to treat ADHD in patients with comorbid bipolar disorder because of concern for possible induction of a mixed/manic episode in such patients. Prior to initiating treatment with a stimulant, patients with comorbid depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression.

### Emergence of New Psychotic or Manic Symptoms

Treatment emergent psychotic or manic symptoms, e.g., hallucinations, delusional thinking, or mania in children and adolescents without a prior history of psychotic illness

or mania can be caused by stimulants at usual doses. If such symptoms occur, consideration should be given to a possible causal role of the stimulant, and discontinuation of treatment may be appropriate. In a pooled analysis of multiple short-term, placebo-controlled studies, such symptoms occurred in about 0.1% (4 patients with events out of 3482 exposed to methylphenidate or amphetamine for several weeks at usual doses) of stimulant-treated patients compared to 0 in placebo-treated patients.

### Aggression

Aggressive behavior or hostility is often observed in children and adolescents with ADHD, and has been reported in clinical trials and the postmarketing experience of some medications indicated for the treatment of ADHD. Although there is no systematic evidence that stimulants cause aggressive behavior or hostility, patients beginning treatment for ADHD should be monitored for the appearance of or worsening of aggressive behavior or hostility.

### **Long-Term Suppression of Growth**

Careful follow-up of weight and height in children ages 7 to 10 years who were randomized to either methylphenidate or non-medication treatment groups over 14 months, as well as in naturalistic subgroups of newly methylphenidate-treated and non-medication treated children over 36 months (to the ages of 10 to 13 years), suggests that consistently medicated children (i.e., treatment for 7 days per week throughout the year) have a temporary slowing in growth rate (on average, a total of about 2 cm less growth in height and 2.7 kg less growth in weight over 3 years), without evidence of growth rebound during this period of development. Published data are inadequate to determine whether chronic use of amphetamines may cause a similar suppression of growth, however, it is anticipated that they likely have this effect as well. Therefore, growth should be monitored during treatment with stimulants, and patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted.

### **Seizures**

There is some clinical evidence that stimulants may lower the convulsive threshold in patients with prior history of seizures, in patients with prior EEG abnormalities in absence of seizures, and, very rarely, in patients without a history of seizures and no prior EEG evidence of seizures. In the presence of seizures, the drug should be discontinued.

### **Visual Disturbance**

Difficulties with accommodation and blurring of vision have been reported with stimulant treatment.

**Use in Children Under Six Years of Age**

Daytrana should not be used in children under six years of age, since safety and efficacy in this age group have not been established.

**Drug Dependence**

Daytrana should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during withdrawal from abusive use, since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that may require follow-up.

Submit twenty copies of final printed labeling, ten of which are individually mounted on heavyweight paper or similar material, exactly as specified above as a "Supplement - Changes Being effected." Incorporate all previous revisions as reflected in the most recently approved package insert. To facilitate review of your submission, provide a highlighted or marked-up copy that shows the changes that are being made.

The above changes should be implemented immediately, and they should be submitted within 30 days from the date of this letter.

If you have any questions, call Susan Player, M.S, APRN, BC, Regulatory Project Manager, at 301-796-9838.

Sincerely,

*{See appended electronic signature page}*

Thomas Laughren, M.D.  
Director  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/

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Thomas Laughren  
5/22/2006 03:27:32 PM

**MEMORANDUM**

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

---

**DATE:** May 10, 2006

**TO:** Thomas Laughren, M.D., Director  
Division of Psychiatry Products  
Office of New Drugs (OND)  
and  
M. Dianne Murphy, M.D.  
Director, Office of Pediatric Therapeutics (OPT), OIASI  
Office of the Commissioner  
and  
Solomon Iyasu, M.D., M.P.H., Acting Deputy Director  
Division of Pediatric Drug Development  
Office of Counter-Terrorism and Pediatric Drug Development  
(OCTAP)

**THROUGH:** Mark Avigan, M.D., C.M., Director  
Division of Drug Risk Evaluation (DDRE)  
Office of Drug Safety (ODS)

**FROM:** Andrew Mosholder, M.D., M.P.H., Epidemiologist (DDRE)

**SUBJECT:** **Addendum to:** Psychiatric Adverse Events in Clinical Trials of Drugs for  
Attention Deficit Hyperactivity Disorder (ADHD)

**PID:** D060163

## Drugs:

NDA #	Name (generic) (Sponsor)
21-303	Adderall XR (mixed salts of a single entity amphetamine product) Extended-Release Capsules (Shire)
21-278	Focalin (dexamethylphenidate HCL) Tablets (Novartis)
21-802	Focalin XR (dexamethylphenidate HCL) Extended-Release Capsules (Novartis)
21-121	Concerta (methylphenidate HCL) Extended-Release Tablets (McNeil)
21-259	Metadate CD (methylphenidate HCL) Extended-Release Capsules (UCB Pharma)
21-284	Ritalin LA (methylphenidate HCL) Extended-Release Capsules (Novartis)
21-411	Strattera (atomoxetine HCL) Capsules (Lilly)
21-514	Methylphenidate transdermal system (MTS) (Noven/Shire)
<b>Pending NDA</b>	
20-717	Provigil (modafinil) Tablets (Cephalon)

## Executive Summary

This memorandum provides additional information and analyses regarding the occurrence of selected psychiatric adverse events in clinical trials of drugs for ADHD, as discussed at the March 22, 2006 meeting of the Pediatric Advisory Committee. It is intended to provide clarification on certain points that were raised during the advisory committee meeting and in subsequent internal discussions. The specific elements of this memorandum are (1) an exploration of the influence of wear time for the methylphenidate transdermal system; (2) statistical meta-analyses of aggregated trial data; (3) a subgroup analysis of adult only data; (4) a literature article regarding efficacy of stimulants for aggression; and (5) clinical characteristics of the psychosis/mania events. The overall conclusions from these additional analyses are not materially different from those of the previous consult dated March 3, 2006, but the additional information presented herein may be of use in terms of labeling revisions for these drugs.

## Background

Please refer to the previous consult on this topic dated March 3, 2006.<sup>1</sup> Findings from that consult were presented at the March 22 Pediatrics Advisory Committee meeting.<sup>2</sup> In the Advisory Committee discussions and in subsequent internal discussions, various questions about the clinical trial data analyzed in the March 3 consult were raised. The purpose of this memorandum is to address those requests for additional information.

The previous consult summarized data from clinical ADHD trials submitted in response to FDA's requests. Sponsors of products for ADHD were asked to search their clinical trial databases for adverse psychiatric events in three primary categories: psychosis and mania,

<sup>1</sup> PID D060163, available at [www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4210b\\_10\\_01\\_Mosholder.pdf](http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4210b_10_01_Mosholder.pdf)

<sup>2</sup> Available at [www.fda.gov/ohrms/dockets/ac/06/slides/2006-4210s\\_14\\_Mosholder\\_Psychiatric%20Adverse%20Events.ppt](http://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4210s_14_Mosholder_Psychiatric%20Adverse%20Events.ppt)

suicidal events, and aggression. This search was conducted electronically using selected, prespecified adverse event terms. Data on the duration of exposure to treatment in the trials and subject characteristics were also requested, as were clinical descriptions of the events and descriptions of the clinical trials in the ADHD development programs. Data were pooled within development programs to estimate the rates of the events of interest. The findings are subject to the usual limitations of such safety analyses, which include potential lack of consistency of ascertainment of adverse events across the various trials, the possibility of misclassification of cases, and statistical power limitations imposed by the sample sizes. In addition, many of the trials excluded subjects known to be intolerant of stimulants, limiting generalizability of the safety findings to the treatment-naïve population. The main findings included an apparent association of active drug treatment with symptoms of psychosis and mania, a possible weaker association with aggression, and for two compounds (atomoxetine and modafinil) a greater frequency of suicidal events compared to placebo.

### Additional information and analyses

The following summarizes some additional information and calculations from these clinical trial data.

#### 1. Methylphenidate transdermal system (MTS) wear time

It was pointed out by the sponsor and by the Division of Psychiatry Products that in the more recent trials with the MTS, the wear time for the patch had been reduced to 9 hours in the two most recent trials (SPD485201 and SPD485302) in an effort to limit side effects. Thus, the observed imbalance between drug and placebo for the psychosis/mania and aggression categories of events may have reflected events occurring with the longer wear times employed in the older trials. (Similarly, the 6 psychosis/mania events observed in adults participating in the skin sensitization trials occurred with extended duration of wear.)

To explore whether wear time was a factor, the clinical trial data was subgrouped by wear time. The results are displayed in the following table.

**Table 1. Psychiatric adverse events in pediatric placebo-controlled ADHD trials with MTS, by wear time for patch**

Treatment group	All MTS	Wear time >9 H	Wear time = 9 H	Placebo
N	471	293	178	464
Person yrs	30.3	16.7	13.6	23.8
Psychosis/mania events	4	4	0	0
Suicidal events	0	0	0	0
Aggression events	6	2	4	1

It will be seen that there were more subjects enrolled in trials with longer wear times, although the duration of exposure was only 3.1 person-years greater than for the 9 hour duration of wear. All 4 psychosis/mania events occurred in trials with longer wear time, consistent with the hypothesis that longer wear times may have contributed to this apparent adverse reaction. A case

report form and narrative was provided for only one of these subjects, an 8 year old male (#11-08) in study N17010 who discontinued from the trial. The day prior to the event he had worn the patch for 13.5 hours; also, the patch size had just been increased to 25 sq. cm. Information on the specific duration of wear for the other 3 subjects with psychosis/mania events was not available. In the aggression category of events, 4 of the 6 events occurred with 9 hour duration of wear.

## 2. Statistical meta-analyses

In the March 3 consult the clinical trial data were not aggregated across drugs in a meta-analysis. As stated in that consult, a formal meta-analysis was not undertaken at the time because of the sparse nature of the data from individual trials.

During the March 22 Advisory Committee meeting, an aggregated analysis was proposed by Dr. Thomas Newman of the Pediatric Advisory Committee.<sup>3</sup> The following tables display the results obtained by pooling the pediatric double blind trial data. Note that data from active control arms were omitted from these analyses; only the principle drug and placebo data were aggregated. Statistical comparisons were made with Stata software (version 7). Tables 2A-C show the data for all trials, and tables 2D-F show the data for the subgroup of stimulant trials alone.

**Table 2A. Aggregated adverse event data from pediatric double-blind trials.**

Treatment	N	Person- yrs	Mean duration of treatment	Psychosis/ mania events	Suicidal events	Aggression events
Placebo	3990	425	39 days	0	4	30
Active drugs*	5717	801	51 days	13	13	83

\*Adderall XR, atomoxetine, modafinil, oral methylphenidates, methylphenidate transdermal system

**Table 2B. Percentage of patients with selected adverse events in pediatric double-blind trials**

Treatment	N	Percentage of patients with events		
		Psychosis/ mania events	Suicidal events	Aggression events
Placebo	3990	0	0.10%	0.75%
Active drugs*	5717	0.23%	0.23%	1.45%
p-value (Fisher's exact)		0.001	0.22	0.001

\*Adderall XR, atomoxetine, modafinil, oral methylphenidates, methylphenidate transdermal system

<sup>3</sup> See transcript at [www.fda.gov/ohrms/dockets/ac/06/transcripts/2006-4210t\\_01\\_Draft%20-%20Transcript%200322fda.htm](http://www.fda.gov/ohrms/dockets/ac/06/transcripts/2006-4210t_01_Draft%20-%20Transcript%200322fda.htm)

**Table 2C. Rates of selected adverse events in pediatric double-blind trials**

Treatment	N	Person-yrs	Rate of events per 100 person-years		
			Psychosis/ mania events	Suicidal events	Aggression events
Placebo	3990	425	0	0.9	7.1
Active drugs*	5717	801	1.6	1.6	10.4
p-value			0.004	0.35	0.07

\*Adderall XR, atomoxetine, modafinil, oral methylphenidates, methylphenidate transdermal system

**Table 2D. Aggregated adverse event data from pediatric double-blind trials of stimulants.**

Treatment	N	Person-yrs	Mean duration of treatment	Psychosis/ mania events	Suicidal events	Aggression events
Placebo	2626	137	19 days	0	1	10
Stimulants*	3114	201	24 days	7	1	29

\*Adderall XR, oral methylphenidates, methylphenidate transdermal system

**Table 2E. Percentage of patients with selected adverse events in pediatric double-blind trials of stimulants**

Treatment	N	Percentage of patients with events		
		Psychosis/ mania events	Suicidal events	Aggression events
Placebo	2626	0	0.03%	0.38%
Stimulants*	3114	0.22%	0.04%	0.93%
p-value (Fisher's exact)		0.018	1	0.015

\*Adderall XR, oral methylphenidates, methylphenidate transdermal system

**Table 2F. Rates of selected adverse events in pediatric double-blind trials, stimulants only**

Treatment	N	Person-yrs	Rate of events per 100 person-years		
			Psychosis/ mania events	Suicidal events	Aggression events
Placebo	2626	137	0	0.7	7.3
Stimulants*	3114	201	3.5	0.5	14.4
p-value			0.026	0.8	0.057

\*Adderall XR, oral methylphenidates, methylphenidate transdermal system

In addition, when the data were stratified by drug (combining oral methylphenidates) there were sufficient events in the aggression category to permit a more formal meta-analysis using the Mantel-Haenszel method. Using rates per person-year, the Mantel-Haenszel combined estimate of the rate ratio for aggression events calculated in this way was 1.35 (95% c.i. 0.89-2.04). The statistical test for lack of homogeneity between drugs was not statistically significant (p-value = 0.6), which supports aggregating the data to calculate a combined risk ratio. For the stimulants (without modafinil and atomoxetine) the estimated combined rate ratio was 1.47 (0.72- 2.98).

### 3. Adult clinical trial data

The original consult provided data for the subgroup of pediatric trials but not separately for adult trials. Table 3 presents the data from adult clinical trials (i.e., trials with subjects > 17 years old).

**Table 3. Summary of trial data for adult ADHD subjects**

Study treatment	N	Pt- yrs	Psychosis/ mania events	Suicidal events	Aggres sion events	Psychosis/ mania events/ 100 pt-yrs	Suicidal events/100 pt-yrs	Aggression events/100 pt-years
Concerta OL	136	75.4	0	0	0	0	0	0
Placebo	58	7.3	0	0	0	0	0	0
Modafinil DB	109	10.4	0	0	0	0	0	0
Modafinil OL	125	14.2	0	0	0	0	0	0
Placebo	79	4.7	0	0	0	0	0	0
Adderall XR DB	210	13.4	0	0	2	0	0	14.9
Adderall XR OL	944	486.7	5	0	16	1.0	0	3.3
Placebo	387	94.7	0	1	3	0	1.1	3.2
Atomoxetine DB	520	130.2	0	1	4	0	0.8	3.1
Atomoxetine OL	601	548.5	0	0	7	0	0	1.3
Placebo	53	4.8	0	0	0	0	0	0
d-MPH DB	165	15.0	3	0	1	20.0	0	6.7
d-MPH OL	170	59.2	1	0	2	1.7	0	3.4

Abbreviations: DB double blind, OL open label, d-MPH dextromethylphenidate

### 4. Efficacy of stimulant treatments for aggressive behaviors

One of the points made during the advisory committee discussion was that stimulant treatment of children with ADHD reduces aggressive behaviors. However, in clinical development programs for ADHD drug products, this is not usually a measured outcome. Following the meeting, Dr. Ben Vitiello of NIMH kindly provided a reference supporting this observation. Connor and his co-authors conducted a literature search for trials with stimulants that included measures of aggression in children.<sup>4</sup> They identified 28 placebo-controlled trials that included such outcomes and concluded that stimulants reduce such behaviors, with a weighted overall effect size of 0.84 for overt aggression and slightly less (0.69) for covert aggression. One important distinction between these trials and the analysis presented at the Pediatric Advisory Committee meeting is that in the former, aggression was rated as a study outcome, while in the latter, aggressive behaviors were captured as adverse events. Conceivably, aggressive behaviors for the majority of

<sup>4</sup> Connor DF, Glatt SJ, Lopez ID, et al. Psychopharmacology and Aggression.I: A Meta-Analysis of Stimulant Effects on Overt/Covert Aggression-Related Behaviors in ADHDJ. *Am. Acad. Child Adolesc. Psychiatry*, 2002, 41(3):253-261.

patients could be reduced on average by drug treatment, while a small subgroup of patients might have a paradoxical response resulting in more pronounced aggressive behaviors.

#### **5. Clinical characteristics of psychosis/mania events**

The table that follows displays a summary of the clinical characteristics of the events in the psychosis/mania category from pediatric double blind ADHD trials. Although the data are limited a few observations are possible. Only four of these events required discontinuation of the ADHD drug, with the remaining presumably milder events resolving without intervention. One of the atomoxetine related events required hospitalization. One event of hypomania with the MTS (patient 11-08) was noted to have occurred after the subject's patch size was increased.

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**Table 4. Clinical characteristics of pediatric psychosis/mania events in double blind ADHD trials**

Study	Patient ID	Sex	Age	Treatment	Daily dose at time of event	Duration at time of event (days)	Event description	Premature dropout (Y/n)	Serious (Y/n)	Comments
N17-015	104	m	6	MTS	37.5 cm2	1	Hallucinations	N	N	Resolved
N17-018	02 07	f	11	MTS	37.5 cm2	8	Hallucinations	N	N	Resolved
N17-010	02 03	m	7	MTS	25 cm2	15	Hallucinations	N	N	Resolved
N17-010	11 08	m	8	MTS	25 cm2	15	Hallucinations, mania	Y	N	Also experienced depersonalization. Recurred on day 16; later resolved. Patch size had just been increased.
SPD485-302	54-011	m	9	Concerta*	54 mg	28	Paranoid thoughts	N	N	Resolved
213	15010	m	6	Modafinil	300 mg	6	Hallucinations	N	N	Resolved
310	40629	m	9	Modafinil	425 mg	11	Hallucinations	Y	N	Resolved
97-M-03	97-M-03/18/15	MALE	7	d-MPH	10 mg	27	Paranoid behavior/thinks flies getting into his ears	N	N	Concomitant methylphenidate
CRIT124D 0 007	0502_00001	M	8	Ritalin LA	30 mg	18	Visual illusion	N	N	
CRIT124D 0 007	0503_00004	M	6	Ritalin LA	10 mg	2**	Hypomania	Y	N	Worsening of irritable mood, increase physical aggression, decreased need for sleep
LYAC	7267	M	9	Atomoxetine	?	212	Psychotic disorder	Y	Y	Required hospitalization
LYBI	8102	M	13	Atomoxetine	30 mg	2	Hallucinations seeing things	N	N	
LYAQ	3251	M	12	Atomoxetine	40 mg	21	Hypomania	N	N	
LYAS	4053	M	8	Atomoxetine	15 mg	20	Visual hallucinations	N	N	

\*Not included in primary analysis since this event occurred in an active control treatment arm

\*\* Although this event is listed in the sponsor's 2-3-06 submission as occurring during double blind treatment, Dr. Robert Levin, Division of Psychiatry Products, noted that the narrative for this patient states the patent was not randomized. Dr. Levin subsequently learned from Novartis that this event actually occurred during single blind Ritalin LA treatment. In submitting the data for study 007, Novartis combined single-blind Ritalin LA exposure with double-blind exposure.

## 6. Omission of single-blind exposure data from Ritalin LA Study 007

As noted above in the footnote to Table 4, Novartis combined double blind and single blind data from Ritalin LA protocol 007 in the double blind category for their response to our data request. It was not possible to separate the single blind and double blind data in the spreadsheet submitted by the sponsor. Alternatively, the data from protocol 007 can be omitted altogether. In protocol 007, there were 15.8 person-years of exposure to active drug and 2.7 to placebo, and there were 2 psychosis/mania events and 2 aggression events, all on active treatment. The following tables show the aggregated data without data from protocol 007. Omitting the data from this protocol does not change the overall pattern of these adverse events.

**Revised Table G from original consult. Frequency of patients experiencing selected psychiatric events in Ritalin LA clinical safety and efficacy studies, minus Study 007.**

Study design	Treatment	N	Person-yrs	Psychosis/mania events	Suicidal events	Aggression events
DB	Placebo	188	8.60	0	1*	0
DB	Ritalin LA	244	9.91	0	0	0
Open	Ritalin LA OL	125	25.95	0	1	0
DB	Concerta	89	2.82	0	0	0

\*One additional suicidal event occurred within 30 days of the end of treatment in a patient who had been randomized to placebo

**Revised Table 2D. Aggregated adverse event data from pediatric double-blind trials of stimulants minus Study 007.**

Treatment	N	Person-yrs	Mean duration of treatment	Psychosis/mania events	Suicidal events	Aggression events
Placebo	2555	134	19 days	0	1	10
Stimulants*	2953	185	23 days	5	1	27

\*Adderall XR, oral methylphenidates, methylphenidate transdermal system

**Revised Table 2E. Percentage of patients with selected adverse events in pediatric double-blind trials of stimulants, minus Study 007**

Treatment	N	Percentage of patients with events		
		Psychosis/mania events	Suicidal events	Aggression events
Placebo	2555	0	0.04%	0.39%
Stimulants*	2953	0.17%	0.03%	0.91%
p-value (Fisher's exact)		0.07	1.0	0.02

\*Adderall XR, oral methylphenidates, methylphenidate transdermal system

**Revised Table 2F. Rates of selected adverse events in pediatric double-blind trials, stimulants only, minus Study 007**

Treatment	N	Person-yrs	Rate of events per 100 person-years		
			Psychosis/ mania events	Suicidal events	Aggression events
Placebo	2555	134	0	0.7	7.5
Stimulants*	2953	185	2.7	0.5	14.6
p-value			0.07	0.84	0.06

\*Adderall XR, oral methylphenidates, methylphenidate transdermal system

### Conclusions

It is hoped that these additional analyses provide clarification on various points of interest, and may inform the proposed revisions to the labels for these products. On balance, the conclusions in the original review regarding these adverse events with ADHD drug treatment are not materially affected by these analyses. To reiterate, the main findings included an apparent association of active drug treatment with symptoms of psychosis and mania, a possible weaker association with aggression, and for two compounds (atomoxetine and modafinil) a greater frequency of suicidal events compared to placebo. It bears emphasis that the clinical trial population for these studies was in many cases screened for a history of intolerance to stimulants, so rates of adverse reactions observed among these subjects may be an underestimate of the rates in a less select group of patients.

Andrew D. Mosholder, M.D., M.P.H.  
Epidemiologist, DDRE

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/s/

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Andy Mosholder  
5/10/2006 09:50:40 AM  
DRUG SAFETY OFFICE REVIEWER

Mark Avigan  
5/10/2006 05:26:47 PM  
DRUG SAFETY OFFICE REVIEWER

**MEMORANDUM**  
**DEPARTMENT OF HEALTH AND HUMAN SERVICES**  
**FOOD AND DRUG ADMINISTRATION**  
**CENTER FOR DRUG EVALUATION AND RESEARCH**  
**CONTROLLED SUBSTANCE STAFF**

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**Date:** April 7, 2006

**To:** Thomas P. Laughren, M.D., Director  
Division of Psychiatry Products (HFD-130)

**Through:** Deborah Leiderman, M.D., Director  
Silvia Calderon, Ph.D., Team Leader

**From:** Geoffrey Zeldes, M.D., Pharm.D., Medical Officer  
Controlled Substance Staff (HFD-009)

**Subject:** CSS Consultation regarding sponsor resubmission for NDA 21-514  
(methylphenidate transdermal system)  
**Indication:** Treatment of attention deficit hyperactivity disorder  
**Sponsor:** Noven Pharmaceuticals

This memorandum responds to the Division of Psychiatry Products (HFD-130) regarding Noven Pharmaceuticals response to the approvable letter sent on December 12, 2005.

The CSS recommendations to the Sponsor have not been followed.

On October 28, 2005, CSS recommended that the Sponsor:

1. Revise the Drug Dependence black box warning to conform with current accepted terminology as defined by the American Society of Addiction Medicine.
2. Clarify the wording of the Risk Management Program to include definitions of terms to be used in the monitoring and reporting of abuse, misuse or diversion of the product.
3. Revise the labeling for the patient to reflect the recommended nine hour wear time.

**Recommendations**

CSS recommends the following to the Division:

1. Request the Sponsor to update the Drug Dependence and Abuse section of the label, including the black box warning to conform with current accepted terminology.

2. Request the Sponsor provide a definition and description of cases to be included under the terms "abuse" and "misuse" to be reported as a component of the proposed RMP.

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Geoffrey Zeldes  
4/14/2006 10:26:09 AM  
MEDICAL OFFICER

Silvia Calderon  
4/24/2006 04:49:26 PM  
CHEMIST

Deborah Leiderman  
4/26/2006 03:32:37 PM  
MEDICAL OFFICER

**From:** Laughren, Thomas P  
**Sent:** Monday, April 03, 2006 2:39 PM  
**To:** Player, Susan; Andreason, Paul J; Levin, Robert  
**Cc:** Laughren, Thomas P  
**Subject:** RE: Daytrana revised labeling 21-514  
Susan,

This looks fine to me.

Tom

---

**From:** Player, Susan  
**Sent:** Monday, April 03, 2006 1:09 PM  
**To:** Laughren, Thomas P; Andreason, Paul J; Levin, Robert  
**Subject:** FW: Daytrana revised labeling 21-514  
**Importance:** High

Shire has responded with the proposed wording (above & outlined below) to the label for Daytrana. If these are acceptable, my understanding is that this is final agreement on the labeling and I will finish drafting the approval letter and finish putting together the action package.

Thanks!

---

**From:** Rotman, Harris [mailto:hrotman@us.shire.com]  
**Sent:** Monday, April 03, 2006 1:04 PM  
**To:** Player, Susan  
**Cc:** LaPree, Charles; Rotman, Harris  
**Subject:** RE: Daytrana revised labeling 21-514  
**Importance:** High

Dear Susan,

Thanks again for your help during these labeling discussions. Per our agreement with the Division at the end of the teleconference today, please find attached a modified label, based on the two remaining changes discussed this morning. These changes are in yellow highlight for ease of review.

Per our agreement, we have modified the language in the "Contact Sensitization" section to read:

Patients sensitized from use of Daytrana™, as evidenced by development of an allergic contact dermatitis, may develop systemic sensitization or other systemic reactions if methylphenidate-containing products are taken via other routes, e.g., orally.

Additionally, we have researched the 6 subjects who experienced affect lability. Per our discussion we have added a footnote into Table 1 to better describe these cases (seen below):

\* Six subjects had affect lability, all judged as mild and described as increased emotionally sensitive, emotionality, emotional instability, emotional lability, and intermittent emotional lability.

Please note, specifically regarding aggression, we have determined following the call that the cases of "aggression" in pivotal study 302 were coded separately from "affect lability", and were present at an incidence of 2% in MTS-treated patients, and so did not make the cut-off for Table 1 in the package insert.

We hope these revisions aid the Division in finalizing their review.

Thanks!

Harris

\*\*\*\*\*

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/s/

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Susan Player  
4/5/2006 01:21:11 PM  
CSO

**From:** Rotman, Harris [hrotman@us.shire.com]  
**Sent:** Wednesday, April 05, 2006 12:21 PM  
**To:** Player, Susan  
**Cc:** Rotman, Harris; LaPree, Charles  
**Subject:** Postmarketing commitment- Daytrana (NDA 21-514)  
Dear Susan-

As per our phone call earlier today, Shire hereby commits to conduct a study to estimate the risk of contact sensitization with the use of Daytrana as a post-approval activity for Daytrana (MTS) NDA 21-514. We commit to submitting a protocol for this study to the Division by 2 months after the date of final NDA approval. We also commit to finalizing the study and submitting a final clinical study report to the Division by two and a half years after the date of final NDA approval.

We will work diligently to submit a draft synopsis of such a protocol to the Division as soon as possible, pending approval of the NDA, and ask that the Division meet with us (via teleconference or in a face-to-face meeting) to finalize study details as soon as is feasible after submission of a synopsis.

Many thanks!

Harris

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/s/

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Susan Player  
4/5/2006 01:02:33 PM  
CSO

Susan Player  
4/5/2006 01:03:26 PM  
CSO

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

**DATE:**            April 4, 2006

**FROM:**            Thomas P. Laughren, M.D.  
Director, Division of Psychiatry Products  
HFD-130

**SUBJECT:**        Approval Action for Methlyphenidate Transdermal System (MTS) for ADHD

**TO:**                File NDA 21-514  
[Note: This overview should be filed with the 2-9-06 response to FDA's 12-23-05  
approvable letter.]

**1.0    BACKGROUND**

MTS is a patch formulation of methylphenidate, a stimulant that is available in a variety of immediate and controlled release forms for the treatment of ADHD. This NDA provides data in support of a claim for MTS in the short-term treatment of ADHD in children aged 6 to 12. The available strengths are 10, 15, 20, and 30 mg/9 hours. The patch is administered in the morning and is to be left on for 9 hours. The intended advantage of the patch is in patients who have difficulty with pill-taking. The patch would also have the advantage of not interacting with food consumption and of flexibility in early removal if desired.

This NDA was first submitted to the FDA on 6-27-02. FDA issued a non-approvable letter on 4-25-03. This letter acknowledged positive efficacy findings, but noted concerns about unacceptable levels of certain adverse events, including insomnia, anorexia, and weight loss. The letter also raised concerns about the potential for diversion and abuse, and of skin sensitization. FDA suggested shorter wear times and additional studies to demonstrate efficacy and acceptable safety at the shorter wear times, including a skin sensitization study. FDA also requested that the sponsor propose a comprehensive risk management plan. The sponsor conducted the additional studies requested and resubmitted the NDA on 6-28-05. The resubmission included responses to CMC issues raised in the 4-25-03 letter, additional pharmacokinetic information, and revised product labeling. This application was discussed at a 12-2-05 meeting of the PDAC. They recommended that the application could be approved, however, with fairly strong labeling, given concerns about the possibility of contact sensitization. We issued an approvable letter with draft labeling 12-23-05.

## RESPONSE TO FDA's REQUESTS IN APPROVABLE LETTER

### Concern About Possible Contact Sensitization

The major topic for discussion at the 12-2-05 PDAC meeting for this application was the possibility for contact sensitization, along with the possibility of not being able to use oral methylphenidate subsequent to such sensitization. Given the importance of methylphenidate products in the treatment of ADHD, the committee expressed great concern that a substantial, but unknown, fraction of patients with ADHD who are exposed to MTS might develop sensitization to methylphenidate and never again be able to take methylphenidate in any form. Thus, there was unanimous agreement that this concern should be prominently placed in MTS labeling (i.e., Warnings). There was considerable discussion about the type of advice to be given to clinicians. In the end, a single committee member voted in favor of strong language advising clinicians to use MTS only in patients who were not able to take oral formulations (11-1 against on this vote). On the other hand, the vote was unanimous (12-0) that language advising clinicians to generally consider restricting the use of MTS to this population would be appropriate. The population in question would be those, among others, who cannot swallow tablets, who have significant compliance problems with oral formulations, or who have a medical condition that limits the administration of oral formulations. In the draft labeling attached to the 12-23-05 approvable letter, we had included a Warning and other language in Indications and elsewhere to convey this recommendation.

In the meantime, the sponsor sought outside consultation on the contact sensitization issue, and argued that several features of our proposed labeling were stronger than justified.

-Incidence of Contact Sensitization with MTS: For one thing, they argued that there were no cases of contact sensitization among the 765 patients exposed to MTS in the manner it is intended to be used, i.e., no more than 9 hours per day and alternating sites. At the 12-2-05 PDAC meeting, the sponsor reported that there had been a single case of sensitization observed, i.e., patient 31-002 in Study SPD485-303. However, after further review of that case, they concluded that was not a documented case of sensitization, and our dermatology consultants have agreed with that assessment. The sponsor suggested that this case was prominent in the minds of the PDAC members, and heavily influenced their labeling recommendations.

Comment: I think this case was important, but was not the only source of concern. A provocative skin sensitization study (N17-020) revealed a signal for MTS to be an irritant and also a contact sensitizer. This study involved an induction phase consisting of continuous exposure to the same skin site for 3 weeks, followed by a 2 week rest period, and then challenge/rechallenge. Under conditions of the study, MTS was more irritating than both the placebo patch control and the negative control (saline). Of 133 subjects who participated in the challenge phase of the sensitization study, at least 18 (13.5%) were confirmed to have been sensitized to MTS based on the results of the challenge and/or re-challenge phases of the study. Sensitization could not be excluded for an additional 11 subjects, and if these subjects are considered to have been sensitized, the rate of sensitization becomes 21.8% (29/133 subjects).

However, it is also true that using MTS as prescribed, alternating application sites on the hip, no cases of contact sensitization were reported. Since patients were not specifically assessed for sensitization in the clinical effectiveness studies, it is unknown what the true incidence of sensitization is when MTS is used as directed. However, as the sponsor and their expert dermatologist point out, most of the patients who dropped out for skin reactions were subsequently given oral methylphenidate and tolerated this without problem. Further, they argue that it is unlikely that cases of true sensitization would be missed, since these reactions are generally quite persistent and extend beyond the patch site. Our own dermatologists now tend to agree with this view, but also still feel that there is some risk, albeit difficult to quantify, of contact sensitization with MTS. Thus, we have modified labeling to reflect this view.

-Risk of Systemic Reaction in Patients Given Oral Methylphenidate Subsequent to Sensitization by Dermal Route: The sponsor and their expert now argue that our draft label advice that, once sensitized to methylphenidate, patients could never again take methylphenidate in any form is also not justified. They argue, and provide references, that systemic reactions following sensitization through the skin are almost unheard of, and that the response is generally dermatologic, usually at the initial site of sensitization or sometimes a more general dermatological response. Much less commonly, systemic effects might be seen, including headache, fever, malaise, nausea, vomiting, diarrhea, and rarely, anaphylaxis. Our dermatologists now agree with this assessment as well, and they agree with the sponsor's view that re-challenge by the oral route can occur, however, under close medical supervision. We have also discussed the details of this concern with an FDA allergist who agrees that a type I systemic reaction is extremely unlikely, given sensitization by the dermal route, and advised us that rechallenge could occur under the psychiatrist's observation.

Comment: Based on this reassessment of the risk of rechallenge, we have agreed to labeling which permits rechallenge even if sensitization should occur, but under careful medical supervision.

-Labeling for Contact Sensitization: We have now agreed upon labeling which is less restricting than that originally proposed. We still have a Warning statement about the possibility of contact sensitization, however, we have removed the language from Indications essentially making MTS a second line drug. The risk of sensitization under usual conditions of use appears to be quite low, and even if sensitization were to occur, it would not necessarily mean that a patient would never again be able to take oral methylphenidate. This seemed to be the major concern of the PDAC. The labeling does, however, make clear that there is the possibility of contact sensitization, and advises specific diagnostic testing if sensitization is suspected. It also notes that, although rare, systemic reactions to oral challenge following sensitization via the skin could occur, but does not suggest that sensitized patients may never be challenged with oral drug. It does, however, suggest that there is the possibility that some patients may in fact not be able to continue with oral methylphenidate, depending on their response to oral challenge.

## Other Issues in Approvable Letter and Sponsor's Responses

Drs. Andreason and Levin, in their reviews of the sponsor's responses to the approvable letter, have provided more detailed comments on these issues, so I will be brief.

- Ph 4 commitment to conduct contact sensitization study: Although they have not provided a specific protocol, they have agreed to do such a study, and we will work with them in the planning of this study.
- Propose program to educate prescribers about identifying and properly diagnosing contact sensitization: They have outlined what they plan to do, and they seem committed to doing this. In the meantime, the agreed upon labeling and PPI should adequately address this concern.
- Add skin irritation section to labeling: We had asked the sponsor to add a section to Adverse Reactions to make clear that transient erythema is quite a common reaction to the patch, and needs to be distinguished from sensitization. They have done this.
- AEs stratified by age: We had asked for this stratification because of somewhat higher exposures seen in smaller children. They have done this, and there is no indication of more prominent adverse events in the younger children.
- Concerns about abuse, misuse or diversion: We had asked for responses to several issues pertinent to possible abuse, etc, and the sponsor has responded adequately (see Dr. Levin's review).
- Comments on educational plan and PPI: They have adequately responded to our questions.
- Misc carton and patch labeling issues: The sponsor has adequately responded to these issues.
- PREA: The sponsor has committed to conduct a study in adolescents (13-17).
- Labeling: As noted, we have reached agreement on final labeling.
- Safety Update: They have provided this, and it did not reveal any new safety concerns.

## 11.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Noven has submitted sufficient data to support the conclusion that MTS is effective and acceptably safe in the treatment of ADHD. We have now reached agreement on labeling and the review team is in agreement that we can move forward to approving this product. I agree.

cc:

Orig NDA 21-514 (MTS/ADHD)  
HFD-130  
HFD-130/TLaughren/PAndreason/RLevin/SPlayer

DOC: Methylphenidate TS Laughren AP Memo.doc

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Thomas Laughren  
4/4/2006 06:41:58 PM  
MEDICAL OFFICER

**MEMORANDUM**

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

**DATE:** April 3, 2006

**FROM:** Paul J. Andreason, M.D.  
Acting Deputy Director,  
Division of Psychiatry Products  
HFD-130

**SUBJECT:** Recommendation for Approval of NDA 21-514 Daytrana (methylphenidate transdermal delivery system) for the Treatment of Attention Deficit Hyperactive Disorder in Children 6-12 Years Old.

**TO:** File NDA 21-514  
[Note: This memo should be filed with the original February 9, 2006 submission of this NDA.]

**SUMMARY**

NDA 21-514 Daytrana (methylphenidate transdermal patch system [MTS]) is an alternate route of administration of methylphenidate for the treatment of Attention Deficit Hyperactive Disorder (ADHD). This submission represents a complete response to the Division's Approvable (AE) Action letter dated December 23, 2005.

The Division presented the MTS June 28, 2005 response to the Not Approved action to the Psychiatric Drug Advisory Committee (PDAC) on December 2, 2005. The PDAC discussed the safety and efficacy of the Methylphenidate Transdermal System (MTS) in the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children ages 6-12 years.

The 12/2/2005 committee voted in favor of approving MTS for the treatment of ADHD and felt that it was both effective and safe with one caveat. Based on the results of the skin sensitization study the PDAC felt that MTS should generally be used only in patients who would not take oral methylphenidate. The risk of sensitization to the oral form seemed quite low in clinical experience; however, the MTS sensitization study produced showed that at least 13% of subjects became sensitized to methylphenidate when it was administered transdermally under conditions of extreme wear. There was also the report of one patient who developed skin hypersensitivity and on oral re-challenge developed a rash at the site of the previously sensitized area.

I believe that the sponsor adequately addressed the Division's outstanding clinical concerns from the December 23, 2005 AE action letter. The following sections summarize the AE letter points

**Contact Skin Sensitization**

Following the PDAC meeting on December 16, 2005, the sponsor provided information that this case of the dermal hypersensitivity response to oral re-challenge actually did not occur and there was no dermal response to the oral re-challenge. Even though this kind of inconsistency in reporting is generally unsettling, the presence or absence of this case is not particularly concerning

to me. The case as originally reported was not particularly compelling because this original report of dermal hypersensitivity response was not serious, it was said to be self-limited and occurred in only one patient in the entire development program. Additionally, I do not believe that the PDAC was particularly swayed by this case in their suggestion to use MTS exclusively in patients that would not take oral methylphenidate. There was no expert dermatologist at the PDAC meeting on December 23, 2005.

Subsequent input from both the sponsor's and our dermatologists mitigate against the conservative "generally use only in patients who can or will not take oral forms" approach suggested by the PDAC.

The rate of skin sensitization in actual use appeared to be immeasurably low and even if it was occurring at a higher-than-observed-rate and was missed, it did not seem to result in any serious reactions. By the same token, patients were not systematically re-challenged with oral methylphenidate if they developed skin hypersensitivity or rashes to MTS in the trials.

The Division met in consultation with our own Dermatologists Markham Luke, MD and Brenda Carr, MD as well as Erin Warshaw, MD of the University of Minnesota in March 2006. Dr Warshaw provided the copy of a manuscript that is accepted for peer-reviewed publication. In it she sites many references that "Most patients are able to successfully transition to oral medication after failing transdermal therapy because of allergic contact dermatitis." She also goes on to state, "However, most drug manufacturers do not recommend oral challenge for patients topically sensitized to drugs." They gave examples of other transdermally delivered drugs where oral re-challenge was performed.

"A literature search found no reports of patients with contact allergy to nicotine who experienced a relapse of dermatitis or systemic skin reactions after stopping the TTS and restarting smoking<sup>1</sup>. However a case report discussed earlier in this paper reported a woman who began chewing nicotine-replacement gum after discontinuing nicotine TTS due to widespread cutaneous reaction, and positive patch testing to nicotine. Her cutaneous symptoms progressed despite treatment with topical corticosteroids. Her widespread dermatitis was possibly worsened by her continued nicotine intake. There were no local reactions in her mouth, however, and the patient continued to smoke after stopping the gum. Her skin lesions cleared two weeks after cessation of the nicotine gum and the dermatitis did not return<sup>2</sup>.

In 29 patients with patch test-confirmed allergic contact dermatitis to clonidine TTS, who were subsequently challenged orally, only one (3.4%) had a skin reaction following oral clonidine consisting of localized erythema and edema at a previous clonidine TTS site. None of the rechallenged patients experienced a systemic reaction<sup>3</sup>.

### **Erythema and Irritation Associated with the MTS**

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<sup>1</sup> Boekhorst JC. Allergic Contact Dermatitis with Transdermal Clonidine. *The Lancet*. 1983; Oct: 1031-1032  
Groth H, Vetter H, Knuesel, Vetter W. Allergic Skin Reactions to transdermal clonidine. *The Lancet* 1983; 2: 850-851

<sup>2</sup> Färm G. Contact allergy to nicotine from a nicotine patch. *Contact Dermatitis*. 1993; 29(4):214-5

<sup>3</sup> Hogan DJ, Maibach HI. Adverse dermatologic reactions to transdermal drug delivery systems. *Journal of the American Academy of Dermatology*. 1990; 22(5 Pt 1):811-4

The sponsor added a section to labeling entitled **Skin Irritation** to labeling to help distinguish skin irritation from contact dermatitis.

#### **Adverse Events Stratified by Age**

The sponsor provided case report tabulations from all of the studies stratified by age groups. The adverse events associated with higher mg/kg dose are easily monitored and highly variable from child to child. I believe that the adverse event profile of MTS is adequately characterized to inform prescribing across the age ranges.

#### **Monitoring and Reporting on Abuse, Misuse, or Diversion with Methylphenidate Transdermal System (MTS):**

I believe that the sponsor's risk management plan efforts for monitoring abuse and diversion are acceptable. I note that the sponsor is re-evaluating the community assessment tool. They report that the pilot community endorsed, "17% (n=80) of respondents reported that ADHD patches *are* a problem in their community. Another 4% (n=20) said that the problem with ADHD patches had changed over the past year. Given that there is no ADHD patch currently approved for marketing, these results point to a need to assess and revise the current protocol and questionnaire."

#### **Class Labeling for Stimulants for Psychiatric and Cardiovascular Adverse Events**

The FDA Pediatric Advisory Committee (PAC) met on March 22, 2006 to discuss class labeling for stimulants used in the treatment of ADHD. The consensus was that labeling should be updated to better inform non-psychiatric prescribers of stimulants for patients with ADHD. They felt that psychiatric terms-of-art such as toxic psychosis, emotional lability and agitation could be better understood by pediatricians and family practitioners if terms such as hallucinations and referential thinking at usual doses and aggression were used. The PAC also discussed the February 9, 2006 recommendation from the Drug Safety and Risk Management committee that stimulants carry a black-box warning for cardiovascular risk factors. The PAC, that was made up of pediatricians, child psychiatrists and a pediatric cardiologist on March 22, 2006 stated that there were no pediatric cardiovascular risk factors associated with stimulant use at usual doses in patients with ADHD that needed to be labeled with a black-box.

As part of the PAC briefing, Andy Mosholder, MD of the Division of Drug Risk Evaluation presented a pooled analysis of psychiatric adverse events for the various stimulant drug development programs. Psychiatric adverse events from the placebo controlled trials were grouped into categories of Psychosis/Mania, Aggression, Suicidality, and Other. The following table represents the psychiatric adverse events for Daytrana when they were grouped in this manner

Study design	Treatment	N	Person-years	Psychosis/mania events	Suicidal events	Aggression events
DB	Placebo	464	23.84	0	0	1
DB	MTS	471	30.26	4	0	6

Aggressive behavior or hostility is often observed in children and adolescents with ADHD, and has been reported in clinical trials and the postmarketing experience of some medications indicated for the treatment of ADHD. Although none of the 6 events grouped as aggression-events in Dr. Mosholder's analysis of the double blind treatment met criteria for serious, one did result in a suspension from school. These events are mentioned in the proposed draft labeling as emotional lability. This term may likely be changed as part of a class labeling update, but I believe it is

reasonable to continue to describe these events as emotional lability until this type of change is effected for the ADHD drugs as a class.

#### **CONCLUSIONS AND RECOMMENDATIONS**

I agree with Dr Levin that Daytrana may be approved after labeling is negotiated. In the end, there were no serious or fatal reports of patients restarting oral therapy after experiencing contact skin sensitization with MTS or any other transdermally delivered agent in the literature. That said, the dermatologists agreed that, reports of skin contact sensitization should be verified by diagnostic testing and that oral rechallenge after skin contact sensitization should be done under qualified medical supervision. Therefore, I do not believe that MTS should be reserved for patients who can or will not take oral formulations from a regulatory standpoint.

I believe that the sponsor has adequately addressed our concerns outlined in the Division's December 23, 2005 AE action letter. Once suitable labeling is agreed upon I recommend Daytrana (MTS) be approved for the treatment of ADHD in children aged 6-12 years.

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/s/

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Paul Andreason  
4/3/2006 10:30:32 AM  
MEDICAL OFFICER

# MEMORANDUM

Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Research and Evaluation  
Office of Drug Evaluation III  
Division of Dermatology and Dental Products

Tel 301-796-2110

FAX 301-796-9894

---

**From:** Brenda Carr, M.D./Medical Officer, Dermatology

**Via:** Markham Luke, M.D., Ph.D./Dermatology Team Leader  
Stanka Kukich, M.D./Acting Division Director, DDDP

**To:** Thomas Laughren, M.D./Director Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

**cc:** Mary-Jean Kozma-Fornaro/Supervisory Project Management, DDDP  
Bronwyn Collier/Associate Director for Regulatory Affairs, Office of Drug  
Evaluation III

**HFD-540 Consult #:** 840

**Subject:** resubmission of dated February 9, 2006

**Material Reviewed:** Materials included in the sponsor's submission dated February 9, 2006

**Date:** March 27, 2006; revised March 30, 2006

**Background:** NDA 21-514 was submitted on June 27, 2002 by Noven Pharmaceuticals for their product, Methylphenidate Transdermal System (MTS). The product was developed for the once-daily treatment of Attention Deficit Hyperactivity Disorder (ADHD) by a patch delivery system. In support of the NDA, the applicant conducted a combined skin sensitization and irritation study (N17-008). Study N17-008 revealed the applicant's product to be an irritant, and the product's role as a potential sensitizer could not be excluded.

On June 28, 2005, the review division received a resubmission from the applicant in response to the Not-Approvable action taken on NDA 21-514. Results from a contact

sensitization study, N17-020 were included in the resubmission. Study N17-020 reaffirmed that the applicant's product is an irritant. The study also revealed a signal for the product to induce contact sensitization. On December 23, 2005, the applicant received an approvable letter. On February 9, 2006, the applicant submitted draft labeling in response to the draft labeling they received from the review division with the approvable letter. The submission also included an overview of dermatologic events seen with MTS.

### **Consult Reply:**

The information provided by the sponsor in the submission dated February 9, 2006 does not change this reviewer's conclusions regarding the contact sensitization study, N17-020 (Please see dermatology consult #754). Study N17-020 revealed the sponsor's topically-applied product to be an irritant and a potential sensitizer, and the reviewer considers the study results to adequately serve as a basis for labeling the product as such, i.e. an irritant and potential sensitizer.

Since the provocative conditions of testing in study N17-020 differ from the proposed conditions of actual use, the extent to which the rates of occurrence of contact sensitization seen in that study (approximately 13% to 22%) might be seen under actual-use conditions is unclear. The proposed conditions of actual use (9-hour application times with a daily change in the site of application) could decrease the potential for irritancy; however, it is unclear to what extent the potential for sensitization might be impacted.

If an individual is sensitized to a substance via the dermal route, subsequent exposure to the allergen (or a chemically-related substance) via a systemic route could result in an allergic reaction of some sort. Most often, the reaction is a "systemic contact dermatitis" which may present as an eczematous dermatitis localized to sites of previous dermatitis (including the site of initial sensitization) or as an eczematous dermatitis of generalized distribution. Other reported (and rarer) reaction patterns include urticaria, erythroderma, erythema multiforme and vasculitis. Anaphylaxis has also been reported. Other systemic effects may include headache, fever, malaise, nausea, vomiting, and diarrhea.

Some authors are of the opinion that systemic exposure to the allergen should be avoided altogether, once sensitization has occurred via the topical route. Ghadially and Ramsay state that, "...the systemic administration of such contact allergens must be avoided to prevent severe reactions with systemic symptoms and even type 1 anaphylaxis." In their discussion of systemic contact-type dermatitis, Rietschel and Fowler also speak to the potential risks from systemic exposure, stating "It is much safer to perform a patch test with a drug suspected of producing an eczematous dermatitis medicamentosa (drug rash) than to readminister even a tiny fractional dose of the drug to prove that it is the culprit. Such proof may result in a widespread, disabling eruption."

However, other opinions have also been expressed. In a reference provided by the sponsor and co-authored by their consultant, the authors state that, "Most patients are able to successfully transition to oral medication after failing transdermal therapy because of allergic contact dermatitis..." However, it is noted that the authors goes on to state,

“However, most drug manufacturers do not recommend oral challenge for patients topically sensitized to drugs.”

The reviewer is unaware of any testing methodologies that might be predictive of which topically-sensitized individuals might experience a reaction if exposed to the allergen via a systemic route, or what the nature of the reaction might be should one manifest. Therefore, it would seem appropriate that the label advise of the risk of systemic sensitization following systemic exposure to methylphenidate in topically-sensitized individuals, although the level of risk is unclear. Should topically-sensitized individuals later require treatment with oral methylphenidate, it might be appropriate that the oral therapy be initiated under the supervision of an allergist.

**Conclusions:** Systemic exposure to an allergen to which an individual has been sensitized via the topical route may result in a variety of cutaneous reactions, and these reactions may be accompanied by systemic signs and symptoms. Based on the available information, the level of risk for systemic reactions in patients sensitized to methylphenidate via the topical route, should they be exposed to the substance via the oral route, is unknown; however, the risk cannot be discounted, in the reviewer’s opinion. It would seem appropriate that the label advise of the risk of systemic sensitization following systemic exposure to methylphenidate in topically-sensitized individuals, although the level of risk is unclear.

**Recommendations:** 1. It is recommended that the label advise of the risk of systemic sensitization following systemic exposure to methylphenidate in topically-sensitized individuals; however, the level of risk is unclear. It is also recommended that the label include the results from the contact sensitization study. Please see the proposed wording on the following page.  
2. It is recommended that the review division consider obtaining a consult from the Pulmonary and Allergy Division.

\*\*\*\*\*  
Please do not hesitate to contact the Division of Dermatology and Dental Products with any additional questions or concerns.

1   Page(s) Withheld

       Trade Secret / Confidential (b4)

       Draft Labeling (b4)

       Draft Labeling (b5)

       Deliberative Process (b5)

## REFERENCES

Rietschel RL and Fowler JF, editors. Fisher's Contact Dermatitis, 4<sup>th</sup> edition. Baltimore: Williams & Wilkins; 1995.

Fitzpatrick TB, Eisen AZ, Wolff K, Freedberg IM, Austen KF, editors Dermatology in General Medicine, 4<sup>th</sup> edition. New York: McGraw-Hill, Inc.; 1993

Ghadially R and Ramsay CA. Gentamycin: Systemic exposure to a contact allergen. J Am Acad Dermatol 1988;428-30.

Ash S and Scheman AJ. Systemic Contact Dermatitis to Hydroxyzine. Am J Contact Dermatitis 8:2-5,1997.

Musel AL and Warshaw AM. Cutaneous Reactions to Transdermal Therapeutic Systems (unpublished; per sponsor scheduled for publication in March 2007 issue of "Dermatitis")

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/s/

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Brenda Carr  
3/30/2006 01:26:19 PM  
MEDICAL OFFICER

Markham Luke  
3/30/2006 01:52:00 PM  
MEDICAL OFFICER  
Proposed wording for labeling is for your consideration. Please  
revise as reasonable.

Stanka Kukich  
3/30/2006 04:44:52 PM  
MEDICAL OFFICER



NDA 21-514

Noven Pharmaceuticals, Incorporated  
Co-Development Partner Shire Pharmaceuticals, Incorporated  
Attention: Harris L. Rotman, Ph.D.  
725 Chesterbrook Boulevard  
Wayne, PA 19087-5637

Dear Dr. Rotman:

We acknowledge receipt on February 9, 2006 of your February 9, 2006 resubmission to your new drug application for Daytrana (methylphenidate) Transdermal System.

We consider this a complete, class 1 response to our December 23, 2005 action letter. Therefore, the user fee goal date is April 9, 2006.

**Pediatric Research Equity Act (PREA)**

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We reference the deferral and waiver granted on December 23, 2005 for the pediatric study requirement for this application.

If you have any questions, call Susan Player, Regulatory Project Manager, at (301) 796-1074.

Sincerely,

*{See appended electronic signature page}*

CAPT Paul A. David, R.Ph.  
Chief Project Manager  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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Paul David

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

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**DATE:**                    **March 3, 2006**

**TO:**                      Thomas Laughren, M.D., Director  
Division of Psychiatry Products, HFD-130  
Office of New Drugs (OND)  
and  
M. Dianne Murphy, M.D.  
Director, Office of Pediatric Therapeutics (OPT), OIASI  
Office of the Commissioner  
and  
Solomon Iyasu, M.D., M.P.H., Acting Deputy Director  
Division of Pediatric Drug Development  
Office of Counter-Terrorism and Pediatric Drug Development  
(OCTAP)

**THROUGH:**            Mark Avigan, M.D., C.M., Director  
Division of Drug Risk Evaluation (DDRE)  
Office of Drug Safety (ODS)

**FROM:**                    Andrew Mosholder, M.D., M.P.H., Epidemiologist

**SUBJECT:**              Psychiatric Adverse Events in Clinical Trials of Drugs for  
Attention Deficit Hyperactivity Disorder (ADHD)

**PID:**                      D060163

**DRUGS:****Table 1. Drugs indicated for ADHD included in this review**

<b>Approved Products</b>			
<b>NDA #</b>	<b>Name</b>	<b>Company</b>	<b>Date of Approval</b>
21-303	Adderall XR (mixed salts of a single entity amphetamine product) Extended-Release Capsules	Shire Pharmaceuticals, Inc.	10/11/2001
21-278	Focalin (dexmethylphenidate HCL) Tablets	Novartis Pharmaceuticals Corporation	11/13/2001
21-802	Focalin XR (dexmethylphenidate HCL) Extended-Release Capsules	Novartis Pharmaceuticals Corporation	5/26/05
21-121	Concerta (methylphenidate HCL) Extended-Release Tablets	McNeil Consumer and Specialty Pharmaceuticals	8/11/2000
21-259	Metadate CD (methylphenidate HCL) Extended-Release Capsules	UCB Pharma, Inc.	4/3/2001
21-284	Ritalin LA (methylphenidate HCL) Extended-Release Capsules	Novartis Pharmaceuticals Corporation	6/5/2002
21-411	Strattera (atomoxetine HCL) Capsules	Eli Lilly & Company	11/26/2002
<b>Pending NDAs/sNDAs</b>			
20-717	Provigil (modafinil) Tablets	Cephalon, Inc.	pending
21-514	Methylphenidate transdermal system (MTS)	Noven Pharmaceuticals, Inc (Shire is a co-development partner with Noven)	pending

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## 1 EXECUTIVE SUMMARY

In follow-up to the June 2005 Pediatric Advisory Committee meeting discussion of adverse events with Concerta, it was decided to conduct a review of psychiatric adverse events with drugs for attention deficit hyperactivity disorder (ADHD). Results of the analysis of postmarketing reports will be presented separately. This consult summarizes the data from approximately 90 clinical trials that was submitted in response to the agency's request. Sponsors of marketed products for ADHD and drugs under review for that indication were asked to search their clinical trial databases for adverse psychiatric events in three primary categories: psychosis and mania, suicidal events, and aggression. This search was conducted electronically using selected, prespecified adverse event terms. They were also asked to search their databases for additional miscellaneous psychiatric events if the outcome was serious. Data on the duration of exposure to treatment in the trials and subject characteristics were also requested, as were clinical descriptions of the events and descriptions of the clinical trials in the ADHD development programs. Data were pooled within development programs to estimate the rates of the events of interest. The findings are subject to the usual limitations of such safety analyses, which include potential lack of consistency of ascertainment of adverse events across the various trials, the possibility of misclassification of cases, and statistical power limitations imposed by the sample sizes.

With these limitations in mind, specific observations about these clinical trial data are as follows. With respect to the clinical trial design, a large number of the controlled trials required subjects who were known to respond to stimulants, or who had no history of intolerance to stimulants. Also, many of the controlled trials were of very short duration. These factors limit the utility and external generalizability of the safety datasets obtained from the trials. With respect to specific findings, suicidal events were more frequent with atomoxetine and modafinil treatment than with placebo. It should be noted that there were no completed suicides in ADHD trials with these drugs (one completed suicide was reported in a placebo patient in an atomoxetine trial for another indication). Aggressive events were more frequent with the methylphenidate transdermal patch, and to a lesser degree with atomoxetine, than with placebo. None of these imbalances in rates reached customary levels of statistical significance in this analysis, although Lilly's previous analysis of suicidal events with atomoxetine did show a statistically significant association. For aggression events, there was little evidence in these trials that drug treatment reduced their frequency relative to placebo; only for modafinil was the event rate numerically lower than for placebo and this was not statistically significant. With respect to psychosis and mania events, although the numbers of such events with drug treatment were small, the complete absence of such events with placebo treatment was notable. For 4028 pediatric ADHD patients in these trials, there were no such events in 425 person-years of aggregated placebo treatment. Similarly, there were no psychosis or mania events in these trials among adult ADHD patients receiving placebo. Psychosis/mania events occurred during double-blind treatment with every compound except Adderall XR (although there were psychosis/mania events with open label

Adderall XR treatment). Furthermore, as noted above, some subjects in Phase I studies of these drugs experienced this type of event.

Patients and physicians should be aware of the possibility that these events, when they arise in the course of drug treatment of ADHD, may represent adverse reactions to drugs. In terms of future clinical trial designs, it should be borne in mind that short-duration trials and trials which exclude subjects who are naïve to this class of drug, while they may be efficient for determining efficacy, have limitations for defining the safety profile of the drug.

## **2 BACKGROUND**

The present effort to characterize psychiatric adverse events among patients treated with drugs for attention deficit hyperactivity disorder (ADHD) arose from a discussion at the June 30, 2005 meeting of FDA's Pediatric Advisory Committee. The rationale for this project was summarized in the letter FDA's Division of Psychiatry Products sent to the sponsors of products for ADHD, in September 2005:

At a June 30, 2005 meeting of the Pediatric Advisory Committee, a concern was raised about reports of psychiatric adverse events occurring in patients being treated with various drug products for ADHD. The reports considered at that meeting were for the drug Concerta, but it was acknowledged that similar reports have been made for other ADHD products. Although some psychiatric adverse events are already mentioned in the labeling for various ADHD products, there was general support for the view that labeling may need to be enhanced to better characterize these events. However, there was also agreement that such labeling changes should await a more comprehensive review of psychiatric events for ADHD products. In order to facilitate this more comprehensive review, we are requesting psychiatric adverse event data for various products approved for the treatment of ADHD.<sup>1</sup>

An analysis of postmarketing reports of adverse psychiatric events will be presented in a separate document. This document will present data on the psychiatric adverse events of interest from the clinical trial programs for the various ADHD products.

## **3. METHODS**

In the Information Request letters sent to the sponsors of ADHD drugs, the Division of Psychiatry Products asked the sponsors to conduct a search of their clinical trial databases for the adverse events of interest. The primary categories of adverse events to be analyzed were (1) psychosis and mania; (2) suicidal events; and (3) aggression. In addition, sponsors were asked to provide data on serious adverse events (i.e., those meeting the regulatory criteria for "serious") for a variety of miscellaneous psychiatric outcomes. Sponsors were to perform a string search of their electronic clinical trial databases for both preferred adverse event terms (e.g., MedDRA, COSTART) and investigator verbatim terms that might reflect one of the categories of interest. The

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<sup>1</sup> Dr. Thomas Laughren, FDA Division of Psychiatry Products, September 14, 2005.

following table lists the event terms suggested in FDA's request. The complete letter is reproduced in the consult describing postmarketing reports of these adverse events.<sup>2</sup>

**Table 2. Psychiatric event terms recommended for search by FDA**

Psychosis/mania	Suicidal ideation and behavior	Aggression and violent behavior	Miscellaneous (serious outcome only)
<ul style="list-style-type: none"> <li>o Hallucination (any type, including visual, auditory, tactile, mixed, etc)</li> <li>o Delusion (any type including somatic, persecutory, grandeur, reference)</li> <li>o Schizophrenia (any type)</li> <li>o Psychotic disorder</li> <li>o Transient psychosis</li> <li>o Acute psychosis</li> <li>o Paranoia</li> <li>o Childhood psychosis</li> <li>o Schizophreniform disorder</li> <li>o Schizoaffective disorder</li> <li>o Catatonia</li> <li>o Mania</li> <li>o Hypomania</li> </ul>	<ul style="list-style-type: none"> <li>o Depression suicidal</li> <li>o Gun shot wound</li> <li>o Intentional self-injury</li> <li>o Non-accidental overdose</li> <li>o Overdose</li> <li>o Self injurious behavior</li> <li>o Self injurious ideation</li> <li>o Self-mutilation</li> <li>o Suicidal ideation</li> <li>o Suicide attempt</li> <li>o Completed suicide</li> </ul>	<ul style="list-style-type: none"> <li>o Aggression</li> <li>o Anger</li> <li>o Hostility</li> <li>o Homicidal ideation</li> <li>o Sexual offense</li> <li>o Murder</li> <li>o Imprisonment</li> </ul>	<ul style="list-style-type: none"> <li>o Abnormal behavior</li> <li>o Agitation</li> <li>o Amnesia</li> <li>o Confusional state</li> <li>o Depressed mood</li> <li>o Depression</li> <li>o Disorientation</li> <li>o Emotional disorder</li> <li>o Emotional distress</li> <li>o Feeling abnormal</li> <li>o Memory impairment</li> <li>o Mood altered</li> <li>o Mood swings</li> <li>o Personality change</li> <li>o Thinking abnormal</li> <li>o Anxiety</li> <li>o Fearfulness</li> <li>o Phobia</li> <li>o Panic attack</li> <li>o Sleep disturbance</li> <li>o Tics</li> <li>o Obsessive or compulsive behavior</li> <li>o Trichotillomania</li> </ul>

The sponsors were instructed to enumerate events in these categories for both open label and double blind clinical trials. Events occurring either within 48 hours of the end of study treatment or within 30 days of the end of study treatment were to be enumerated separately. The sponsors were asked to provide synopses of the clinical trials, to assist in classifying the type of study for the purpose of aggregating data across trials. Sponsors were also asked to stratify data from their trials by age and gender subgroups, and to provide the duration of treatment (person-days) for each age and gender strata by trial, along with a count of patients who had events meeting the criteria for one of the categories of interest. However, we found that in some cases sponsors provided exposure time in person-days for each dose administered during the trial, resulting in the counting of some patients more than once according to how many doses they had received in that trial. In such instances the number of patients treated in the trial was determined from the clinical trial synopsis. Clinical trial exposure was to be classified as open label extension, open label run-in, or double blind. Patients with more than one event were to be counted only once per trial per category. In addition, the sponsor was asked to provide an

<sup>2</sup> PID D050243

accompanying listing of patients who had such events, with clinical information including patient characteristics, dose, concomitant medications, whether the event required discontinuation of treatment, and whether the event met criteria for "serious." (However, some sponsors provided this listing without specifying the category in which the event had been counted, making it difficult to reconcile the summary data with the listing of individual events.) Sponsors were also requested to provide clinical summaries of cases involving a serious outcome or premature discontinuation of treatment.

The drug products included in this analysis are those listed at the beginning of this document. All sponsors provided the requested data.

The submitted data were reviewed and data on the frequency of events were aggregated across trials within each product's clinical development program. Pooling across development programs was avoided because of apparent differences between the several development programs in patient populations and ascertainment of the selected adverse events. The event data were too sparse to permit a meaningful meta-analysis stratified by trial, as there were many trials with no events. However, the pediatric placebo exposure was aggregated to provide an estimate of the rates of events in a cohort of unmedicated pediatric ADHD patients. Statistical computing was accomplished with Microsoft Excel, JMP 5.1, and Stata 7.0.

#### **4. RESULTS**

##### **Summary results**

The data requests yielded data on 100 separate clinical trials in the development programs for these products. The table on the following page presents an overview of the clinical trials and the events. Note that this table includes all age groups and omits active control treatments for simplicity.

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**Table 3. Summary of ADHD clinical trials and psychiatric adverse events (all age groups)**

Drug	Type of trial	No. of Trials	Duration of trials (range)	Category of exposure	N	Patient-years	Psychosis /mania events	Suicidal events	Aggression events
Concerta	DB	4	6-28 dys	Placebo	317	10.20	0	0	0
				Drug DB	321	12.68	0	0	0
	OL	7	≤ 12 mos.	Drug OL	2824	1397.40	8	6	52
Metadate CD	DB	4	7-21 dys	Placebo	572	19.44	0	0	3
				Drug DB	493	19.13	0	0	3
	OL	2	NS	Drug OL	322	19.55	0	0	6
MTS	DB	8	1-49 dys	Placebo	464	23.84	0	0	1
				Drug DB	471	30.26	4	0	6
	OL	4	NS	Drug OL	617	341.97	6	1	7
Modafinil	DB	6	1-9 wks	Placebo	366	39.87	0	0	5
				Drug DB	772	85.50	2	4	9
	OL	3	≤ 1 yr	Drug OL	924	383.53	2	0	14
Adderall XR	DB	7	1-4 wks	Placebo	678	28.00	0	0	6
				Drug DB	1236	77.18	0	1	20
	OL	6	≤ 2 yrs	Drug OL	5177	1767.47	14	8	166
Atomoxetine	DB	20	≤ 78 wks	Placebo	1443	350.73	0	4	18
				Drug DB	2459	654.87	4	9	49
	OL	10	≤ 96 wks	Drug OL	5270	5095.27	12	44	198
Ritalin LA	DB	5	1-14 dys	Placebo	259	11.31	0	1	0
				Drug DB	383	25.66	2	0	2
	OL	1	NS	Drug OL	125	25.95	0	1	0
d-MPH	DB	8	≤ 49 dys	Placebo	468	53.24	0	0	0
				Drug DB	588	64.75	4	0	1
	OL	5	≤ 1 yr	Drug OL	740	362.09	3	1	13

Abbreviations: DB double blind, OL open label, NS not specified, MTS methylphenidate transdermal system, d-MPH dextromethylphenidate

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**Summary of comparison of rates in double blind, pediatric trials**

The following summary table displays the comparisons between the drug products and placebo for the three categories of events, within each development program, for pediatric subjects. Active controls were omitted from this summary. At the bottom of the table the pooled results for placebo are shown.

**Table 4. Summary of double blind trial data for pediatric subjects**

Treatment	N	Person- yrs	Psychosis/ mania events	Suicidal events	Aggression events	Psychosis/ mania events/ 100 pt-yrs	Suicidal events/100 pt-yrs	Aggression events/100 pt-years
Placebo	317	10.2	0	0	0	0.00	0.00	0.00
Concerta	321	12.68	0	0	0	0.00	0.00	0.00
Placebo	572	19.44	0	0	3	0.00	0.00	15.43
Metadate	493							
CD		19.13	0	0	3	0.00	0.00	15.68
Placebo	464	23.84	0	0	1	0.00	0.00	4.19
MTS	471	30.26	4	0	6	13.22	0.00	19.83
Placebo	308	32.55	0	0	5	0.00	0.00	15.36
Modafinil	664	75.11	2	4	9	2.66	5.33	11.98
Placebo	599	23.34	0	0	6	0.00	0.00	25.71
Adderall XR	1026	63.78	0	1	18	0.00	1.57	28.22
Placebo	1056	256.02	0	3	15	0.00	1.17	5.86
Atomoxetine	1939	524.64	4	8	45	0.76	1.52	8.58
Placebo	259	11.31	0	1	0	0.00	8.84	0.00
Ritalin LA	383	25.66	2	0	2	7.79	0.00	7.79
Placebo	415	48.47	0	0	0	0.00	0.00	0.00
d-MPH	420	49.73	1	0	0	2.01	0.00	0.00
Placebo (Pooled across drugs)	3990	425.11*	0	4	30	0	0.94	7.06

\*Age categories varied slightly by sponsor, but subgroup exposures may be summarized as follows: adolescent males 58 pyrs, adolescent females 18 pyrs, male children 274 pyrs, female children 75 pyrs.

## Summaries of psychiatric adverse events by clinical development program

In the following pages, the findings with respect to the psychiatric adverse events of interest are presented for each drug product.

### A. Concerta (NDA 21-121, McNeil)

Concerta is an extended release formulation of methylphenidate marketed by McNeil. Safety and efficacy studies contributing data to this analysis are summarized in Appendix Table A. Omitted from the analysis were studies in which the primary focus was on clinical pharmacology or bioavailability. Also, McNeil omitted from their response data from studies in which no Concerta was administered; i.e., involving non-Concerta formulations of methylphenidate only. In addition, there were a total of 17 non-U.S. studies of Concerta for which only limited data were available, and these have been omitted from the analysis. (The information currently available to the sponsor indicates no adverse events of interest occurred among subjects in these trials, but data are incomplete.)

It will be noted from the appendix table that all of the double blind exposure to Concerta in these trials occurred among patients who were already methylphenidate users, or had undergone open label treatment with methylphenidate prior to randomization (i.e., in study 011146).

The table below provides a summary of the adverse events of interest in the safety and efficacy trials with Concerta. There was only one relevant event during double blind treatment, an aggression event associated with use of Ritalin as an active control.

**Table A. Frequency of patients experiencing selected psychiatric events in Concerta clinical safety and efficacy studies.**

Study design	Treatment	Person- yrs	Person- yrs	Psychosis/ mania events	Suicidal events	Aggression events
DB	Placebo	317	10.20	0	0	0
DB	Concerta	321	12.68	0	0	0
DB	Ritalin	236	9.69	0	0	1
OL	Concerta	2824	1397.40	8	6	52
OL	Ritalin	76	11.81	0	0	4
OL	Atomoxetine	472	27.94	1	0	4
OL run in	Concerta	330	16.96	1	1	3

Five of the 52 aggressive events occurring during open label Concerta treatment were deemed serious.

The only study to enroll adult (>18 years old) ADHD subjects was open label study C99018, and in that study there were no events from these three categories among the adult subjects.

There were no miscellaneous adverse events deemed “serious” during double blind treatment. During open label treatment, one atomoxetine treated subject (172101 in study 12101) developed severe fearfulness that was considered serious, and Concerta-treated patient 19603 in the same study developed emotional distress that was considered serious and persisted post-treatment (see below). This patient, an 11-year old boy, was psychiatrically hospitalized and was eventually diagnosed with bipolar disorder, mixed with psychotic features.

There were a few relevant adverse events observed post-treatment (these are not shown in the table above). No events meeting the search criteria occurred within 48 hours of treatment discontinuation in these trials. With respect to events occurring between 48 hours and 30 days after treatment discontinuation, one subject became delusional five days after discontinuing Concerta, one subject was hospitalized for depression with a suicidal attempt 25 days after discontinuing Concerta, and in the “Miscellaneous” category, subjects 19603 (see above) and 19604 in open label study 12101 experienced “emotional distress” that was considered a serious adverse event 23 and 20 days, respectively, after study treatment ended. The narrative for patient 19604 also noted violent behaviors requiring psychiatric hospitalization, although the event was not categorized under aggression; the patient’s diagnoses included bipolar disorder and intermittent explosive disorder.

#### **B. Metadate CD (NDA 21-259, UCB Pharma, Inc.)**

Metadate CD is an extended release preparation of methylphenidate. The sponsor’s development program included 4 randomized, double blind efficacy trials and 2 open label safety trials; only pediatric subjects were enrolled in Metadate CD safety and efficacy trials. Appendix table B provides an overview of the clinical trials for studies in ADHD patients. All double-blind trials enrolled subjects who had been treated previously with methylphenidate. The sponsor’s search for the adverse psychiatric events of interest yielded no psychosis or mania events, no suicidal events, and 6 aggression events in double blind trials (3 each with Metadate and placebo). There were an additional 6 aggression events with open label treatment. All of the aggression events in both double blind and open label studies occurred in boys. There was only one serious psychiatric adverse event in these studies, in a Metadate-treated patient (termed “abnormal behavior”) which resulted in hospitalization (Study CD00500 / Patient #2003). This event was counted as aggression, in the open-label trial category.

There were no relevant psychiatric events in the sponsor’s bioavailability/pharmacokinetic trials, and no relevant events were reported up to 30 days post-treatment.

The following is a summary of the exposures and events in the Metadate CD safety and efficacy clinical trial program.

**Table B. Frequency of patients experiencing selected psychiatric events in Metadate CD clinical safety and efficacy studies.**

Study design	Treatment	N	Person- yrs	Psychosis/mania events	Suicidal events	Aggression events
DB	Placebo*	572	19.44	0	0	3
DB	Metadate CD	493	19.13	0	0	3
DB	Ritalin	158	7.61	0	0	0
DB	Concerta	180	3.29	0	0	0
OL	Metadate CD	322	19.55	0	0	6

\*includes single-blind placebo treatment in study MAI00104

In addition to the events enumerated above, patient 11-218 in study CD00600 experienced euphoria on the first day of treatment with placebo, and patient 1-10 in study CD00700 experienced euphoria on day 1 of Metadate CD, but these events were not included in the category of psychosis/mania as enumerated above.

### C. Methylphenidate transdermal system (MTS) (Noven, NDA 21-514)

The methylphenidate transdermal system (MTS) is a patch that delivers methylphenidate through the skin and is worn throughout the day and removed in the evening. This product is not yet approved. The development program included 8 randomized efficacy trials and 3 completed open label safety trials. All ADHD safety and efficacy trials involved only pediatric subjects. The characteristics of these trials are summarized in Appendix table C, and the summary data on psychiatric adverse events of interest are summarized in the table below.

**Table C. Frequency of patients experiencing selected psychiatric events in MTS clinical safety and efficacy studies.**

Study design	Treatment	N	Person- yrs	Psychosis/mania events	Suicidal events	Aggression events
DB	Placebo	464	23.84	0	0	1
DB	MTS	471	30.26	4*	0	6**
DB	Ritalin	10	0.19	0	0	0
DB	Concerta	91	11.10	1	0	1
Open	MTS	617	341.97	6	1	7

\*Rate ratio undefined, rate difference 0.13/person year, p-value versus placebo 0.10 (Stata version 7.0)

\*\*Rate ratio versus placebo 4.7, p-value 0.13 (Stata version 7.0).

Of the four psychosis/mania events during double blind treatment, two involved hallucinations, one a manic episode with hallucinations, and one paranoia. Two of the 7 aggression events occurring during open label treatment met criteria for "serious." Although none of the 6 aggression events during double blind treatment met criteria for serious, one did result in a suspension from school.

Additionally, in study SPD485201 there was an open-label run-in period prior to randomization that enrolled 93 patients (80 eventually were randomized), and during this run-in period there were 2 aggression events.

There were also clinical data from 9 bioavailability studies (4 involving pediatric ADHD patients), and 2 special skin sensitization studies in healthy adults. Review of the sponsor's listing of adverse events showed that in the biopharmaceutics trials, one child receiving Concerta, and 1 adult administered MTS buccally experienced psychosis/mania events. In the two open-label special skin sensitization protocols, which together exposed 315 healthy adult volunteers, there were 6 psychosis/mania events and one aggression event. Data from a special study of abuse potential in adults (N17-007) showed 2 psychosis/mania events with MTS, and four such events with the active controls.

The sponsor identified no relevant adverse events occurring after treatment discontinuation. Also, there were no serious psychiatric adverse events in the miscellaneous category.

#### **D. Modafinil (NDA 20-717 S-019, Cephalon, Inc.)**

Modafinil (Provigil, marketed by Cephalon, Inc.) is a non-sympathomimetic stimulant marketed for the treatment of excessive daytime sleepiness associated with sleep disorders. An indication for ADHD is under review, and will be the topic at the March 23 Psychopharmacologic Drugs Advisory Committee meeting.

With respect to psychotic adverse reactions, the current modafinil labeling notes (in the Precautions section) one such episode in a normal volunteer:

One healthy male volunteer developed ideas of reference, paranoid delusions, and auditory hallucinations in association with multiple daily 600 mg doses of PROVIGIL and sleep deprivation. There was no evidence of psychosis 36 hours after drug discontinuation.<sup>3</sup>

#### **Analysis of Psychiatric Adverse Events in Response to Approvable Letter**

The sponsor provided the following analysis in reply to our September 14, 2005 request as part of their response to the approvable letter for the indication of ADHD.

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<sup>3</sup> Provigil prescribing information available at [www.provigil.com](http://www.provigil.com)

**Table D1. Frequency of patients with psychiatric adverse events in ADHD trials (response to approvable letter)**

Study design	Treatment	N	Psychosis/mania events	Suicidal events	Aggression events
DB	Placebo	308	0	0	5
DB	Modafinil	664	2	4	9
Open	Modafinil	799	2	0	14

Analysis in response to FDA request 9-14-05

The sponsor also provided data on the adverse events of interest in a separate submission 1-6-06, responding specifically to the agency's request letter of 9-14-05. It appeared that this later submission included additional clinical trial data, although a list of the specific studies included was provided only for the 1-6-06 submission, so this could not be verified.

**Table D2. Frequency of patients with psychiatric adverse events in ADHD trials (sponsor's 1-6-06 submission)**

Study design	Treatment	N	Patient years of exposure	Psychosis/mania events	Suicidal events	Aggression events
DB	Placebo	366	39.87	0	0	5
DB	Modafinil	772	85.50	2	4	9
Open	Modafinil	924	383.53	2	0	14

There were no serious adverse events in the miscellaneous category.

There were more events in all categories among modafinil treated patients compared to placebo, but the exposure to modafinil was greater. It will be noted, however, that the frequency of these events during double blind treatment was higher than during open label treatment.

The table below displays the data for the subgroup of pediatric patients only (i.e., eliminating study 205 in adults, in which there were no events of interest).

**Table D3. Frequency of pediatric patients with psychiatric adverse events in ADHD trials (from 1-6-06 submission)**

Study design	Treatment	N	Patient years of exposure	Psychosis/mania events	Suicidal events	Aggression events
DB	Placebo	308	32.55	0	0	5
DB	Modafinil	664	75.11	2	4	9
Open	Modafinil	799	369.35	2	0	14

It should be noted that the NDA review by the Division of Psychiatry Products identified two additional probable cases of aggression during double blind treatment, in study 207 (patients 410 and 411).<sup>4</sup>

<sup>4</sup> Drs. June Cai and Glenn Mannheim, Division of Psychiatry Products

In addition, the sponsor noted that there were no events in the miscellaneous category that met criteria for “serious.”

With respect to events occurring after study treatment, one modafinil-treated subject (#410 in study 207) experienced formication (coded as psychosis) within 48 hours of treatment discontinuation, and one 6-year old female (subject 312-014016) was hospitalized for self-harmful behavior (putting a rope around her neck) two days after discontinuing open label treatment with modafinil. There were no psychiatric adverse events during the period from 48 hours to 30 days after treatment discontinuation.

One of the two psychosis/mania events during open label treatment required psychiatric hospitalization for a psychotic episode with suicidal ideation (patient 213-11002, an 8-year old boy who had a history of such symptoms, although this was apparently not known at study entry). This case was counted by the sponsor only in the psychosis/mania category, although it perhaps could have been counted as a suicidal event as well. The only two patients with serious psychiatric adverse events in these clinical trials were 312-014016 and 213-11002. (An additional case of suicidal ideation in a modafinil treated patient, requiring hospitalization, was included in the sponsor’s safety update for the ADHD supplement (patient 016001 from ongoing Study 312), but this apparently occurred after the cutoff date for the present data set.<sup>5</sup>)

Appendix table D displays the characteristics of the ADHD clinical trials. In addition, the sponsor provided data on the psychiatric events of interest from other indications. These data are summarized below.

**Table D4. Frequency of patients with selected psychiatric adverse events in studies of other indications**

Study design	Indication	Treatment	Patient years of exposure	Psychosis/mania events	Suicidal events	Aggression events	Miscellaneous serious events
DB	Excessive sleepiness	Placebo	96.65	1	0	0	1
DB	Excessive sleepiness	Modafinil	168.44	3	1	4	2
Open	Excessive sleepiness	Modafinil	1988.31	4	6	17	4
DB	Other*	Placebo	26.56	0	0	0	0
DB	Other*	Modafinil	98.37	8	2	13	6
Open	Other*	Modafinil	89.98	10	3	12	3

\*Clinical pharmacology, depression, dementia, head trauma, and other disorders

<sup>5</sup> Dr. June Cai, FDA Division of Psychiatric Products, personal communication

### E. Adderall XR (NDA 21-303, Shire)

Adderall and Adderall XR are formulations of mixed amphetamine salts. The active ingredient is a mixture of 25% l-amphetamine and 75% d-amphetamine. Adderall XR is an extended release, once-a-day formulation. There were no clinical safety and efficacy trial data available for Adderall, so the results below are for Adderall XR exclusively.

The Adderall XR development program included 3 randomized, double blind, placebo controlled trials in pediatric patients and one in adult ADHD patients. The Adderall XR safety and efficacy trials are summarized in Appendix table E.

The table below displays the summary data for the psychiatric events of interest.

**Table E1. Frequency of patients experiencing selected psychiatric events in Adderall XR clinical safety and efficacy studies.**

Study design	Treatment	N	Person- yrs	Psychosis/mania events	Suicidal events	Aggression events
DB	Placebo	678	28.00	0	0	6
DB	Adderall XR**	1236	77.18	0	1	20
Open	Adderall XR	5177	1767.47	14	8	166
DB	Atomoxetine	108	4.83	1	0	1

\*N not available \*\*includes 48 subjects in study 201 who received both Adderall and Adderall XR

The table below shows the data for the subgroup of trials involving only subjects of pediatric age.

**Table E2. Frequency of patients experiencing events in pediatric trials**

Study design	Treatment	N	Person- yrs	Psychosis/mania events	Suicidal events	Aggression events
DB	Placebo	599	23.34	0	0	6
DB	Adderall XR*	1026	63.78	0	1	18
Open	Adderall XR	4233	1280.80	9	8	150
DB	Atomoxetine	108	4.83	1	0	1

\*includes 48 subjects in study 201 who received both Adderall and Adderall XR

There were relatively few events in the categories of psychosis/mania and suicidal events in the double blind trials. There were somewhat more aggression events, but the distribution of events between drug and placebo was roughly proportional to the exposures. Of the 26 aggression events during double blind treatment, 11 occurred in study 201, a laboratory school study. Conceivably, closer observation of the subjects in that setting might have led to more reports of aggressive behaviors.

One trial included in the data above involved pediatric patients with Oppositional Defiant Disorder. Although the data were included in the totals above, they will be noted here

separately since this is a different albeit related indication. Study 311 was a 4 week randomized, double blind, placebo controlled, parallel group study involving five treatment arms (four fixed doses of Adderall XR and placebo). There was one aggression category event among the 60 patients who received placebo, and one suicidal event and seven aggression events among the 237 patients treated with Adderall XR. The pattern of events did not appear dose-related.

The sponsor reported no adverse events of interest in any Phase 1 trials.

With respect to events occurring after the end of treatment, there were a total of 4 subjects with such events. Patient 027-002 in study 311, a 17 year old girl, made a suicide attempt (overdose) 4 days after discontinuing Adderall XR 30 mg. Patient 041-010 in study 302, an 8 year old girl, was hospitalized for suicidal threats and explosive temper one day after discontinuing Adderall XR 30 mg and beginning diazepam. Patient 102-021 in study 304, an adult who had discontinued Adderall XR for a hypomanic episode, developed suicidal ideation subsequently. Lastly, patient 455-001 in study 305, a 9 year old female, developed defiant behaviors after discontinuing Adderall XR.

There were 4 serious events in the “miscellaneous” category, all with open-label treatment (one “personality disorder” and 3 “depression” events). The three events coded as depression (in subject 007-026/study 302, a 9-year old female, and subject 320-009, study 305, 10 year old girl, and subject 027-002, study 315, 14 year old female) involved hospitalization for suicidal ideation, and perhaps could have been classified in the suicidal event category. Other serious adverse events, all with open label treatment, included 2 aggression events in boys, two suicidal events in adolescent females, and one event designated amphetamine psychosis in an adult male. One of the serious events in the aggression category (subject 010-006, study 302, 10 year old boy) involved not only aggression and threats to others but also threats of self harm.

Also with respect to classification, one event in study 305 described in the clinical narrative as leading to discontinuation was “aggression towards himself” (subject 276-003), but this was categorized as an aggression event.

#### **F. Atomoxetine (Strattera, NDA 21-411, Lilly)**

Atomoxetine is a specific norepinephrine reuptake inhibitor marketed for the indication of ADHD in both children and adults. A previous development program for the indication of depression in adults was not successful.

The current labeling for atomoxetine includes the following Warning regarding suicidal events in atomoxetine clinical trials:

##### **Suicidal Ideation**

STRATTERA increased the risk of suicidal ideation in short-term studies in children and adolescents with Attention-Deficit/Hyperactivity Disorder (ADHD). Pooled analyses of short-term (6 to 18 weeks) placebo-controlled trials of

STRATTERA in children and adolescents have revealed a greater risk of suicidal ideation early during treatment in those receiving STRATTERA. There were a total of 12 trials (11 in ADHD and 1 in enuresis) involving over 2200 patients (including 1357 patients receiving STRATTERA and 851 receiving placebo). The average risk of suicidal ideation in patients receiving STRATTERA was 0.4% (5/1357 patients), compared to none in placebo-treated patients. There was 1 suicide attempt among these approximately 2200 patients, occurring in a patient treated with STRATTERA. No suicides occurred in these trials. All events occurred in children 12 years of age or younger. All events occurred during the first month of treatment. It is unknown whether the risk of suicidal ideation in pediatric patients extends to longer-term use. A similar analysis in adult patients treated with STRATTERA for either ADHD or major depressive disorder (MDD) did not reveal an increased risk of suicidal ideation or behavior in association with the use of STRATTERA...

With respect to aggressive behaviors, the current labeling includes the following statement (under the Precautions section):

**Aggressive Behavior or Hostility** — Aggressive behavior or hostility is often observed in children and adolescents with ADHD, and has been reported in clinical trials and the postmarketing experience of some medications indicated for the treatment of ADHD. Although there is no conclusive evidence that STRATTERA causes aggressive behavior or hostility, aggressive behavior or hostility was more frequently observed in clinical trials among children and adolescents treated with STRATTERA compared to placebo (overall risk ratio of 1.33 – not statistically significant). Patients beginning treatment for ADHD should be monitored for the appearance of or worsening of aggressive behavior or hostility.

#### Lilly suicidal event analysis

The labeling cited above for suicidal ideation was based on an analysis by Lilly of suicidal events in atomoxetine randomized, double-blind trials, requested by FDA in December 2004, and completed and submitted by Lilly in September 2005. Briefly, their methods and findings were as follows. Adverse event preferred terms, verbatim terms and comment fields were searched for text strings that might represent suicidal behaviors or ideation. Two different sets of text string terms were used for these searches, one requested by FDA and one devised by Lilly. False positives returned by these searches were excluded by review, and the events were classified into one of several categories of self injury or suicidal ideation. Statistical testing was performed using the Mantel-Haenzel incidence difference test. The results for the pediatric and adult atomoxetine trials are shown in the table below. By the FDA criteria, there were a total of 6 events classified as suicidal behavior or ideation among atomoxetine treated pediatric patients (6/1357, 0.4%) versus no such events among 851 placebo-treated patients (p-value = 0.01). Of the six pediatric events, one involved suicidal behavior and 5 involved suicidal ideation.

Overall, there was not the same imbalance between drug and placebo in the adult trials that was observed in the pediatric trials. The events in adult trials included one adult completed suicide on placebo. By indication, only one event occurred in an adult ADHD trial (on placebo).

**Table F1. Lilly analysis of suicidal events in atomoxetine clinical trials**

Category of events	Pediatric studies		Adult studies	
	Atomoxetine (n = 1357)	Placebo (n = 851)	Atomoxetine (n = 1718)	Placebo (n = 1072)
Suicidal events, FDA definition	6 (0.4%)*	0	15 (0.9%)	10 (0.9%)
Suicidal events, Lilly definition	7 (0.5%)**	1 (0.1%)	11 (0.6%)	8 (0.7%)

\*p-value versus placebo = 0.01

\*\*p-value versus placebo = 0.07

#### Lilly analysis of hostility and aggression

In April 2005, Lilly submitted an analysis of hostility and aggression in their pediatric atomoxetine double blind clinical trials. As with the analysis described above, they searched their clinical trial preferred terms, verbatim terms and comments fields for a variety of text strings that possibly represented hostility or aggression. Events returned by the search were reviewed by two health care professionals blind to treatment, and were classified into one of 6 possible categories of hostility or aggression, or were excluded. This yielded the results displayed in the following table. The combined risk ratio for aggressive events (atomoxetine:placebo) was 1.33 (0.67-2.64).

**Table F2. Lilly analysis of aggression in atomoxetine pediatric clinical trials**

Category of events	Frequency in pediatric double blind trials		
	Atomoxetine (n = 1308)	Placebo (n = 806)	MPH active control (n = 472)
Aggression and hostility, Lilly definition	21 (1.6%)	9 (1.1%)	4 (0.8%)

#### Response to September 2005 Data Request

The following tables display the results of the requested search. There were a total of 18 randomized, double blind trials of atomoxetine in pediatric patients with ADHD, and 3 such trials in adults. The ADHD safety and efficacy trials contributing data are summarized in Appendix table F.

The next table shows the summary results for all ages combined.