

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-514**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 21-514

SUPPL # 0

HFD # 130

Trade Name Daytrana

Generic Name Methylphenidate Transdermal System

Applicant Name Shire Pharmaceuticals, Incorporated and Noven Pharmaceuticals, Incorporated

Approval Date, If Known April 6, 2006

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES  NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES  NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES  NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES  NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 10-187

Ritalin (methylphenidate) Approval Date: 12-5-1955

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)  
IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a)

is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES  NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES  NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES  NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES  NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies 201, & 302

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

201, 302

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1  
IND # 54732            YES             ! NO   
! Explain:

Investigation #2  
IND # 54732            YES             ! NO   
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES   
Explain:

!  
!  
! NO   
! Explain:

Investigation #2

YES   
Explain:

!  
!  
! NO   
! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES  NO

If yes, explain:

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Name of person completing form: Susan E. Player  
Title: Regulatory Project Manager  
Date: May 23, 2006

Name of Office/Division Director signing form:  
Title:

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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/s/

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Thomas Laughren  
5/25/2006 01:22:56 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville MD 20857

NDA 21-514

Noven Pharmaceuticals, Inc.  
Attention: David Lucking  
Executive Director, Regulatory Affairs  
11960 Southwest 144<sup>th</sup> Street  
Miami, Florida 33186

Dear Mr. Lucking:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:                     ® (methylphenidate transdermal system)

Review Priority Classification: Standard (S)

Date of Application: June 27, 2002

Date of Receipt: June 27, 2002

Our Reference Number: NDA 21-514

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on August 27, 2002, in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be April 27, 2003.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Neuropharmacological Drug  
Products, HFD-120  
Attention: Division Document Room 4008  
5600 Fishers Lane  
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Neuropharmacological Drug  
Products, HFD-120  
Attention: Division Document Room 4008  
1451 Rockville Pike  
Rockville, Maryland 20852-1420

NDA 21-514

Page 2

If you should have any questions, please call Ms. Anna Marie H. Weikel, R.Ph., Regulatory Health Project Manager, at (301) 594-5535.

Sincerely,

*{See appended electronic signature page}*

John S. Purvis  
Chief, Project Management Staff  
Division of Neuropharmacological Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/

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Anna-Marie Homonnay  
7/22/02 09:53:30 AM

# 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

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

**Via:** Jill Lindstrom, M.D./Dermatology Team Leader  
Susan Walker, M.D./Director, Division of Dermatology and Dental Products

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

**HFD-540 Consult #:** 947

**Subject:** NDA 21-514 (S-003) Changes Being Effected Labeling Supplement

**Material Reviewed:** sponsor cover letter, proposed new wording for package insert, approved package insert for Daytrana, MedWach forms

**Date:** revised and final April 25, 2007

**Background:** The sponsor's product is a methylphenidate transdermal system marketed under the trade name Daytrana™ for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children aged 6-12 years (NDA 21-514; approved on April 6, 2006.)

The sponsor submitted a Changes Being Effected (CBE) supplement in a correspondence dated January 12, 2007. The proposed new wording provides for a "Postmarketing Reports" section with the following text:

"Postmarketing reports of hypersensitivity reactions including generalized erythematous and urticarial rashes, contact dermatitis, angioedema, and anaphylaxis, have been received. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to Daytrana™ exposure."

The consult requests “input about whether the sponsor’s proposed language regarding the hypersensitivity reactions is appropriate. Specifically, should labeling include ‘allergic contact dermatitis’ in addition to contact dermatitis? Also, would you recommend any more detailed description of the rashes and syndromes discussed in the proposed label?”

### **CONSULT REPLY**

From review of the provided MedWatch reports (40 were forwarded with the consult), the list of reactions proposed in the CBE supplement appears to be appropriately reflective of some of the events that have been reported from the marketplace (at least in regards to the MedWatch reports that were forwarded with the consult). The statement proposed in the CBE supplement categorizes the listed reactions as being hypersensitive in nature. Since an allergic contact dermatitis is a type of hypersensitivity reaction, it might be redundant for the statement to read “hypersensitivity reactions including... allergic contact dermatitis...” However, “allergic contact dermatitis” also reflects the verbatim wording from some of the reports, and its use could therefore perhaps be justified on that basis.

Several of the MedWatch reports of contact dermatitis did not qualify the nature of the dermatitis, i.e. irritant or allergic. It is possible that some of these reports were of irritant contact dermatitis, and the sponsor’s proposed wording does not appear to allow for this. Additionally, the proposed wording does not include certain other reported skin reactions that were not classified as contact dermatitis of any sort. Thus, despite the redundancy, insertion of “allergic” is recommended as it could serve to allow for the following (or similar) wording, as proposed by the consultant in this consult:

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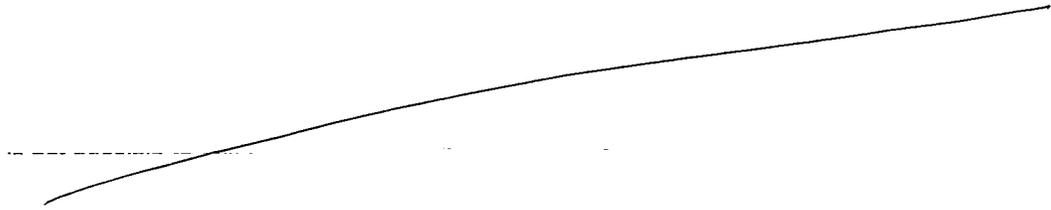
While, causality for the reactions cannot be established from the MedWatch reports, causality is more strongly suggested in some of the reports than others, particularly as pertains to certain accounts of reactions at the site(s) of application. However, the provided information did not always permit an opinion on the possible nature of certain local reactions (irritant versus allergic). One report did state that allergic contact dermatitis was diagnosed by a dermatologist.

It is noted that the WARNINGS section of the package insert includes a rather detailed discussion of the risk of contact sensitization, and the ADVERSE REACTIONS section includes a discussion of irritancy in a paragraph entitled, “Skin Irritation”. Thus, the potential for sensitization and irritation is addressed in the approved package insert, and

the marketplace may be bearing out some of what was learned about the product in its development.

**Recommendations:**

It is recommended that the review division consider the following (or similar) alternative wording to that which the sponsor has proposed:



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

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/s/

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Brenda Carr  
4/25/2007 01:50:09 PM  
MEDICAL OFFICER

Jill Lindstrom  
4/27/2007 04:03:58 PM  
MEDICAL OFFICER

Susan Walker  
5/8/2007 01:42:06 PM  
DIRECTOR

**Curtis, Felecia**

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**To:** Rotman, Harris  
**Cc:** Curtis, Felecia  
**Subject:** NDA 21-514 MG email  
**Attachments:** DaytranaMG 012007.doc

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 our letter dated February 21, 2007, requesting Medication Guides for all of the ADHD products. Based upon feedback from sponsors, we are making additional changes to the MG. Attached is a slightly revised Medication Guide.

Additionally, we inadvertently omitted informing you that you should also include the following revisions to product and container labeling:

1. You must reference the medication guide under "PRECAUTIONS-Information for Patients," section of the product labeling. For companies who don't have an Information for Patients section, please create one and reference the medication guide. We ask that you include the following language in this section:

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with *<insert amphetamine, dextroamphetamine or methylphenidate>* and should counsel them in its appropriate use. A patient Medication Guide is available for *<insert drug name>*. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

2. Per 21 CFR 208, the container label is required to instruct the authorized dispenser to provide a medication guide to each patient and to state how it is provided.

3. Please make the following grammatical revisions:

- Change "for awhile" to "for a while".

- When the medication guide says, "you and your child's" change to "your and your child's".

Please include this information as part of the "Supplement - Changes Being Effected" submission. While we realize that the medication guides will take some time before they enter commercial distribution, we would expect that you will update the label on your internet site once labeling has been approved.

You may submit final printed labeling electronically as a word document and Structured Product Labeling (SPL) format, 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 21 days from the date of this letter. Your submission should also address how you intend to ensure that there are adequate numbers of Medication Guides to ensure that every patient receives one when they receive the drug.

If you have any questions, feel free to contact me via email.

*Felecia Curtis, RN, LT, USPHS  
Regulatory Health Project Manager  
Division of Psychiatry Products  
U.S. Food and Drug Administration  
10903 New Hampshire Ave Bldg 22 RM 4399 Silver Spring, MD 20993-0002  
301-796-0877 [felecia.curtis@fda.hhs.gov](mailto:felecia.curtis@fda.hhs.gov)*

6 Page(s) Withheld

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

✓  
           § 552(b)(4) Draft Labeling

           § 552(b)(5) Deliberative Process

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/s/

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Felicia Curtis  
3/19/2007 02:47:50 PM  
CSO

<b>DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION</b>			<b>REQUEST FOR CONSULTATION</b>	
<b>TO:</b> Dermatology/ Attn: Vick Lutwak, RPM HFD: 150			<b>FROM:</b> Division of Psychiatry Products HFD-130/PSYCHIATRIC PRODUCTS	
<b>Date:</b> Feb. 27, 2007	<b>IND No.</b>	<b>NDA No:</b> 21-514	<b>TYPE OF DOCUMENT</b>	<b>DATE OF DOCUMENT</b>
<b>NAME OF DRUG:</b> Daytrana (Methylphenidate Transdermal System)				
<b>NAME OF DRUG COMPANY:</b> Shire				
<b>INDICATION OF DRUG:</b> ADHD; pediatric patients (ages 6-12)				
<b>DESIRED COMPLETION DATE:</b> April 16, 2007				
<b><u>REASON FOR REQUEST</u></b>				
<p>The sponsor has submitted a CBE supplement in order to add language about hypersensitivity reactions to the Adverse Events, Postmarketing section. We would appreciate input about whether the sponsor's proposed language regarding the hypersensitivity reactions is appropriate. Specifically, should labeling language include "allergic contact dermatitis" in addition to "contact dermatitis?" Also, would you recommend any more detailed description of the rashes and syndromes discussed in the proposed label? DPP (Dr. Levin) has discussed these questions with Dr. Brenda Carr, and we have forwarded the relevant information submitted by the sponsor (cover letter, proposed label, six representative clinical cases, and additional MedWatch cases). Thank you.</p>				
<b>SIGNATURE OF REQUESTER</b> Thomas Laughren, MD Director, DPP			<b>METHOD OF DELIVERY (CHECK ONE)</b> <input checked="" type="checkbox"/> MAIL <input type="checkbox"/> HAND	
<b>SIGNATURE OF RECEIVER</b>			<b>SIGNATURE OF DELIVERER</b>	

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/s/

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Thomas Laughren  
3/1/2007 11:31:40 AM



**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of New Drugs - Immediate Office  
Pediatric and Maternal Health Staff  
Silver Spring, MD 20993  
Telephone 301-796-2200  
FAX 301-796-9744

**M E M O R A N D U M**

**Date:** February 26, 2007

**From:** Felicia Collins, MD, MPH, Medical Officer  
Pediatric and Maternal Health Staff, Office of New Drugs

**Through:** Jean Temeck, MD, Team Leader  
Pediatric and Maternal Health Staff, Office of New Drugs

**Through:** Lisa Mathis, MD, OND Associate Director  
Pediatric and Maternal Health Staff, Office of New Drugs

**To:** Thomas Laughren, MD, Director  
Division of Psychiatry Products, Office of New Drugs

**Re:** Proposed Pediatric Study Request

**Drug:** Daytrana™ (methylphenidate transdermal system)

**Sponsor:** Shire Pharmaceutical Development, Inc.

**Number:** NDA 21-514/IND 54,732

**Division Question:**

The Sponsor has submitted a Proposed Pediatric Study Request (PPSR) to the Division of Psychiatry Products (Division) based on its anticipated post-marketing commitment study. The Division has consulted the Pediatric and Maternal Health Staff (PMHS) to get its recommendation regarding whether there is sufficient justification to issue a Written Request (WR) for this product.

**Material Reviewed:**

- Daytrana™ (methylphenidate transdermal system) labeling (July 27, 2006)
- Division File System (DFS) documents for NDA 21-514 and IND 54,732
- Pediatric Proposed Study Request (NDA 21-514, October 9, 2006)

- Written Requests and Proposed Pediatric Study Request inadequate letter for other ADHD drugs
- Biomedical literature (PubMed)

### **Background Information:**

#### ***General Information***

Daytrana™ (methylphenidate transdermal system (MTS)) is an adhesive-based patch that contains a central nervous system (CNS) stimulant approved for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children 6 – 12 years old. Its mode of therapeutic action in ADHD is not known, but methylphenidate is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and to increase the release of these monoamines into the extraneuronal space. In a study of children 6 – 12 years old composed of a 5-week, open-label, dose optimization phase followed by a 2-week, randomized, double-blind, placebo-controlled crossover treatment phase, there was a statistically significant difference in favor of Daytrana™ beginning at 2 hours and remaining through 12 hours after Daytrana™ application. The effectiveness of Daytrana™ for long-term use (i.e., more than 7 weeks) has not been systemically evaluated in controlled trials. Like other methylphenidate products, Daytrana™ is classified as a Schedule II controlled substance by Federal regulation, and there is a black box warning concerning drug dependence in its drug labeling (Daytrana™ (methylphenidate transdermal system) drug labeling, July 27, 2006).

Per a review of the FDA's *Orange Book*, Daytrana™ has current marketing exclusivity that expires April 6, 2009 and patent protections expiring September 30, 2018.

#### ***Regulatory History***

On June 27, 2002, the Sponsor first submitted its Daytrana™ NDA 21-514 for the treatment of ADHD in children 6 – 12 years old. On April 25, 2003, the FDA issued a non-approvable letter that acknowledged the positive efficacy findings but noted concerns about unacceptable levels of certain adverse events (e.g., insomnia, anorexia, weight loss) with a patch wear time of 12 hours. The letter also raised concerns about the potential for diversion and abuse and of skin sensitization. The FDA suggested shorter wear times and the inclusion of a skin sensitization study and comprehensive risk management plan in the drug development program (Laughren, T., Division Director Memo for an Approvable Action, December 23, 2005).

On June 28, 2005, the Sponsor resubmitted NDA 21-514 that included two randomized, double-blind, placebo-controlled studies with a 9-hour patch wear time in children 6 – 12 years old with ADHD (Daytrana™ (methylphenidate transdermal system) drug labeling, July 27, 2006). The Sponsor also had conducted a contact sensitization study (N17-020) that reaffirmed that the product is an irritant and revealed a signal for the product to induce contact sensitization (Carr, B., Memorandum from the Division of Dermatology and Dental Products, March 30, 2006). The contact sensitization study involved continuous exposure to the same skin site for 3 weeks followed by a 2-week rest period and then a challenge/re-challenge period (Laughren, T., Division Director Memo for an Approvable Action, December 23, 2005).

On April 6, 2006, the FDA approved the Sponsor's NDA 21-514 for Daytrana™ for the treatment of ADHD in children 6 – 12 years old. In its approval letter, per the Pediatric Research Equity Act (PREA), the FDA noted that it had waived pediatric studies of Daytrana™ for pediatric patients 2 – 5 years old and had deferred studies in pediatric patients 13 – 17 years old with ADHD until April 2009. The letter also noted the Sponsor's agreement to conduct a post-marketing study for estimating the risk of sensitization in a clinical setting.

On October 9, 2006, the Sponsor submitted a Proposed Pediatric Study Request (PPSR) based on its planned post-marketing commitment protocol. On November 29, 2006, the Division Medical Officer concluded that the PPSR was reasonably safe to proceed as written. The Medical Officer also noted that the proposed daily doses and duration of the study drug exposure were identical to those used in the studies in children 6 – 12 years old (Levin, R., PPSR for 75-Day Expedited Review, November 29, 2006).

#### ***Proposed Pediatric Study Request***

The Sponsor's PPSR consists of its planned post-marketing commitment study titled "A Phase 3b, Randomized, Double-Blind, Multi-Center, Parallel-Group, Placebo-Controlled, Dose Optimization Study Designed to Evaluate the Safety and Efficacy of Daytrana™ Methylphenidate Transdermal System in Adolescent Patients Aged 13 – 17 Years with Attention-Deficit/Hyperactivity Disorder" (SPD485-409). The primary study objective is to evaluate the efficacy of Daytrana™ in the symptomatic treatment of adolescents diagnosed with ADHD by DSM-IV-TR criteria as determined by the change in the clinician-completed ADHD-RS-IV (the ADHD-RS consists of 18 items designed to reflect symptoms of ADHD). The secondary objectives are to assess: (1) the safety and tolerability of Daytrana™; (2) the efficacy of Daytrana™ in the home environment; (3) clinicians' and parents' global impressions of ADHD severity and improvement with Daytrana™; (4) skin tolerance of Daytrana™/Placebo Transdermal System (PTS); and (5) the relationship between plasma exposure and the safety and efficacy measures of Daytrana™ via sparse sampling. The planned study period is April 2007 to February 2008 (Shire Pharmaceutical Development, FDA Electronic Document Room, NDA 21-514, Pediatric Proposed Study Request, October 9, 2006).

Per the study protocol, 210 patients with ADHD, 13 - 17 years old, will be randomized in a 2 drug : 1 placebo ratio to receive 7 weeks of treatment with Daytrana™ or matching placebo transdermal patches via 5 weeks of dose optimization and 2 weeks of maintenance treatment. Daytrana™ dosages will include 10, 15, 20, and 30 mg per 9 hours. All drug-treated patients will be initiated on the 10 mg dose with titration to the next dose based on the overall response after a minimum of one week. Downward titration will be allowed once to optimize tolerability and effectiveness during the optimization period.

During the treatment period, efficacy and safety will be assessed weekly. The primary efficacy outcome will be assessed by the ADHD-RS-IV. Secondary efficacy outcomes will be assessed by multiple tools: Conners' Parent Rating Scale-Revised [CPRS-R]: Short Form, Clinical Global Impressions of Improvement, and Parent Global Assessment. Safety and tolerance will be assessed by clinical laboratory tests (i.e., hematology (CBC), serum chemistry, and urinalysis), physical examinations, vital signs, height (via a calibrated stadiometer), weight (via a calibrated scale), electrocardiograms (ECGs), adverse events reporting, and application skin site evaluation (i.e., via the Dermal Response Scale and Experience of Discomfort and Pruritus). At 30 days post-discontinuation or completion of the study drug, a follow-up telephone contact will occur to collect information on any new or ongoing adverse events. Additionally, patients that discontinue due to an application site reaction may be contacted up to 1 year after the last dose of study medication (Shire Pharmaceutical Development, FDA Electronic Document Room, NDA 21-514, Pediatric Proposed Study Request, October 9, 2006).

For the pharmacokinetic/pharmacodynamic assessment, the Sponsor will draw blood to assess plasma *d*-MPH and *l*-MPH concentrations as the measure of systemic exposure at the end of the dose optimization period (week 5) and during the dose maintenance period (weeks 6 and 7) (the Sponsor notes that regression analyses conducted in earlier studies have previously demonstrated that the drug concentrations at these sampling times are highly correlated with the area under the plasma

concentration-time curve (AUC) in pediatric patients). The Sponsor will explore relationships between any treatment-related changes in relevant efficacy parameters (e.g., via ADHD-RS-IV and CPRS-R ratings) and systemic exposure. If appropriate, the Sponsor also will explore relationships between relevant safety parameters (e.g., change in systolic blood pressure, diastolic blood pressure, or pulse and treatment-emergent adverse events including weight loss or sleep changes) and systemic exposure (Shire Pharmaceutical Development, FDA Electronic Document Room, NDA 21-514, Pediatric Proposed Study Request, October 9, 2006).

### **Discussion:**

#### ***Prevalence and Manifestations of ADHD in Children and Adolescents***

ADHD is one of the most frequently diagnosed and best-studied clinical syndromes in child psychology (Smith *et al.*, 2000). Two authors report that the estimated prevalence of ADHD in school-aged children is 5 % (Phillips and Soffer, 1996; Biederman, 2006), whereas another author cites epidemiologic studies estimating the prevalence of ADHD in school-aged children as 8 – 10 % (McGough *et al.*, 2006). Numerous authors agree that the majority of children diagnosed with ADHD continue to manifest symptoms into adolescence and adulthood (Phillips and Soffer, 1996; Garland, 1998; Smith *et al.*, 2000; Mott *et al.*, 2004; Biederman, 2006; Schonwald and Lechner, 2006; McGough *et al.*, 2006); however, prevalence data in these adolescent and adult populations are limited (Biederman, 2006).

The core symptoms of ADHD in children are poor concentration, hyperactivity, and impulsivity. However, by adolescence, it is common to see a decrease in motor overactivity and a greater concern regarding the effect that inattention and impulsivity have on academic and social performance (Phillips and Soffer, 1996). The majority of adolescents with a childhood history of ADHD suffer more problems than adolescent controls. These problems include school failure and conduct disorder, substance abuse, affective disorders and risk behaviors such as motor vehicle accidents (Phillips and Soffer, 1996; Garland, 1998; Smith *et al.*, 2000).

#### ***ADHD Studies in Adolescent Populations***

Until the 1980s, there was a dearth of high-quality research on adolescents with ADHD. The lack of research has been attributed to the hypothesis that ADHD was a self-limiting disorder of childhood with the remission of symptoms after puberty (Smith *et al.*, 2000). Although some studies of ADHD in adolescents now exist, the patients in most ADHD medication studies have been school-aged children (Mott *et al.*, 2004). One author's review published in 2000 cited more than 127 published research studies on methylphenidate treatment for ADHD but identified only 8 well-controlled studies that provided data on ADHD treatment in adolescence. Multiple authors have reported that most reviews of the treatment for adolescents with ADHD have made upward extrapolations from studies on children (Smith *et al.*, 2000; Mott *et al.*, 2004). One of these authors has asserted that the limited data specific to adolescents is a serious limitation to the understanding of the treatment of ADHD because: (1) the presentation and treatment psychopathology likely differ as a function of age; and (2) elaboration of developmental changes as they interact with ADHD in adolescent populations has not been subjected to focused research (Smith *et al.*, 2000). Moreover, the paucity of research confirming a beneficial effect of pharmacotherapy on long-term outcomes in adolescents also leads to controversy regarding the balance between the risks and benefits of treatment in adolescents (Garland, 1998).

#### ***ADHD Treatment in Children and Adolescents***

Oral, extended-release forms of methylphenidate administered once daily have similar benefits as immediate-release preparations and are useful in patients who experience severe symptom rebound or find ingesting medication every 4 hours to be inconvenient, stigmatizing, or unduly difficult

(McGough *et al.*, 2006). Such extended-release methylphenidate preparations often are preferred by teens, especially if they eliminate the need to take medication at school (Mott *et al.*, 2004). Given the unique psychosocial, environmental, and scheduling challenges of adolescence, the American Academy of Child and Adolescent Psychiatry agrees that extended-release methylphenidate is “well-suited for treatment of adolescents” (Mott *et al.*, 2004). However, “while sustained release preparations effective for about 8 hours can be helpful options, ... after school dosing often is still needed for homework and evening effects” (Garland, 1998). Thus, issues of noncompliance with multiple medication doses resurface for adolescents. Given that an adolescent’s day typically includes early morning departure for school, late afternoon after-school activities, and evening homework, medications whose effects are sustained throughout the entire day are clinically important to this population and could enhance adolescent adherence to the prescribed treatment regimen.

Concerta<sup>®</sup> (methylphenidate HCl) and Adderall XR<sup>®</sup> (mixed salts of amphetamine) are existing extended-release stimulant medications approved for the treatment of ADHD in adolescent populations. The variation in the description of the pharmacokinetic parameters in the drug labeling for Concerta<sup>®</sup>, Adderall XR<sup>®</sup>, and Daytrana<sup>™</sup> makes pharmacokinetic comparisons difficult amongst the three drugs. In addition, the lack of a study in which Daytrana<sup>™</sup> is compared to Concerta<sup>®</sup> and/or Adderall XR<sup>®</sup> makes it difficult to determine if the 12 hours of efficacy seen in Daytrana’s<sup>™</sup> clinical pediatric trial differs significantly from that of the other drugs.

***Written Requests and Inadequate Letter for Studies of ADHD Treatment in Adolescents***

On May 6, 2003, the FDA issued a WR to Shire Pharmaceutical Development Inc. seeking a drug development program to establish the safety and efficacy of Adderall XR<sup>®</sup> (mixed salts of amphetamine) extended-release capsules in pediatric patients 13 - 17 years old with ADHD and to develop pharmacokinetic data pertinent to this population. The current WR includes a: (1) pediatric pharmacokinetic study to provide adolescent dosing information; (2) pediatric efficacy and safety study via a randomized, double-blind, parallel group, placebo-controlled trial of at least 3 to 4 weeks; and (3) pediatric safety study to obtain longer-term safety data for a minimum duration of 6 months. Full study reports and analysis are due in September 2008. Of note, this reviewer believes that the Shire Pharmaceutical Development Inc. Sponsor for the Adderall XR<sup>®</sup> WR is the same sponsor as that for the Daytrana<sup>™</sup> PPSR.

On June 25, 2003, the FDA issued a WR to another sponsor seeking a drug development program to establish the safety and efficacy of Concerta<sup>®</sup> (methylphenidate HCl) extended-release tablets in pediatric patients 13 -17 years old with ADHD and to develop pharmacokinetic data pertinent to this population. The current WR has study types, objectives, designs, and endpoints identical to the Adderall XR<sup>®</sup> WR. Full study reports and analysis also are due in September 2008.

On September 22, 2004, the Division notified the sponsor of Ritalin LA<sup>®</sup> (methylphenidate hydrochloride) extended-release capsules that it was unable to issue a WR based on its proposed pediatric study request, because there was no apparent public health benefit for studies of ADHD treatment in only female patients aged 12 – 17 years old. The FDA also noted that Ritalin LA<sup>®</sup> did not provide a significant public health benefit over existing therapies.

***Pediatric Research Equity Act and the Best Pharmaceuticals for Children Act***

The Pediatric Research Equity Act (PREA) requires sponsors to submit pediatric assessments when they submit an application or supplemental application for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration. These assessments may be

completed as a post-marketing commitment after the sponsor has obtained FDA approval of the drug for adults.

The Best Pharmaceuticals for Children Act (BPCA) allows the FDA to issue a Written Request (WR) for pediatric studies to sponsors holding approved drug applications protected by patent or market exclusivity. Sponsors that successfully carry out these studies on a voluntary basis may qualify to receive 6 months of additional marketing exclusivity. According to Section VIII of the FDA's guidance on PREA, the FDA's policy is to offer an opportunity for pediatric exclusivity to sponsors with post-marketing commitments under PREA. In addition, when considering the appropriateness of issuing a WR for pediatric studies, the FDA considers if there is a potential public health benefit that would result from such studies.

**Conclusions:**

Since the FDA's policy is to offer an opportunity for pediatric exclusivity to sponsors with post-marketing commitments under PREA, it would be appropriate to issue a WR to study Daytrana<sup>TM</sup> in adolescent patients with ADHD. Moreover, given the physiological and developmental differences between children and adolescents and an author's report that extended-release stimulant medications labeled as once daily medications have effects that may not last through evening after-school activities and homework time for adolescents, this reviewer believes that studies of Daytrana<sup>TM</sup> in adolescent populations have the potential to result in public health benefit.

There are cases when a Sponsor's pediatric post-marketing study protocol is an adequate PPSR and results in the FDA issuing a WR for pediatric studies with the possibility of the Sponsor obtaining marketing exclusivity per the provisions of BPCA. However, it is common that WR studies are held to a higher standard than the post-marketing commitments required under PREA which are not associated with marketing exclusivity. In the case of Daytrana<sup>TM</sup>, the Sponsor has submitted its pediatric post-marketing commitment protocol as a PPSR. The PPSR includes an efficacy/safety study and a pharmacokinetic/pharmacodynamic sub-study that appear reasonable. Given the contraindication of Daytrana<sup>TM</sup> in patients with motor tics or a family history or diagnosis of Tourette's syndrome and in patients on monoamine oxidase inhibitor treatment concomitantly or within 14 days of discontinuation, these issues should be added to the exclusion criteria of the PPSR. Moreover, the Division may want to consider requesting longer-term safety studies analogous to those included in the WRs for Concerta<sup>®</sup> and Adderall XR<sup>®</sup>. This reviewer believes that the Daytrana<sup>TM</sup> sponsor also is the sponsor for the Adderall XR<sup>®</sup> WR and thus would be familiar with the longer-term study request for adolescent patients with ADHD.

**Response to Division's Question:**

*Is there sufficient justification to issue a WR given that there are other methylphenidate products approved for use in adolescents (Note that this formulation is a dermal patch, which is unique)?*

Yes, there is sufficient justification to issue a WR for Daytrana<sup>TM</sup>. If the Division decides to issue a Daytrana<sup>TM</sup> WR, PMHS recommends that it present the proposed WR to the Pediatric Drug and Implementation Team (PdIT) for its review and concurrence.

## Reference List

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/s/

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Felicia Collins  
2/26/2007 01:34:54 PM  
MEDICAL OFFICER

Jean Temeck  
2/26/2007 07:54:38 PM  
MEDICAL OFFICER

Lisa Mathis  
2/27/2007 10:41:07 AM  
MEDICAL OFFICER



**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.

Reference is also made to an Agency letter dated May 22, 2006, informing you of our request to change class product labeling for all CNS stimulant products to treat Attention-Deficit Hyperactivity Disorder (ADHD).

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 a Medication Guide is warranted in order to caution practitioners, patients, family members or caregivers about these adverse events.

The Medication Guide must be in the format as outlined under 21 CFR 208. We have attached a draft Medication Guide for your product and we ask that you adopt this language verbatim. We would also highly recommend that your product be distributed in unit-of-use packaging to ensure that every patient receives the Medication Guide.

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.

**MEDICATION GUIDE**  
**DAYTRANA™ (day-TRON-ah)**  
**(methylphenidate transdermal system) CII**

**Important: For Skin Use Only**

Read the Medication Guide that comes with DAYTRANA™ before you or your child starts taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your doctor about you or your child's treatment with DAYTRANA™.

**What is the most important information I should know about DAYTRANA™?**

The following have been reported with use of DAYTRANA™ and other stimulant medicines.

**1. Heart-related problems:**

- sudden death in patients who have heart problems or heart defects
- stroke and heart attack in adults
- increased blood pressure and heart rate

Tell your doctor if you or your child have any heart problems, heart defects, high blood pressure, or a family history of these problems.

Your doctor should check you or your child carefully for heart problems before starting DAYTRANA™.

Your doctor should check you or your child's blood pressure and heart rate regularly during treatment with DAYTRANA™.

**Call your doctor right away if you or your child has any signs of heart problems such as chest pain, shortness of breath, or fainting while taking DAYTRANA™.**

**2. Mental (Psychiatric) problems:**

**All Patients**

- new or worse behavior and thought problems
- new or worse bipolar illness
- new or worse aggressive behavior or hostility

**Children and Teenagers**

- new psychotic symptoms (such as hearing voices, believing things that are not true, are suspicious) or new manic symptoms

Tell your doctor about any mental problems you or your child have, or about a family history of suicide, bipolar illness, or depression.

**Call your doctor right away if you or your child have any new or worsening mental symptoms or problems while taking DAYTRANA™, especially seeing or hearing things that are not real, believing things that are not real, or are suspicious.**

**What Is DAYTRANA™?**

DAYTRANA™ is a central nervous system stimulant prescription medicine. DAYTRANA™ is a skin patch that releases the medication contained in the adhesive (glue) through clean and intact skin areas into the bloodstream when applied to the skin on the hips. **It is used for the treatment of attention deficit and hyperactivity disorder (ADHD).** DAYTRANA™ may help increase attention and decrease impulsiveness and hyperactivity in patients with ADHD.

DAYTRANA™ should be used as a part of a total treatment program for ADHD that may include counseling or other therapies.

**DAYTRANA™ is a federally controlled substance (CII) because it can be abused or lead to dependence. Keep DAYTRANA™ in a safe place to prevent misuse and abuse. Selling or giving away DAYTRANA™ may harm others, and is against the law.**

Tell your doctor if you or your child have (or have a family history of) ever abused or been dependent on alcohol, prescription medicines or street drugs.

### **Who should not take DAYTRANA™?**

**DAYTRANA™ should not be taken if you or your child:**

- are very anxious, tense, or agitated
- have an eye problem called glaucoma
- have tics or Tourette's syndrome, or a family history of Tourette's syndrome. Tics are hard to control repeated movements or sounds.
- are taking or have taken within the past 14 days an anti-depression medicine called a monoamine oxidase inhibitor or MAOI.
- are allergic to anything in DAYTRANA™. DAYTRANA™ is a skin patch that contains methylphenidate in an acrylic and silicone adhesive (glue).

DAYTRANA™ should not be used in children less than 6 years old because it has not been studied in this age group.

**DAYTRANA™ may not be right for you or your child. Before starting DAYTRANA™ tell your or your child's doctor about all health conditions (or a family history of) including:**

- heart problems, heart defects, high blood pressure
- mental problems including psychosis, mania, bipolar illness, or depression
- tics or Tourette's syndrome
- liver or kidney problems
- seizures or have had an abnormal brain wave test (EEG)
- skin problems such as eczema or psoriasis, or have skin reactions to soaps, lotions, make-up, or adhesives (glues)

Tell your doctor if you or your child is pregnant, planning to become pregnant, or breastfeeding.

### **Can DAYTRANA™ be taken with other medicines?**

**Tell your doctor about all of the medicines that you or your child take including prescription and nonprescription medicines, vitamins, and herbal supplements.** DAYTRANA™ and some medicines may interact with each other and cause serious side effects. Sometimes the doses of other medicines will need to be adjusted while taking DAYTRANA™.

Your doctor will decide whether DAYTRANA™ can be taken with other medicines.

**Especially tell your doctor if you or your child takes:**

- anti-depression medicines including MAOIs
- seizure medicines
- blood thinner medicines
- blood pressure medicines
- cold or allergy medicines that contain decongestants

Know the medicines that you or your child takes. Keep a list of your medicines with you to show your doctor and pharmacist.

**Do not start any new medicine while taking DAYTRANA™ without talking to your doctor first.**

### **How should DAYTRANA™ be used?**

**Do not use heating pads, electric blankets, heated water beds or other heat sources while wearing a DAYTRANA™ patch. Too much medicine can pass into you or your child's body and cause serious side effects.**

See the complete instructions for applying DAYTRANA™ at the end of this Medication Guide.

- Use DAYTRANA™ exactly as prescribed. DAYTRANA™ comes in four different size (strength) patches. Your doctor may adjust the dose until it is right for you or your child.
- From time to time, your doctor may stop DAYTRANA™ treatment for awhile to check ADHD symptoms.
- Your doctor may do regular checks of the blood, heart, and blood pressure while taking DAYTRANA™. Children should have their height and weight checked often while taking DAYTRANA™. DAYTRANA™ treatment may be stopped if a problem is found during these check-ups.
- If you or your child uses too much DAYTRANA™ or overdoses, call your doctor or poison control center right away, or get emergency treatment.

**What are possible side effects of DAYTRANA™?**

**Skin reactions including skin irritation and allergic skin rash can happen with DAYTRANA™. Skin redness or itching at the application site happens in many people. You can keep using DAYTRANA™ if this happens. Stop using DAYTRANA™ and see your doctor right away if swelling, bumps, or blisters happen at or around the application site. You may have a skin allergy to DAYTRANA™. People that have skin allergies with DAYTRANA™ may develop an allergy to all medicines that contain methylphenidate, even those taken by mouth.**

See “What is the most important information I should know about DAYTRANA™” for information on reported heart and mental problems.

**Other serious side effects include:**

- slowing of growth (height and weight) in children
- seizures, mainly in patients with a history of seizures
- eyesight changes or blurred vision

**Common side effects include:**

- nausea
- decreased appetite
- vomiting
- decreased weight
- trouble sleeping
- tics
- mood swings

Talk to your doctor if you or your child has side effects that are bothersome or do not go away.

This is not a complete list of possible side effects. Ask your doctor or pharmacist for more information

**How should I store DAYTRANA™?**

- Store DAYTRANA™ in a safe place at room temperature, 59 to 86° F (15 to 30° C). Keep DAYTRANA™ Patches in their unopened pouches until ready to use.
- Once a tray of patches has been opened, use or discard the patches within 2 months.
- Keep DAYTRANA™ and all medicines out of the reach of children.

**General information about DAYTRANA™**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use DAYTRANA™ for a condition for which it was not prescribed. Do not give DAYTRANA™ to other people, even if they have the same condition. It may harm them and it is against the law.

This Medication Guide summarizes the most important information about DAYTRANA™. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about DAYTRANA™ that was written for healthcare professionals. For more information about DAYTRANA™ call 1-800-828-2088 or visit [www.shire.com](http://www.shire.com).

### **Instructions for Applying DAYTRANA™ USING THE ADMINISTRATION CHART**

Each carton of DAYTRANA™ contains an administration chart to help parents or caregivers keep track of when the patch is applied each morning, when it is removed and the method of disposal used. DAYTRANA™ should be worn for about 9 hours.

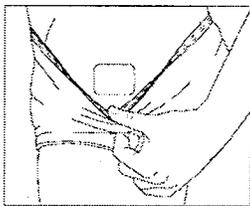
To use the administration chart, follow these instructions:

- Each day, when a new patch is applied, write down the date and time that the patch is applied.
- Use the timetable below to calculate when to remove the patch. For example, if the patch is applied at 6:00 a.m., it should be removed at 3:00 p.m. later the same day.
- After removing and disposing of the patch, write down the time the patch was removed and how it was disposed.
- If the applied patch is missing, ask the child when and how the patch came off.

### **Timetable for 9-Hour DAYTRANA™ Application and Removal**

<b>If you applied the patch at:</b>	<b>Remove the patch at:</b>
5:00 a.m.	2:00 p.m.
6:00 a.m.	3:00 p.m.
7:00 a.m.	4:00 p.m.
8:00 a.m.	5:00 p.m.
9:00 a.m.	6:00 p.m.
10:00 a.m.	7:00 p.m.
11:00 a.m.	8:00 p.m.
12:00 p.m.	9:00 p.m.

## **2. WHERE TO APPLY DAYTRANA™**



- Apply patch to the hip area. Avoid the waistline, since clothing may cause the patch to rub off.
- When applying a new patch the next morning, use the child's other hip. Make sure there is no irritation at the site where the patch is going to be applied.

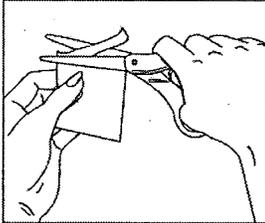
## **3. BEFORE YOU APPLY DAYTRANA™**

Make sure the child's skin is:

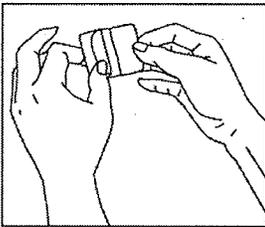
- Clean (freshly washed), dry, and cool.
- Free of any powder, oil, or lotion.
- Free of cuts and irritation (rashes, inflammation, redness, or other skin problems).

## **4. HOW TO APPLY DAYTRANA™**

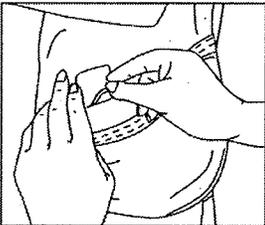
- **Open the tray containing DAYTRANA™ and discard the small packet (drying agent) included in the tray.**
- **Each patch is sealed in its own protective pouch.**
- Carefully cut the protective pouch open with scissors, being careful not to cut the patch. Do not use patches that have been cut or damaged in any way.
- Remove the patch from the pouch.



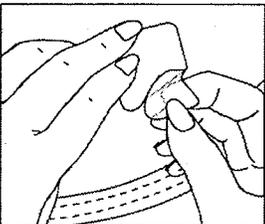
- **Apply the patch right away after removing from pouch.**
- Holding the patch with the rigid protective liner facing you, remove **half** of the liner, which covers the sticky surface of the patch.
- Avoid touching the sticky side of the patch with your fingers.



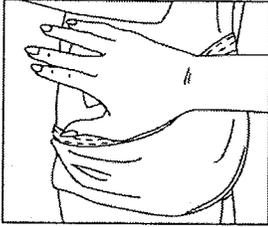
- Using the other half of the protective liner as a handle, apply the sticky side of the patch to the selected area of the child's hip.
- Press the sticky side of the patch firmly into place and smooth it down.



- While still holding the sticky side down, fold back the other half of the patch.
- Grasp an edge of the remaining protective liner and gently pull it off.



- Avoid touching the sticky side of the patch with your fingers.



- **Press the entire patch firmly into place with the palm of your hand over the patch, for about 30 seconds.**
- Make sure that the patch firmly sticks to your child's skin.
- Go over the edges with your fingers to assure good contact around the patch.
- Wash your hands after applying the patch.
- After the patch is applied, record the time on the administration chart on each carton, and use the timetable to calculate what time the patch should be removed.

**PLEASE NOTE:**

- **Contact with water while bathing, swimming, or showering should not affect the patch or make it fall off if it has been applied the right way.**
- **If a patch should fall off, avoid touching the sticky side of the patch with your fingers. A new patch may be applied to a different area of the same hip. If a new patch is applied, remove it 9 hours after the first patch for that day was applied. Always wash your hands after handling a patch.**
- If you forget to apply a patch in the morning, you may do so later in the day. However, you should remove the child's patch at the usual time of day to reduce the chance of later day side effects. You can use the timetable above to know when to remove the patch.

**5. HOW TO REMOVE AND DISCARD DAYTRANA™**

- When you remove the patch, peel it off slowly.
- Fold the used DAYTRANA™ patch in half and press firmly so that the sticky side sticks to itself. **Flush the used patch down the toilet or dispose of in a lidded container right away.**
- Do not flush the pouches or the protective liners down the toilet. These items should be thrown away in a lidded container.
- If any sticky material (adhesive) remains on the child's skin after removing the patch, gently rub the area with oil or lotion to remove the adhesive from the skin.
- Wash your hands after handling the patch.
- After the patch is removed and disposed of, record this time on the administration chart.

**UNUSED PATCHES**

- Throw away any unused DAYTRANA™ patches that are left over from the prescription as soon as they are no longer needed. Remove the leftover patches from their protective pouches and remove the protective liners. **Fold the patches in half with the sticky sides together, and flush the patches down the toilet or dispose of in a lidded container.**

**This Medication Guide has been approved by the U.S. Food and Drug Administration.**

NDA 21-514

Page 2

The above changes should be implemented immediately, and they should be submitted within 30 days from the date of this letter. Your submission should also address how you intend to ensure that there are adequate numbers of Medication Guides to ensure that every patient receives one when they receive the drug.

Simultaneous with this supplement request, FDA has issued a Press Release as well as updated our internet site with the Medication Guides to alert the community to this action. Since there are so many ADHD products, we feel that these actions are a better way to alert the community than individual Dear Health Care Professional (DHCP) letters for each of these products. Thus, we are not requesting individual DHCP letters.

If you have any questions, call LT Felecia Curtis, Regulatory Project Manager, at 301-796-1074.

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

Attachment

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this page is the manifestation of the electronic signature.**  
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/s/

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Thomas Laughren  
2/21/2007 07:48:29 AM



**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-514: N-000

Shire Development Incorporated  
725 Chesterbrook Boulevard  
Wayne, PA 19087

Dear Applicant:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Daytrana (methylphenidate) TDP.

Since 2000, FDA has conducted several comprehensive inspections of bioequivalence studies in which the bioanalytical analysis was conducted by \_\_\_\_\_ . The findings of these inspections raise significant concerns about the validity of the reported results of these analytical studies conducted in support of drug applications for marketing. Our findings from these inspections include, but are not limited to, the following:

- Failure to conduct a systematic and thorough evaluation to identify and correct sources of contamination.
- Failure to investigate anomalous results.
- Lack of assay reproducibility between original and repeat results.
- Assay accuracy not assured under the conditions of sample processing.
- Biased exclusion of study data resulting in the acceptance of failed runs.
- Failure to demonstrate the accuracy of analytical methods with appropriate validation experiments and documentation.

As a result of these findings, \_\_\_\_\_ agreed to conduct an audit of data from all its bioequivalence studies generated from January 2000 to December 2004. However, FDA identified significant deficiencies with the \_\_\_\_\_ audit during its most recent inspection. Thus, serious questions remain about the validity of any data generated by \_\_\_\_\_ in studies during this time period that have not been inspected by FDA. In view of these findings, FDA is informing holders of approved NDAs of these issues.

The impact of the data from these studies (which may include bioequivalence, pharmacokinetic, drug-drug interaction and others) cannot be assessed without knowing the details regarding the

study and how the data in question were considered in the overall development and approval of your drug product. At this time, the Office of New Drugs is searching available documentation to determine which NDAs are impacted by the above findings.

To further expedite this process, we ask that you inform us within 30 days of receipt of this letter if you have submitted any studies conducted by — during the time period of concern (January 2000 through December 2004). Please submit information on each of the studies submitted, including supplement number (if appropriate), study name/protocol number, and date of submission. This information should be submitted as correspondence to your NDA. In addition, please provide a desk copy to:

Office of New Drugs  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
Bldg. 22, Room 6300  
Silver Spring, MD 20993-0002

Once we have made an assessment regarding the potential impact of these data, we will contact you regarding the steps that need to be taken, if any, to assure the accuracy of the data submitted to your application.

If you have any questions, call Felecia Curtis, Regulatory Project Manager, at 301-796-0877.

Sincerely,

*{See appended electronic signature page}*

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

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/s/

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Beth Duvall-Miller  
1/24/2007 11:15:39 AM  
for Division Director

Proposed Pediatric Study Request for 75-day Expedited Review

**IND:** 54,732

**Protocol:** SPD485-409

**Reviewer:** Robert Levin, M.D.

<b>Sponsor:</b>	Shire
<b>Drug:</b>	Methylphenidate Transdermal System
<b>Material Submitted:</b>	Proposed Pediatric Study Request
<b>Correspondence Date:</b>	October 9, 2006
<b>Drug Category:</b>	Stimulant
<b>Forms available for study:</b>	Methylphenidate transdermal patch: 10 mg/9 hr; 15 mg/9 hr; 20 mg/9 hr; 30 mg/9 hr

### **I. Background & Description of Compound**

Daytrana (methylphenidate transdermal system) has been approved (April 6, 2006) for the treatment of Attention Deficit-Hyperactivity Disorder (ADHD) in children (ages 6-12). The sponsor proposes an efficacy and safety study in adolescents (ages 13-19) with a diagnosis of ADHD, in order to fulfill a post-approval commitment. The sponsor has requested a 75-Day expedited review of the Proposed Pediatric Study Request.

### **II. Proposed Clinical Study**

This is a Phase 3b, multicenter (20), randomized, double-blind, placebo-controlled, parallel-group, dose-optimization study designed to evaluate the efficacy and safety of Daytrana (methylphenidate transdermal system) in adolescent patients (ages 13-17) with a diagnosis of Attention Deficit/Hyperactivity Disorder (ADHD). The primary objective is to evaluate the efficacy of Daytrana (compared to placebo), as measured by the change from baseline in the clinician-rated ADHD-RS-IV. Secondary objectives include the assessment of: 1) the safety and tolerability of Daytrana; 2) the efficacy of Daytrana in the home environment as rated by parent/caregiver using the Connors' Parent Scale-Revised: Short Form (CPRS-R); 3) global impression ratings (clinician and parent/caregiver); 4) skin tolerance and potential skin sensitization to Daytrana, as measured by the Dermal Response Scale; and 5) the relationship between plasma methylphenidate exposure and safety and efficacy measurement results (through sparse sampling).

## **Subjects**

The sponsor has proposed appropriate psychiatric and medical subject selection criteria. Subjects will include approximately 210 male and female ADHD patients between the ages of 13 and 17, inclusive. Female subjects of child-bearing potential must have a negative bHCG test at screening and a negative urine pregnancy test at baseline. Such subjects must agree to use an acceptable method of contraception throughout the study and for 30 days after the last dose of study medication. Those who are pregnant or lactating will be excluded. Patients with particular cardiovascular and neurological disorders will be excluded. Patients with skin-sensitive syndrome or significant signs or symptoms of skin irritation will be excluded. Patients with allergy, hypersensitivity, or clinically significant intolerance to methylphenidate or any component of Daytrana will be excluded.

## **Treatment with Study Drug**

Approximately 210 subjects will be randomized to methylphenidate transdermal system (Daytrana) or placebo transdermal system (PTS) in a 2:1 ratio for the 5-week, double-blind, stepwise, dose-optimization phase of the study. Daytrana dosages will include 10 mg/9 hr, 15 mg/9 hr, 20 mg/9 hr, and 30 mg/9 hr. All subjects will begin treatment with Daytrana or matching PTS 10 mg/9 hr per day. A new patch will be applied each morning. Subjects will be evaluated on Day 7 for safety, tolerability, and efficacy. On Day 7, and at each 7-day interval, the dose may be increased to the next dosage strength, depending on clinical response and tolerability of the drug. Subjects may be titrated back down to the previous dose to optimize tolerability. The sponsor has specified appropriate criteria for evaluating a subject's response, based on ADHD-RS-IV scores.

In the maintenance phase, subjects will continue treatment with their optimal dose for an additional 2 weeks. They will continue to undergo double-blind efficacy and safety assessments. Thirty (30) days after discontinuing study treatment, subjects will have a follow-up telephone interview to assess new or ongoing adverse events. Subjects who have developed an application site reaction may be contacted up to a year after the last dose of study medication, to obtain information about any subsequent medication treatment for ADHD and tolerability of such medication.

## **Safety Assessments**

Safety assessments will include the following:

- Medical history and physical examination
- Concomitant medication history
- Vital sign monitoring
- ECG monitoring
- Adverse events monitoring
- Clinical laboratory testing
- Pregnancy testing

- Dermatologic monitoring using: 1) Dermal Response Scale; and 2) Experience of Discomfort and Pruritus

### **III. Conclusions and Recommendations**

The proposed study is reasonably safe to proceed as currently written. The proposed daily doses and duration of study drug exposure are identical to those used in the studies in children between the ages of 6 and 12 years-old. The Daytrana NDA was approved based on those studies. The plan for dermatological monitoring and treatment is reasonable.

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Robert L. Levin, M.D.,  
Medical Reviewer, November 28, 2006  
FDA CDER ODE1 DNDP HFD 130

cc: IND  
HFD 130  
T Laughren  
M Mathis  
N Khin  
F Curtis

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/s/

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Thomas Laughren  
1/16/2007 02:23:46 PM

## REQUEST FOR CONSULTATION

TO (Office/Division): CDER/OCTAP/DPDD/HFD-960  
ATTN: Grace Carmouze

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

DATE  
1/10/07

IND NO.  
54732

NDA NO.  
21-514

TYPE OF DOCUMENT  
Background info for PWR

DATE OF DOCUMENT  
10/9/06

NAME OF DRUG  
Daytrana

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG  
ADHD

DESIRED COMPLETION DATE  
Internal Meeting: 2/26/07

NAME OF FIRM: Shire

### 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 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:** Daytrana is approved for ADHD in children 6 to 12 years old. Under PREA, we have requested that the sponsor conduct an efficacy and safety study in adolescents (13 to 17 years old). The sponsor has requested that we issue a written request for this adolescent study.

Is there sufficient justification to issue a written request given that there are other methylphenidate products approved for use in adolescents? (Note that this formulation is a dermal patch, which is unique).

We would appreciate advice and guidance about whether to issue a Written Request.

SIGNATURE OF REQUESTOR  
Felecia Curtis

METHOD OF DELIVERY (Check one)  
 DFS     EMAIL     MAIL     HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

**MEMORANDUM**

**Division of Medication Errors and Technical Support  
Office of Surveillance and Epidemiology  
HFD-420; White Oak Room 4447  
Center for Drug Evaluation and Research**

**To:** Thomas Laughren, MD  
Director, Division of Psychiatry Products, HFD-130

**From:** Kellie Taylor, PharmD, MPH  
Safety Evaluator, Division of Medication Errors and Technical Support, HFD-420

**Through:** Alina Mahmud, RPh, MS, Team Leader  
Denise Toyer, PharmD, Deputy Director  
Carol Holquist, R.Ph., Director  
Division of Medication Errors and Technical Support, HFD-420

**Date:** September 13, 2006

**Subject:** Daytrana (Methylphenidate Transdermal System)  
10 mg (1.1 mg/hr), 15 mg (1.6 mg/hr), 20 mg (2.2 mg/hr), and 30 mg (3.3 mg/hr)  
NDA #: 21-514  
Sponsor: Shire  
Post-Marketing Medication Errors involving Daytrana

**OSE Project#:** 2006-111

**\*\*\*NOTE:** This review contains proprietary and confidential information that should not be released to the public.\*\*\*

**I. Executive Summary**

During routine post-marketing medication error surveillance, a number of safety issues related to Daytrana patches were identified. These safety issues stem from the volume of reports gathered through surveillance of message boards on the internet. These message boards contain first-hand practitioner, patient, and caregiver experience with the patch and, unfortunately, a variety of problems with the use of the Daytrana system are apparent from the postings. Several issues were identified that appear to be related to the design of the product; specifically, the product adhesive that is embedded with methylphenidate, the size of the patch, and the design of the protective backing. The product adhesive along with the other aspects of the product design has resulted in difficulty separating the protective backing from the adhesive; patches curl up on the edges, wrinkle, and have fallen off patients after application; and after removal of the patch, the adhesive (which contains the active drug) is difficult to remove from the patient's skin. Aside from these issues related to the quality of the Daytrana patch, DMETS also has a number of safety concerns related to the misuse of the product in the marketplace, including: storage and exposure of patches to cold temperatures (refrigeration, freezers, ice); application of overlays to secure patches; inadvertent exposure to the medication; exposure of patches to external heat sources after application (compresses, hairdryers); concomitant use of oral ADHD medications; cutting patches; using multiple patches at a time; and failure to remove patch after 9 hours of application. Some of the safety issues identified with the Daytrana patch have been observed with other

transdermal drug delivery systems available in the US market, but a number of the issues identified and/or the root causes appear to be unique to the Daytrana system.

The issues related to the quality of the product and the misuse of the delivery system threatens both the safety and efficacy of Daytrana. In some instances the issues have resulted in ineffective control of ADHD symptoms, and in other instances people appear to have experienced adverse effects (prolonged redness at application site, rash, insomnia, nausea, nervousness, etc) related to the misuse of the Daytrana patch. To date, FDA has received only one report related to the quality of the Daytrana patch. In contrast, hundreds (n=266) of messages are posted on an internet site about this product, which has recorded more than 13,000 'views' of thread. Preliminary recommendations are provided that will enable DMETS to fully assess the nature, scope, and impact of the issues described in this memo, and work with the review division to address the safety concerns identified.

## II: INTRODUCTION

**\*\*\*NOTE: This review contains proprietary and confidential information that should not be released to the public.\*\*\***

Daytrana is the first (and only) methylphenidate-containing transdermal system to be approved by the FDA, and has been available in the US market since June of 2006. Prior to approval, the sponsor of the product submitted a risk management plan to FDA, focused on surveillance and on the education of health care providers and consumers regarding safe storage, use, collection, and disposal of the methylphenidate transdermal system. The Office of Surveillance and Epidemiology, with DMETS input, provided comments to the review Division (PID: D050537, November 30, 2005) and communicated concerns including exposure to heat, concerns with keeping the patch on during the day, concerns with the time interval of application and removal, and concerns regarding the amount of residual drug in the patch. These concerns were, in part, based upon post-marketing adverse event reports involving other patches that deliver drugs transdermally (e.g, fentanyl patches, Ortho Evra).

Over the course of the summer, the number of Daytrana prescriptions dispensed by community pharmacies in the US increased steadily and, at the close of August, totaled \_\_\_\_\_ \*\*\* the month of September when children across the United States return to school, \_\_\_\_\_ \*\* prescriptions for the Daytrana patch were dispensed, nearly doubling the total number dispensed since the product was approved.<sup>2\*\*\*</sup> The most recent data available indicates that the total number of prescriptions dispensed through September 2006 is \_\_\_\_\_<sup>3\*\*\*</sup> A majority of these prescriptions (approximately \_\_\_\_\_ %, n= \_\_\_\_\_ \*\*\*) were dispensed for children under the age of 16.<sup>4</sup>

As the dispensing of Daytrana prescriptions increased, DMETS began to identify a number of issues relating to the safety of Daytrana through surveillance of message boards on the internet. These message boards contain a volume of reports describing first-hand practitioner, patient, and caregiver experience with the patch. Unfortunately, surveillance has found that a number of the concerns that were communicated as potential safety issues prior to approval have been realized and become actual safety issues for some patients using Daytrana.

The safety issues identified appear to be primarily attributable to the product design and consumer misuse of the product. The Daytrana patch consists of three layers: an outside backing, adhesive containing

- 1 \_\_\_\_\_<sup>M</sup> National, Data Extracted 10-2006.
- 2 \_\_\_\_\_<sup>N</sup> National, Data Extracted 11-2006
- 3 \_\_\_\_\_<sup>N</sup> National, Data Extracted 11-2006
- 4 \_\_\_\_\_<sup>N</sup> National, Data Extracted 11-2006.

methylphenidate, and a protective liner that is removed prior to application. The adhesive covers the entire patch surface area (i.e. there is not an “inactive” border near the outer edges of the patch), and the drug is absorbed through the skin from the adhesive. The product is designed to be applied 2 hours before an effect is needed since there is a delayed onset of action as the drug is absorbed from the adhesion layer through the skin. The adhesive formulation appears to be exceedingly sticky, which when combined with the design of the patch, has proven to be troublesome for patients and caregivers. Consumers also appear to be misusing the patch, and in some instances, the misuse appears to be a coping mechanism for the consumer-unfriendly product design. In other instances, the motivating factors of the misuse are less clear, and further data and analysis is required to gain insight to the underlying causes.

### Product Information

Daytrana was approved by FDA on April 6, 2006 for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). Daytrana is available in the following strengths: 10 mg (1.1 mg/hr), 15 mg (1.6 mg/hr), 20 mg (2.2 mg/hr), and 30 mg (3.3 mg/hr). The once-a-day patch is applied to the hip area in the morning and worn for 9 hours after application. The patch may be removed earlier if a shorter duration of effect is desired or late day side effects appear. The patch should be rotated daily to opposite sides of the child's hips. According to the package insert, Daytrana should not be used in children under six years of age, since safety and efficacy in this age group has not been established.

## **III: RISK ASSESSMENT**

### **A. DATABASE SEARCHES**

#### 1. FDA Adverse Event Reporting System (AERS)

DMETS searched the FDA Adverse Event Reporting System (AERS) database in order to determine the extent of post-marketing safety reports with Daytrana. No MedDRA codes were selected. A total of 17 reports were identified on 11/6/06; one of which related to the quality of the product design. The remaining AERS reports appear to describe a variety of adverse events secondary to the patch. The case that related to product quality (ISR 5124678-2, 10/10/2006) was reported by a pharmacist on behalf of a patient who experienced difficulty peeling the protective backing off the 15 mg Daytrana patch. The pharmacist states that “the medication stuck to the backing making the patch unable to stick to the patient’s skin.” The pharmacist also states that they had three boxes of “defective” patches with two different lot numbers (NDC #54092055330, lot # 1934411, expiration date 5/31/2008). According to the report, the “defective” product was returned to the manufacturer, and other strengths of the Daytrana product did not prove to be defective.

#### 2. FDA Drug Quality Reporting System (DQRS)

A DQRS search was also performed which yielded 12 reports (9/14/2006). The majority of reports in DQRS appear to be related to oral methylphenidate products. One report (#1003356135) was identified as related to the patch, but it is a duplicate of a report of ISR#5095504-5 described above.

#### 3. World-wide web

Internet Monitoring was a component of the Risk Management Program submitted by the sponsor to identify potential sentinel occurrence of diversion, tampering, or misuse of the Daytrana. While this seems like a viable information source to detect the abuse and likelihood of drug extraction from the patch at home, the Internet is also a viable information source to detect other forms of misuse not intent on drug abuse, which

may provide insight to the safe use of this product. A Google search of “Daytrana adhesion” on September 12, 2006 uncovered a message board thread on ADHDnews.com discussing the Daytrana patch.<sup>5</sup> The board provides parents and practitioners with a forum to discuss issues related to ADHD, including medication treatment. A parent posted a message on July 13, 2006 asking others if they had any experience with the Daytrana patch. From there, the forum grew and as of November 17th, 2006 a total of 266 messages posted on the thread. Altogether, these postings constituted more than 30 pages when copied onto a Microsoft Word document. In addition to the high volume of posts, DMETS also noted that the site indicates that more than 13,000 ‘views’ of thread, which seems to reflect a very high public interest in the topic. DMETS has concern that a large number of patients and caregivers may be seeking and following the advice and suggestions posted on the site.

Many of the messages reviewed on ADHDnew.com provide first-hand accounts of problems associated with Daytrana. These included: 1) difficulty separating the adhesive backing from the patch; 2) after applied, the patches sometimes curled up on the edges, wrinkle, or fall off; 3) difficulty removing adhesive from the skin; 4) exposing the patches to cold; 5) applying nasal corticosteroids to the skin prior to the application of the patch; 6) inadvertent exposure to the medication; 7) applying overlays to patches; 8) exposing the patches to heat; 9) concomitant therapy with oral ADHD medications; 10) cutting the patches; 11) extending the application time beyond 9 hours; and 12) using multiple Daytrana patches at the same time. In addition, it appears that patients and caregivers have followed the advice and suggestions posted by other individuals on the site, and, in some instances, the advice has encouraged others to misuse the patch (e.g. “Try storing the patch in the refrigerator...”).

DMETS is also aware of forums on other internet sites that are actively discussing issues related to the Daytrana patch similar those described on ADHDnews.com. On one of internet sites, nearly 100 messages have been posted on the “Daytrana Patch Chat” thread since July 2, 2006.<sup>6</sup> Although the content of these posted messages is not included in this report, a cursory review of the messages indicates that the participants have experienced many of the same issues as described on ADHDnews.com. Based on a review of the messages posted on ADHDnews.com and Pharmacist’s Letter, DMETS believes there are a substantial number of issues related to the Daytrana patch that warrant a full evaluation by FDA.

## **B. INVESTIGATION OF CAUSES OF ERROR**

Upon review of the volume of reports obtained from the ADHDnew.com and Pharmacist’s Letter message boards, two themes emerged and provided a framework for investigation: safety issues could be attributed to the design of the product or consumer misuse of the product. The issues relating to product design centered upon the adhesive used to deliver the methylphenidate, the design of the protective backing, and the overall design of the patch itself. Consumers attributed these aspects of the product design to cause difficulty separating the protective backing from the adhesive; patches curling up on the edges, wrinkle, falling off patients after application; and difficulty removing adhesive (which contains the active drug) from the patients’ skin after removal of the patch. These issues were categorized as safety issues related to the physical quality of the Daytrana transdermal delivery system.

The safety issues relating to consumer misuse (both deliberate and unintentional) of the product include: exposure and storage of patches to cold temperatures (refrigeration, freezers, ice); spraying nasal corticosteroids (Nasonex, Flonase) to the skin prior to patch application; application of overlays to secure patches; inadvertent exposure to the medication; exposure of patches to external heat sources after application (compresses, hairdryers); concomitant use

<sup>5</sup> [http://www.adhdnews.com/forum/forum\\_topics.asp?FID=4&PN=1](http://www.adhdnews.com/forum/forum_topics.asp?FID=4&PN=1), accessed 11/17/2006

<sup>6</sup> <http://specialneedseducation.suite101.com/discussion.cfm/1964/85-94>, accessed 12/6/2006

of oral ADHD medications; cutting patches; using multiple patches at a time; and failure to remove patch after 9 hours of application. These issues were categorized as related to consumer use of the Daytrana transdermal delivery system.

Overall, the preliminary analysis of the reports indicates that the safety issues and/or the root causes appear unique to the transdermal delivery system used by the Daytrana product. However, some of the issues have been observed in post-marketing experience with other transdermal drug delivery systems (e.g. Duragesic/fentanyl transdermal systems, Ortho Evra patches), and this is noted below in the discussion of our concerns.

## 1. Safety Issues related to the product design of the Daytrana transdermal delivery system

Post-marketing experience with other transdermal delivery systems has shown the product design of transdermal delivery systems to be an important determinant of safety. Daytrana patches are designed with the medication embedded in the adhesive that holds the patch to the patient's skin. Once applied, the medication is absorbed systemically from the adhesive through the skin. The adhesive component of the Daytrana patch is critical to the safe and efficacious use of the product; and based upon the content of the post messages, it seems that the design of the adhesive used in the Daytrana system is adversely affecting the use of the product.

### a) Patients and their caregivers appear to have difficulty separating the adhesive backing from the patch.

The initial safety signal was detected in late August on the Pharmacist's Letter Message Board<sup>7</sup>, which included the following exchange of information:

**Subject:** DAYTRANA ADVHESIVE **Posted by:** M. Swift **Posted on:** 8/18/2006 10:41:00 AM  
**Message:** Has anyone had complaints from pts regarding problems with the adhesive on Daytrana patches? We had a mother complain that some of the adhesive was coming off with the peel-off backing.

**Subject:** Re: DAYTRANA ADVHESIVE **Posted by:** J. Haskins PharmD **Posted on:** 8/20/2006 7:11:00 PM **Message:** I had the same complaint yesterday. The patient had properly stored them and were within the manufacturer recommended use date. I am not really sure how we are to handle this as far as replacing the items since they must be destroyed. I am curious to see anyone else's opinion. FYI these were the 15 mg patches.

**Subject:** Re: DAYTRANA ADVHESIVE **Posted by:** J. Haskins PharmD **Posted on:** 8/22/2006 7:49:00 AM **Message:** We did hear back from Shire Pharmaceuticals today. They said this is a "known issue" and to direct the patient to their helpline and they will send the patient information on how to prevent this problem with the adhesion. I think this is their phone #: 1-(800) 828-2088

DMETS found a substantial number of messages posted on the ADHDnews website devoted to "Daytrana adhesive-backing problems"<sup>8</sup> (See appendix A). Patients and caregivers are frustrated with the difficulty they have removing the backing, which in some cases leads to pulling away the active ingredient with the backing and/or wasted patches. From a medication safety standpoint, this issue is concerning. If the adhesive that

<sup>7</sup> [http://www.pharmacistsletter.com/\(S\(q14klcvytofzro55ih5qi155\)\)/ColleaguesInteract.aspx?cs=CEPDA&s=PL&li=1&st=2](http://www.pharmacistsletter.com/(S(q14klcvytofzro55ih5qi155))/ColleaguesInteract.aspx?cs=CEPDA&s=PL&li=1&st=2), accessed 08/2006

<sup>8</sup> [http://www.adhdnews.com/forum/forum\\_posts.asp?TID=21785&PN=4](http://www.adhdnews.com/forum/forum_posts.asp?TID=21785&PN=4), accessed 08/2006

delivers the drug is pulled off with the protective backing, the patient may not receive the full dose of the drug. The following case represents one of several messages describing this issue:

*"I am having a HECK of a time with the backing. It seems like half the adhesive is sticking to the peel away part. I know the med is imbedded into the adhesive, so I'm afraid to use a patch where all of the adhesive doesn't pull away. So far I have wasted FIVE patches because of this and I'm really becoming frustrated every morning when it happens again."*

Also, several of the posted messages indicate that the design of the protective backing varies between the different strengths of the product (e.g. horizontal versus diagonal cuts to separate protective backing away from adhesive). Moreover, the caregivers with first-hand experience using various designs indicate that the design of the protective backing affected the ease of separation from the adhesive.

Caregivers have provided extensive descriptions of the methods used to overcome the difficulty in removing the protective backing from the adhesive layer (Appendix A). One patient described her method in great detail and posted photos on the message board to assist others with this problem (Appendix C).<sup>9</sup> Another caregiver that had trouble removing the backing went to the prescriber's office hoping to learn from the doctor and nurse a better application technique. However, the patient went on to say that the doctor and nurse had a very difficult time removing the backing, and accidentally "tore a patch along the side".

**b) After applied, the patches can sometimes curl on the edges, wrinkle, or fall off.**

Since the methylphenidate is imbedded in the adhesive layer, the adhesive layer should maintain contact with the skin to allow for transdermal absorption of the drug. However, a number of the messages indicate that the patch adhesion is failing partially (curling up at the edges, wrinkling) or completely (falling off). In some cases, the adhesion failures (both partial and complete) appear to be associated with subtherapeutic dosages, delayed onset of action, and/or uncontrolled ADHD symptoms (Appendix A).

*"Yesterday XX put the 30mg patch on vertically while he was laying down. Since I wasn't there, I checked it later and saw that it had wrinkeled and was not sticking there or on corners...used pressure again and added adhesive tape to the edges. So it took another 2 hours to finally kick in. He also had not gone to sleep till 2 am the night before so it was an off kind of day. Today he put it on horizontally"*

*"I recieved a note from the teacher today saying X has "had a bad day" today. He was acting out, disrupting the class and being uncontrollable. Well it comes to find out that he fiddled with is patch and made it come off early in the morning. It was stuck to his shorts!! I explained to him how important it is for him to not mess with his patch, but he then told me that it makes him itch really bad."*

Some of the postings attributed the wrinkling/creasing of the patches to the larger size of the 30mg strength patch. These partial adhesion failures are concerning since they may be associated with the delivery of subtherapeutic dosages, but also because they could lead to full adhesion failures. In fact, three of the postings indicate that the adhesive for the system had failed completely (See Appendix A). In two instances, the adhesion failure resulted in total disruption of therapy and loss of ADHD symptom control. Although the prescribing information for Daytrana notes "After proper application, bathing, swimming, or showering have not been shown to affect patch adhesion," exposure to water was implicated as a contributing factor to adhesion failure in two of the cases (See Appendix A).

<sup>9</sup> [http://www.adhdnews.com/forum/forum\\_posts.asp?TID=20458&KW=Daytrana&PN=0&TPN=15](http://www.adhdnews.com/forum/forum_posts.asp?TID=20458&KW=Daytrana&PN=0&TPN=15)

None of the messages reviewed have indicated that adhesion failure of the Daytrana system has resulted in inadvertent patch transfer to another individual. However, other transdermal systems (e.g., Duragesic patches)<sup>10</sup> have been accidentally transferred to other individuals via hugging or by sitting on patches that have fallen off patients. In some instances, the accidental exposure to the patches resulted in serious medical outcomes or death. DMETS believes it is possible for the Daytrana system to be transferred inadvertently to another individual if the adhesion of the patch fails, and is concerned that adverse outcomes may occur as a result of accidental exposure to methylphenidate. Several caregivers discuss this risk in their messages; see Appendix A for examples.

DMETS is also concerned that patients and caregivers are applying overlays to the product to overcome the adhesive-related issues of curling-up, wrinkling, and falling off. A variety of improvised solutions are discussed and suggested to others who visit the site. The bulk of the messages describe using tape, band-aids, or other similar products to ensure the adhesion of the patches by applying over the entire Daytrana system or around the edges of the patch (see Appendix A). The use of overlays may increase the temperature at the application site, and increase the rate and/or extent of absorption of methylphenidate from the adhesive. The prescribing information for the product offers no advice with respect to the use of overlays. However, with other transdermal systems, similar practices have led to adverse outcomes.

**c) The adhesive is difficult to remove from the skin.**

Caregivers and patients also describe having difficulty removing adhesive from the child's skin after removing the Daytrana patch, which have resulted in dermatological adverse events (irritation, redness, soreness) at the application site.

*"The other thing we are now having a problem with is the darn adhesive remaining on his skin. Somebody had posted about it earlier, and we weren't having the problem yet. But, the last few days we have. And, this morning, I noticed the parts around the patch where the adhesive remained, has turned into a sore and scabbed up. Not sure if it's because X has been scratching or picking at the adhesive after we took the patch off. Or, if it's from us using rubbing alcohol and vaseline to try to remove the adhesive. So, that's not good."*

In response, some suggested mineral oil to ease the removal, a recommendation consistent with the product's prescribing information. Since the methylphenidate is contained within the adhesive, the difficulty in removing the adhesive from the skin could unintentionally expose patients to the drug for an extended period of time.

From the messages reviewed, it appears that the design of the Daytrana patch is associated with a number of concerning safety issues. Consumers are attempting to cope with the shortcomings of the product design, and in many instances, the coping mechanisms employed appear to represent an unsafe misuse of the product.

## **2. Misuse of the Daytrana system**

As with product design, proper use of transdermal delivery systems has been shown in post-marketing surveillance to be an important determinant of product safety. A preliminary investigation of the safety issues identified from the message board finds that a number of the issues appear to be caused by the caregiver or patient's misuse of the

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<sup>10</sup> "Dear Healthcare Professional Letter," Janssen, June 2005, page 3. Access at: [http://www.fda.gov/medwatch/SAFETY/2005/duragesic\\_ddl.pdf](http://www.fda.gov/medwatch/SAFETY/2005/duragesic_ddl.pdf)

product. "Misuse of the Daytrana system" is intended to characterize the use of the patch in a manner that is either not specified in the approved labeling or contradicts the specifications in the approved labeling. In some instances, the misuse appears deliberate, while in other instances the misuse appears to be unintentional. Within the broad category of "Misuse," the issues have been organized by the proximal cause of each action (whether deliberate or unintentional) taken by a consumer. Further investigation into these issues is warranted, and may eventually reveal the root cause of the errors to be attributable to labeling, patient education, product quality or some other aspect related to the medication-use process.

**a) Exposing the patches to cold.**

The labeling for Daytrana states that the product should be stored at room temperature (25° C, 77° F). In some instances, the caregivers have attributed the difficult removal of the backing from the patch to the storage of the medicine in warm areas. As a result, several patients and caregivers have resorted to storing patches for varying lengths of time (minutes to overnight) in the refrigerator or freezer. In addition, some caregivers describe applying cold compresses or ice to the backing to ease the removal of the protective layer from the adhesive. In at least one instance, a consumer attributed the exposure of the product to cold to a delayed onset of action and early drop off in the medication's duration (see Appendix B). From a safety perspective, DMETS is concerned that the exposure of the patches to cold could alter the rate and extent of methylphenidate delivered from the product.

**b) Applying nasal corticosteroids to the application site**

Some of the practitioners describe applying nasal corticosteroids (e.g. Flonase, Nasonex) to the application site prior to patch application as a way of reducing or avoiding skin irritation at the application site. This practice is not explicitly addressed in the product labeling. From a safety perspective, DMETS is concerned that this practice could interfere with patch adhesion, or could affect the rate and extent of methylphenidate absorption from the patch.

*"My son and daughter have been on daytrana several months and it is fabulous...except for the burning, itching and huge red patches it leaves on my son. It burned soooo bad he would take it off at school and well we all now what a day at school is like without medications!!! This is going to sound crazy but I tried it this morning (at the doctors request) and it worked. Spray nasonex on the skin, rub it in and let it dry. Do this 2 or 3 times and when the skin is dry, put the patch on top of the medicated area. My son had the patch on for 45 minutes before he left for school and he said it wasn't burning or itching.. And usually by then he would have been crying and scratching. I hope this works as well for everyone else as it did for us"*

In this instance, the practice stemmed from the advice of the prescriber, but in other instances it appears that "word of mouth" has lead others to experiment with this practice (See Appendix B). DMETS is also concerned that patients and caregivers may apply other forms of topical corticosteroids (e.g. creams, ointments) that may have a greater likelihood of interfering with patch adherence and the transdermal delivery of methylphenidate.

**c) Inadvertent exposure to the medication.**

When caregivers apply transdermal medication, inadvertent dermal contact with the product can lead to systemic absorption and adverse effects. The labeling for Daytrana explicitly instructs patients and caregivers to "avoid touching the sticky side of the patch with you fingers" and to "wash your hands after applying the patch," although neither of these instructions link the action with outcome (i.e. to avoid systemic absorption of the drug). At least one caregiver was inadvertently exposed to the medication after applying the Daytrana

patch to their child and described experiencing adverse effects secondary to the accidental exposure to the medication.

*"Well we put the patch on at 6:30 am and let me tell you I have never had so much trouble getting the backing off of a patch. It was so hard and stuck on there that when we finally got it off I don't think the patch is going to stick very good to her. She was still asleep when we put it on and I sure hope that it works because I don't feel as of yet that it is worth the hassle of getting the backing off, it was so stuck. She will usually be up in the morning getting ready for school when we put the patch on. I will update through the day"*

Later that day:

*"She seems to be doing ok on it...the edges aren't stuck very good though. She seems very calm and focused though. Well my hubby called me from work and was telling me he was real jittery, he said his hands were shaky, his stomach didn't feel right. I wonder if he got some of the med on his fingers when trying to get that stupid backing off. He said it only lasted like 2hrs. Could this be possible? would it do this to him if he got it on his fingers?? I'm calling the doc and pharmacist first thing in the morning about this being so hard to get the backing off."*

It is unclear from the information whether the parent washed their hands after applying the patch, but the message seems to indicate that the exposure may have occurred as a result of the difficulty the parents had in removing the backing.

**d) Applying overlays to patches.**

While some patients and caregivers discuss use of overlays in response to adhesion failure of the product (Appendix A), it seems that even in the absence of adhesion problems that caregivers and patients are using additional measures to ensure the adhesion of the patches. The use of overlays is not addressed in the approved prescribing information for Daytrana. The bulk of the messages describe using tape, band-aids, or other similar products to ensure the adhesion of the patches by applying over the entire Daytrana system or around the edges of the patch.

*"I had no problems with the adhesive this morning and even covered the patch with medical tape."*

*"For ensuring the adhesive doesn't peel prematurely there are covering pads by the maker elastoplast with very sticky backing that can be cut to size and work fantastic."*

To our knowledge, the safety and efficacy of the Daytrana system has not been studied under such conditions. At this point, none of the messages posted have indicated that a patient had experienced an adverse outcome related to this misuse of the Daytrana. However, post-marketing experience with the fentanyl transdermal delivery systems has shown practices similar to these to be risky. With fentanyl transdermal products, the use of overlays was found to increase the rate and extent of drug absorption, which resulted in patient harm and death in some cases. The use of bandages, bandaids, and other overlays to secure the patch may unintentionally produce an increase in temperature at the site of absorption. DMETS is concerned that the use of such measures over part of or the entire system could likewise affect the absorption of methylphenidate from the Daytrana transdermal system. The labeling does not explicitly address this practice, but does caution against the use of "external" heat sources. The labeling describes external heat sources as "heating pads, electric blankets, heated water beds, etc." The labeling states that application of external heat sources may affect both the rate and extent of drug absorption, and notes "a potential for temperature-dependent increases in methylphenidate release of greater than 2-fold from the patch." DMETS suspects that the use

of overlays to secure the system could put patients at risk if the drug is delivered too quickly or an excessive dose is delivered.

**e) Exposing the patches to heat to “activate” or “hasten” drug delivery**

DMETS is concerned that patients appear to *deliberately* be using heat sources to increase the rate of drug absorption, a practice. A byproduct of the product design is a delayed onset of action, and the approved labeling recommends that the patch be applied 2 hours before action is needed. However, several caregivers and patients have expressed frustration with the lag time in the onset of action of the drug, and describe using external sources of heat to “activate” or “hasten” the onset of action. In some instances, this misuse appears to have been encouraged by health practitioners.

*“Our psych did say to apply with a heat compress for 30 seconds to activate drug.”*

While none of the postings related any adverse events to these practices, DMETS remains concerned regarding the effects that heat may have on the rate and extent of methylphenidate release from the patch. To our knowledge, the safety and efficacy of the Daytrana system has not been established under this condition of use. In fact, the prescribing information for the product specifically advises against the use of external heat (such as heating pads, electric blankets, heated water beds, etc.) under precautions, and notes that there “is a potential for temperature-dependent increases in methylphenidate release of greater than 2-fold from the patch.” Post-marketing experience with other transdermal delivery systems has identified cases in which inadvertent exposure to heat sources (e.g. use of heating pads with fentanyl transdermal systems; sun exposure with Ortho Evra) resulted in adverse events.

**f) Concomitant therapy with oral ADHD medications**

DMETS is concerned that a number of messages describe concomitant use of oral methylphenidate with the transdermal delivery system. No information is provided in the product labeling regarding concurrent use of oral methylphenidate with the patch. In several instances, it appears that patients and caregivers have been dissatisfied with the delayed onset of action with the transdermal patches and sought short-acting oral medications to bridge the time between patch application and onset of action.

*“that the Daytrana takes hours to kick in. My son's psychiatrist has us giving my son a bit of Ritalin (10mg) when he first gets up, which kicks in relatively quickly and keeps him in control until the Daytrana starts working a couple hours later. Perhaps your doctor would have some ideas.”*

In at least one instance, the concurrent use of oral ADHD medication is used to provide coverage for the time of day that the patch is not worn by the patient (e.g., in the evening after patch is removed). Other messages indicate that patients and caregivers use oral ADHD to provide breaks from the patch due to the skin reactions associated with the application of the system.

*“We have tried giving him the Ritalin 15 mg/ 2x a day on the weekend (Sat and Sun) to give the skin a rest, but I am wondering if that is not a good thing. Does the skin eventually get used to it if you continue it 7 days a week?”*

DMETS is concerned with these practices since the safety and efficacy has not been evaluated under these conditions.

**g) Cutting the patches**

DMETS is concerned that some patients and caregivers are cutting the patches to adjust the dosage of methylphenidate (see example below, and in Appendix B). From a medication safety perspective, DMETS is concerned with these practices since, to our knowledge, the safety and efficacy of the patch has not been studied under these conditions either. Based on our post-marketing experience with other transdermal delivery systems, we suspect that such actions could violate the integrity of the system. The release of the drug may be affected, and possibly pose a health risk to the patients who wear the cut patches. No information in the product labeling specifically addresses this practice.

*"Some people even cut off some after their school/ work time to a dose where they don't need to focus as much...like socializing."*

**h) Using multiple Daytrana patches at the same time**

DMETS is concerned that some patients and caregivers are using multiple Daytrana patches concurrently (see example below). From a medication safety perspective, DMETS is concerned with these practices since, to our knowledge, the safety and efficacy of the patch has not been studied under these conditions either. Post-marketing experience with other transdermal delivery systems has shown the use of multiple patches concurrently (intentionally and unintentionally) to be associated with adverse outcomes related to overdosage of the drug. No information in the product labeling specifically addresses this practice.

*"Combinations of 10s and 15s: He prescribed 10s and 15s for my son to try out in varying combinations to find out what dose works for him. So to answer your question, yes two 10s are the same as one 20. He is using up some left over 10s to come up with a 25 mg dose. 2@10 + 1/2 @10 = 25"*

**i) Failure to remove the Daytrana patch after 9 hours.**

From the review of the messages posted, it appears that use of the Daytrana patch sometimes extends beyond the recommended duration of 9 hours. In some cases, patients or their caregivers have forgotten to remove the patch. In at least one case, the failure to remove the patch was associated by the caregiver with a dermatological adverse reaction.

*"Things have been going so well and then.....x had a rash that lasted three days. I am going to keep my eye on it. I think maybe it was because he had the patch on for a long time. We completely forgot to call daycare and remind them (to take it off). Crappy parents."*

In other instances, it appears that caregivers are interested in learning if they can extend the duration of therapy by intentionally leaving the patches on than the recommended 9 hours and decide to trial the extended duration; sometimes choosing to do so without consulting a health professional or seeing advice from the manufacturer (see examples below, and Appendix B).

*"OK, XX left his patch on last night till 6:30, it should have come off at 4:30. I didn't see any adverse reactions and was asleep by 10:45. I'm just passing this on to others that might have wondered what happens if you don't take it off on time. Has this happened to anyone else?"*

*“ok... here is the down low on what my XX dr said at our appt yesterday....He also said that you can leave the patch on for longer if desired. The patch only has so much medicine to deliver, so leaving it on longer might extend your time but probably not by much b/c all the medicine has already been absorbed by skin within 9 to 10 hrs. But leaving it on longer may extend the time it take for the red spot to go away, but that was about it.”*

The product labeling notes that “residual methylphenidate remains in used patches when worn as recommended.” However, the package insert does state how much methylphenidate is contained within each patch. Using information provided in the package insert to estimate the residual content, it appears that a substantial quantity of methylphenidate remains in the system (see table 1, page 12).

**Table 1. Estimate of residual drug content following 9-hour application of the Daytrana system\*\***

Total methylphenidate content in each patch	Dosage delivery rate	Dose of methylphenidate delivered over 9 hours	Estimate of residual methylphenidate remaining in each patch after 9-hour application**
27.5 mg	1.1 mg/hour	10 mg	17.5 mg
41.3 mg	1.6 mg/hour	15 mg	26.7 mg
55 mg	2.2 mg/hour	20 mg	35 mg
82.5 mg	3.3 mg/hour	30 mg	55.5 mg

\*\*Estimate calculated by Evaluator from information contained in the labeling; not provided in the product labeling by the manufacturer.

It is likely that failure to remove the patch after 9 hours is exposing patients to doses of methylphenidate beyond the intended daily dosage. However, it is impossible to determine the risk that could be associated with this misuse since the manufacturer does not indicate the amount of methylphenidate residing in the patch following 9 hours of exposure, or give an indication of the rate and extent of absorption of the residual drug content. DMETS is concerned about this misuse of the patch since the safety and efficacy of extended application has not been established. It appears from a review of the labeling that the residual content for the patches in all four of the strengths currently marketed is considerable, and may be nearly twice the intended daily dosage (see Table 1 on Page 12).

DMETS is concerned that patients, caregivers, and practitioners may be not be well informed that extending the application time may expose the patient to clinically significant dosages of methylphenidate. The labeling does state that “if the patch is worn longer than the recommended 9 hour, methylphenidate-induced side effect such as insomnia may occur with greater frequency in some children,” but lacks a more detailed explanation of potential risks from this practice.

#### **IV: RECOMMENDATIONS**

There appear to be problems related to the quality and use of Daytrana patches in the marketplace. These issues appear critical to the safe and effective use of the product. In order to fully assess the nature, scope, and impact of the issues described, DMETS proposes the following recommendations be considered by the Division:

- 1) DMETS requests that the sponsor submit to the Agency all quality-related reports and any reports related to medication-errors. DMETS request that reports include verbal communications in addition to written/ electronic reports, as many of the patients, caregivers, and practitioners have indicated in the postings that they have contacted Shire via a toll-free telephone number. Further, DMETS requests that Shire provide a detailed summary of the communications (written and verbal) that they have provided to practitioners, patients, and caregivers who have contacted Shire regarding any of the issues related to product quality (complaints about

product design, difficulty using product, partial and complete adhesion failures) and consumer misuse of the product.

- 2) DMETS requests that the applicant submit to the agency samples of each strength of the product currently distributed in the US, along with current packaging and labeling for each strength of the product. We request that each strength be submitted to the Agency, since a number of the messages indicate that variations in product design between the various strengths impact the safe use of the product.
- 3) DMETS requests a meeting with the review division to evaluate how these issues should be addressed by the Agency.

Given the potential risk to public health, DMETS is requesting a response from the review division(s) concerning this safety review. If you have any questions or concerns regarding this memo please feel free to contact our post-marketing Project Manager, Scott Dallas, 301-796-0144.

**APPEARS THIS WAY ON ORIGINAL**

**Appendix A: Messages related to the Physical Quality of Daytrana**

<p><b>Problem: Patients and their caregivers appear to have difficulty separating the adhesive backing from the patch</b></p>	
<p><b>Patient/caregiver frustration over difficulty removing the backing of the patch</b></p>	<p>"I am really struggling with getting the backing off the patch. I practically rip them apart trying to loosen it. Not happy with that part of it."</p>
	<p>"I'm REALLY getting frustrated with how hard it is to get the backing off the patch to put it on. We rip and tear ours to pieces before we can even get it on!!"</p>
	<p>"For you two that have tried it, did you find the darn things ridiculously hard to peel? I was on the Emsam patch for a while and that came right off but this thing is a fight to say the least to get it unstuck. Regardless of whether I find a decent dosage or not that alone might kill it for me. "</p>
	<p>"We returned our first box of patches to the pharmacy and insisted they had gotten hot in shipment. It was a sticky mess and most of the medication remained on the backing. I think they have a problem with their patch. Our second batch was a little better but still very hard to remove the backing without damaging the patch.I have worn hormone patches and they were not like this"</p>
	<p>"I am having a HECK of a time with the backing. It seems like half the adhesive is sticking to the peel away part. I know the med is imbedded into the adhesive, so I'm afraid to use a patch where all of the adhesive doesn't pull away. So far I have wasted FIVE patches because of this and I'm really becoming frustrated every morning when it happens again."</p>
	<p>"Out of 14 days, we have had to trash two patches. Several patches did not have the full adhesive but we used them anyway. Since the drug is dispersed from the adhesive, I guess he did not get an optimal dosage that day."</p>
	<p>"Hello---We started the patch this morning. None of the advice helped with getting the backing off. It was hard and there was a lot of adhesive left on the backing. What a pain. It stuck well to his skin except on one side so I put the big bandaide over it. NERVOUS!!!! Is he going to get enough medicine? AAARRGGGHHH I called Shire today. The lady said to put the patch on a table, put your finger in the very middle of the patch and pull from there. I will try another one tomorrow and see how it works. Then I will be making some calls. The lady from Shire said he isn't getting all the meds either. Great! So, my son will probably have a horrible day that is not his fault!"</p>
	<p>"I was peeling away the medicine trying to remove the backing. Finally, I noticed that their behavior was different. They started becoming not sure of anything - they looked pale - refused to eat or drink. I mentioned it to the pharmacist. He thought that perhaps they might be getting too much medicine since the integrity of the patch was disrupted as you struggle to get the backing off. I called my doc- and she</p>

	<p>has changed them back to their old meds. The pharmacist contacted the company about the problems with the removal of the backing and he contacted the FDA. The company was going to start an investigation to determine what is happening with the backing. So let contact the FDA if you are having problems. The more info they have - the more they can get resolution on."</p>
<p><b>Design of Protective Backing:</b></p> <p><b>Difficulty may varies between the different strengths of the Daytrana patch</b></p>	<p>"One batch of patches (10mg) had problems with the adhesive sticking to the backing. It occurred along the break line and on one the entire backing pulled off the adhesive. I had kept them in the cool part of the house with the other batch of 15mg patches we were also trying out. We didn't have any problems with the 15mg patches. "</p> <p>"My son recently started Daytrana 10 mg - his first med - and I simply couldn't get the backing off. I called Shire and although it took some time and a call back, I spoke to a very helpful woman. This appeared to be a defective batch. The backing should come off easily. She sent me a card to pay for up to 40 patches, got the lot number from me and said they'd investigate the lot. Importantly, she said that the <u>medicine is in the sticky stuff</u>. So, if anyone has a problem with getting the backing off, make sure you leave as much of the sticky as you can. And call Shire to report the bad batch. They'll listen and you might be able to get a card so you're reimbursed for wasted patches. When I got new patches (20 mg this time), the backing came off easily."</p> <p>"I found the 10 mg patch to be a huge pain to peel off. the 15 and 20mg are not cut down the middle. the break goes from corner to corner and they are much easier to peel off. At least that's what I've found." I was having trouble with the 10 patch too. My pharmasist said I was following the directions correctly so SHE called Shire (the company that makes it) and asked. Shire told her they were having some complaints. I then called Shire at their request. Apparently, people are having trouble peeling off the back and losing some of the medicine. The lady I talked to at Shire was very nice and helpful. She acknowledged the investigation and said the company would send me an envelope to return any unusable patches. (Which they did.) They also sent me another 40 day free trial card to cover any of those patches we couldn't use."</p>
<p><b>Descriptions of removal methods</b></p>	<p>"We picked up the patches yesterday. We had to try 3 pharmacies before we found one that had them in stock. Went to use them this morning and wasted 2 due to the lining not coming off clean. I called Shire and apparently this is a problem they know about and are investigating. Which is no good for us, we're now short 2 patches! I'll try the tweezers tomorrow and see if that helps."</p> <p>"We just started yesterday with the 10mg patch and it has been a complete pain. Half the medicine and the glue sticks to the back when we try to peel the backing off the patch. I spoke with my pharmacist and he was no help because the medicine is so new. Then I called shire and they were no help either. They think that the batch had been exposed to heat but it does me no good when that is the batch I have to work with. This is very frustrating. Was hoping someone could give me tips to make removing the backing easier. I too have resorted to using tweezers and they did not help much. "</p>

	<p>"The Doctor and Nurse tried to apply the two remaining patches today: Very difficult and one tore across the side. We suspect the box had previously been exposed to some heat in a vehicle bringing the partial batch to our pharmacy."</p>
	<p>"This technique is really much harder to explain than it is to use, I'm holding the patch with the medicine/adhesive side down and rubbing my thumbnail against that same (adhesive) side. Yes, the corners I'm rubbing under are the interior corners, the more acute corners (if you remember your high school geometry!) created by the slice in the backing I rub my thumbnails along those corners of the adhesive side, and the corners of the backing just start to stand up. They're free of adhesive and make easy tabs to use to remove the rest of the backing.</p>

**Problem: After applied, the patches can sometimes curl up on the edges, wrinkle, or fall off.**

<p><b>Edges of patch curl up</b></p>	<p>"I just called my pediatrician for a refill of Daytrana. He asked if the sides of the patch were curling up? I said yes. Must be a problem right now. Other than that, he said this patch is an answer to many parents prayers! Mine too!"</p>
	<p>"I am having a hard time getting it to stick to him. I pressed and pressed but it still curls on the corners. Any one have a suggestion short of duck taping it to him? :)"</p>
	<p>"....we are now trying 10 mg of the patch. However it continues to curl up and I am already seeing a regression in my son's behavior. I know he is not receiving the full dosage. I am really nervous for school tomorrow. We were really strating to see some light at the end of the tunnel, but with the patch's ineffectiveness I am concerend we might be back to square one.</p>
	<p>Used patch for the 1st time yest. am. I had read some posts here and also all the accom. literature w/ prescription. I had no concerns about getting the patch on correctly...I WAS WRONG, THE DARN THING IS A PAIN!! I had a terrible time seperating the backing and I am sure I lost some of the meds. My daughter called me from school @ 12:30 to say the patch was coming off. The school nurse put some med. tape over it. My daughter cheered for basketball right after school and I did not get to look @ the area until around 7:00 pm. The patch was certainly "hanging on by a thread" I am not sure how effective it was. This am I had the same problem and had to chunk the 1st patch I tried. However, so far it seems to be staying on better. I will call Shire and her Pediat. 1st thing Monday. In the meantime, does anyone know which 10 mg lots are bad?? This lot # is 1936511 Exp. 05/08.</p>

<b>Wrinkled Patches</b>	<p>"We have used the 10s, 15s and 30s. Tens had problems with adhesive sticking to the backing and the 30s are so long that they wrinkle."</p>
	<p>"Yesterday XX put the 30mg patch on vertically while he was laying down. Since I wasn't there, I checked it later and saw that it had wrinkled and was not sticking there or on corners...used pressure again and added adhesive tape to the edges. So it took another 2 hours to finally kick in. He also had not gone to sleep till 2 am the night before so it was an off kind of day. Today he put it on horizontally"</p>
	<p>"I have noticed sometimes that it doesn't stick all the way. We will have some creases in the patch after about 1/2 the day. And, I wonder if he is actually getting the full amount of medication when the patch does that. It's almost like it bubbles up in a crease like fashion."</p>
<b>Patches falling off</b>	<p>"I recieved a note from the teacher today saying X has "had a bad day" today. He was acting out, disrupting the class and being uncontrollable. Well it comes to find out that he fiddled with is patch and made it come off early in the morning. It was stuck to his shorts!! I explained to him how important it is for him to not mess with his patch, but he then told me that it makes him itch really bad."</p>
<b>Exposure to water causes patches fall off</b>	<p>"XX still can get wrinkling even horizontally. I think it is probably think it is his technique or lack of t I think it may be easier for XX to use two 15mg patches. It will be easier to apply even pressure to get it to stick too. Today when he put it on it ended up more on his thigh than hip and came off in the shower (unusual) So I peeled a new 30mg patch back part way, cut it in half and applied it. no problem."</p>
	<p>"The one thing that I have notice is that it does NOT stay on in water. For the past 2 weekends we have swam at the lake and both times the patch came off. By the time we get back to the lake house (around 5 ) he is impossible and wild as all get out. We actually have to put another patch on him to have a calm evening."</p>
<b>Concerns about accidental exposure to patches that are removed or fall off</b>	<p>"So far, we've really seen good results with the Daytrana. I haven't had any problems with him trying to remove the patch while we aren't looking. Or, trying to give it to a friend. I was a bit concerned with school starting this week, and wondering what would happen if it came off accidentally and ended up on the ground or in the hands of another child. How is the school going to feel about that? And, if it accidentally came off, he would be out of meds for the afternoon and nobody would know. With the oral, it's down the tube and in the body for however long it lasts."</p>
<b>Concerns about accidental exposure to patches that are removed or fall off</b>	<p>"But, with school starting yesterday, I'm a bit concerned with not being able to keep an eye on him. If the patch starts bothering him or itching, he wouldn't think twice about removing it at school...."</p>
	<p>"But, with school starting yesterday, I'm a bit concerned with not being able to keep an eye on him. If the patch starts bothering him or itching, he wouldn't think twice about removing it at school...."</p>

	<p>"Our pediatrician said that if the patch was "removed", the effects of the drug would be null and void.....so, putting the patch on another kid should not be a problem. Also, he said the FDA was considering making the patch available by just calling it in to the pharmacy or getting a good ole refill.....instead of the dreaded written prescription each month. He said FDA is considering this for the patch ONLY because it is safer to use then the pills and cannot be "transferred" to others after wearing it."</p>
<p><b>Application of Overlays to counteract adhesion problems</b></p>	<p>"We had to use bandaids on top of the patch today just to keep it on."</p>
	<p>"We have and continue to have problems with the adhesive and so we just put a large bandaid over it."</p>
	<p>"...we had to secure down all four sides with surgical tape as it was peeling up. "</p>
<p><b>Adhesive is Difficult to Remove from the Skin after patch removal</b></p>	
<p>"Does anyone have any suggestion on how best to get that left over sticky stuff off my son's skin after the patch has been removed? He throws a fit when I try to scrub it off. "</p>	
<p>"The other thing we are now having a problem with is the darn adhesive remaining on his skin. Somebody had posted about it earlier, and we weren't having the problem yet. But, the last few days we have. And, this morning, I noticed the parts around the patch where the adhesive remained, has turned into a sore and scabbed up. Not sure if it's because X has been scratching or picking at the adhesive after we took the patch off. Or, if it's from us using rubbing alcohol and vaseline to try to remove the adhesive. So, that's not good."</p>	

## Appendix B: Messages related to Use of Daytrana

### Storing patches in the Refrigerator

"First off, had enormous difficulty with removing the peeler -- half of the medicine peeled off with it. We had to "practice" with these very expensive patches just to get it down to a sort of science. Since the heat of your fingers heats and melts the med to the back peeler, we decided to try icing it off the peeler and actually had very good luck doing this. We are using the 10mg patch which has a diagonal cut on the back. However, on the days we have done this it definately messed with the dosage drip -- took 4-5 hours before it began to kick in fully and seemed to NOT last the extra 3 hours it is supposed to after removal."

"Regarding chilling them in the fridge -- yes, we tried it once and it does help it (we kept in overnight) peel easier, probably by about 75% better. However, we noticed that when we did that, it took a long time for the meds to fully kick in. His 1st grade teacher let me come in and make copies for her, etc. as I am keeping her in the loop on all med changes. Her and I agreed that he was better than unmedicated, but it wasn't quite what a normal med. morning would be. I left at 11:00 that morning (the patch was put on at 6:30am) kind of feeling like we screwed up the patch by chilling it at what is probably cooler than 77 degrees in my fridge. She sent a note home that at around 12:00 she could tell that he was completely focusing and much more like normal med. day. That same day I took the patch off at 3:30 and he was back to his old self within an hour. .Hope they continue to explore better ways to improve the patch!!"

### Applying nasal corticosteroids to the application site

My son and daughter have been on daytrana several months and it is fabulous...except for the burning, itching and huge red patches it leaves on my son. It burned soooo bad he would take it off at school and well we all now what a day at school is like without medications!!!😬 This is going to sound crazy but I tried it this morning (at the doctors request) and it worked. Spray nasonex on the skin, rub it in and let it dry. Do this 2 or 3 times and when the skin is dry, put the patch on top of the medicated area. My son had the patch on for 45 minutes before he left for school and he said it wasn't burning or itching.. And usually by then he would have been crying and scratching. I hope this works as well for everyone else as it did for us.

OK everyone, I have an apology to make. My doctor told me she was giving me nasonex and I NEVER looked at the bottle until this morning. It isn't Nasonex she gave me, it is Flonase. We have been using it for several days and couldn't be happier with it's results. when I take my sons patches off in the evenings, it is barely red and by the morning they are completely gone.

Thanks for that great info on the patch and flonase. My 8 year dd is also getting the red, itchy welts from the patch. She has been on it two weeks. I have some nasonex, I wonder if it would work like the flonase. Also, cariage have you noticed the flonase interfering with the absorption of the med through the skin or of it not sticking as well? I was worried about that because it says to apply to clean dry skin. The last couple of days her patch has had these big air bubbles in it when she gets home from school where it is not really sticking. Has anybody else experienced that?

I have not noticed any interference with deliverance of medication. I specifically asked the doctor about that and she said it is such a thin layer that it should be fine. We have the patch curling up problem EVERY DAY...with or without the flonase. It's very frustrating. You definitely have to make certain the flonase is completely dry before putting the patch on. Hopefully the manufacturers of the patch with improve that adhesive

we just tried this for the first time today and when my son came home from school he said he had no complaints about the patch. I noticed that it left a red mark, but not nearly as bad as it had been. It had been taking about 2 weeks for the red marks to completely go away. My Dr said that the rash and itching is a side effect that some people experience. I don't know how long the red patch will last with the nasonex, I just know that my son can wear the patch without discomfort and that is huge progress for us. My son would start complaining about the itching and burning within 30 min. of putting the patch on and by the end of the day when the patch came off, the red spot was actually hot to the touch and welpy. So far so good with the nasonex.

AAAAAAAaaaargh!!!! My daughter's butt looks like a war zone! After a month on the patch it started to itch so she scratched like crazy yesterday and the last 4 days of patch turned into hives. There is no place left to put a patch! I put nasonex and topical steroid on it last night and it helped some, but I was still hard pressed to find a patch spot this morning. I put nasonez under her patch today in hopes of nipping any reaction in the bud. Man I hope this problem goes away. This patch has been a godsend.

#### **Inadvertent exposure to the medication**

"Well we put the patch on at 6:30 am and let me tell you I have never had so much trouble getting the backing off of a patch. It was so hard and stuck on there that when we finally got it off I don't think the patch is going to stick very good to her. She was still asleep when we put it on and I sure hope that it works because I don't feel as of yet that it is worth the hassle of getting the backing off, it was so stuck. She will usually be up in the morning getting ready for school when we put the patch on. I will update through the day"

"She seems to be doing ok on it...the edges aren't stuck very good though. She seems very calm and focused though. Well my hubby called me from work and was telling me he was real jittery, he said his hands were shaky, his stomach didn't feel right. I wonder if he got some of the med on his fingers when trying to get that stupid backing off. He said it only lasted like 2hrs. Could this be possible? would it do this to him if he got it on his fingers?? I'm calling the doc and pharmacist first thing in the morning about this being so hard to get the backing off."

#### **Use of Overlays to Ensure Adhesion**

"I had no problems with the adhesive this morning and even covered the patched with medical tape."

"For ensuring the adhesive doesn't peel prematurely there are covering pads by the maker elastoplast with very sticky backing that can be cut to size and work fantastic."

#### **External heat sources**

"Our psych did say to apply with a heat compress for 30 seconds to activate drug."

"Rub the patch with the palm of your hand all over for 30 seconds after applying (the directions say to just press it down, but I think rubbing works better for overall stickiness-- Also, rubbing creates a little bit of heat to encourage quick release of the meds.)"

Do you think a hairdryer would work?

### **Concomitant therapy with oral ADHD medications**

"that the Daytrana takes hours to kick in. My son's psychiatrist has us giving my son a bit of Ritalin (10mg) when he first gets up, which kicks in relatively quickly and keeps him in control until the Daytrana starts working a couple hours later. Perhaps your doctor would have some ideas."

"I'm going to ask my DR if a short acting stim would be possible for the morning until the patch kicks in."

"I have been giving him his oral ADHD meds in the AM between 7-8 and then he puts the patch on himself between 3-4pm and takes it off at about 11pm..... I did ask if he wanted to use the patch in the AM and then the oral meds in the afternoon but he nixed that idea. I will ask again but it really doesnt matter as long as he is covered all day so he can handle school and family life."

"I'm thinking about asking his dr if he can give us a script for the pill (focalin xr) he used to take, just for the weekend. Like a weekend dose. This would help with his red spot as well, giving his skin 2 days to clear up."

"We have tried giving him the Ritalin 15 mg/ 2x a day on the weekend (Sat and Sun) to give the skin a rest, but I am wondering if that is not a good thing. Does the skin eventually get used to it if you continue it 7 days a week?"

### **Cutting the patches**

"Today when he put it on it ended up more on his thigh than hip and came off in the shower (unusual) So I peeled a new 30mg patch back part way, cut it in half and applied it. no problem"

"Check my post on pagd 16 about cutting and combining. It only took a few days for us to figure out the dose for ds. After a few hours the first day, we could see that ten wasn't enough. I cut and added the equivalent of 5mg. the next day we tried 15 and added 5 more in the early afternoon to see how that worked. good luck."

"Some people even cut off some after their school/ work time to a dose where they don't need to focus as much...like socializing."

### **Using multiple Daytrana patches at the same time.**

"Combinations of 10s and 15s: He prescribed 10s and 15s for my son to try out in varying combinations to find out what dose works for him. So to answer your question, yes two 10s are the same as one 20. He is using up some left over 10s to come up with a 25mg dose.  $2@10 + 1/2 @10 = 25$ "

**Failure to remove the Daytrana patch after 9 hours.**

"OK, XX left his patch on last night till 6:30, it should have come off at 4:30. I didn't see any adverse reactions and was asleep by 10:45. I'm just passing this on to others that might have wondered what happens if you don't take it off on time. Has this happened to anyone else?"

Yes, we have left the patch on for more than 9 hours. But, usually only for an extra hour or two. But, we were having some problems with sleep, and instead of going to bed at 8:00, XX couldn't sleep and would go to bed at 11:00. And, That's really only because I was going to bed. So, I started taking it off around 4:00, because we have been putting it on around 7:00. And, the lasting affect for us has been good. It isn't wearing off fast, and we're still seeing results until bedtime. So...all is good...for now!

"so I wanted to try something that we had more control of. He accidentally slept with it on the other night and said he fell asleep almost immediately and slept great and in the morning he was not climbing the walls. He hasn't done that again but its an interesting thing that it lasted that long."

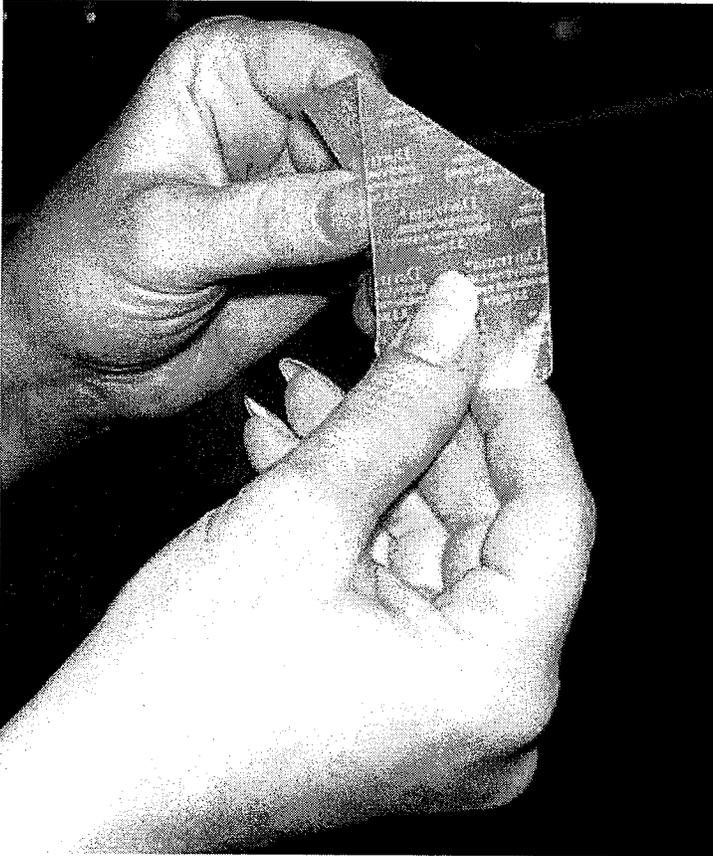
I put the patch on at 6:00 am so if she wears it the whole time that is 15 hours! Has anyone had it on that long? She has once or twice and I thought it started to wane after 13 hours or so. I thought about taking her patch off after school and applying a new one. Has anyone done this? I didn't know if there would be any down time with too little med or time with too much med as one patch wears off and the other kicks in. I just can't quite figure out how to manage this evening so she can have fun and remain in control! Any suggestions???

"Things have been going so well and then.....x had a rash that lasted three days. I am going to keep my eye on it. I think maybe it was because he had the patch on for a long time. We completely forgot to call daycare and remind them. Crappy parents."

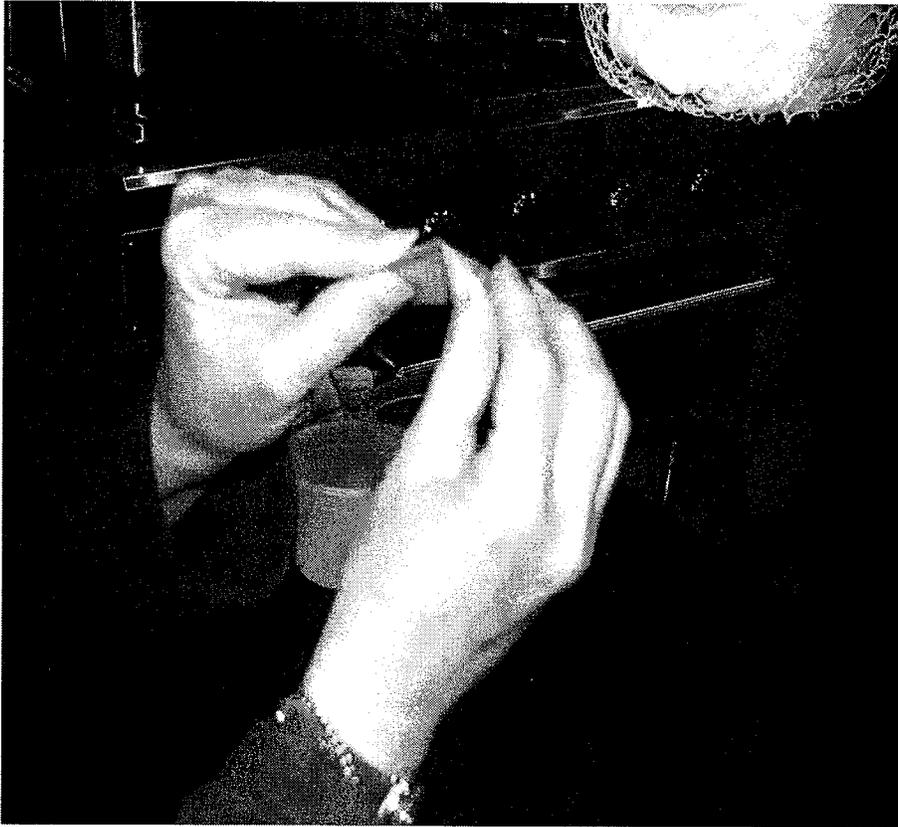
"ok... here is the down low on what my XX dr said at our appt yesterday. Can I put an over sized band-aid over the patch to help keep the child from itching/scratching it off, yes..... He also said that you can leave the patch on for longer if desired. The patch only has so much medicine to deliver, so leaving it on longer might extend your time but probably not by much b/c all the medicine has already been absorbed by skin within 9 to 10 hrs. But leaving it on longer may extend the time it take for the red spot to go away, but that was about it."

"He is almost 18 and has worn it on school days as much as 14 hours, which the doctor thought would be okay."

Appendix C: Photos posted by caregiver to illustrate a method of removing the backing of the Daytrana Patch



Rubbing thumbnail along the adhesive side, holding patch taut.



Corner of backing has come up cleanly.



Corner fully up. Better view of where to rub thumbnail.



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## Proposed Pediatric Study Request for 75-day Expedited Review

**IND:** 54,732

**Protocol:** SPD485-409

**Reviewer:** Robert Levin, M.D.

<b>Sponsor:</b>	Shire
<b>Drug:</b>	Methylphenidate Transdermal System
<b>Material Submitted:</b>	Proposed Pediatric Study Request
<b>Correspondence Date:</b>	October 9, 2006
<b>Drug Category:</b>	Stimulant
<b>Forms available for study:</b>	Methylphenidate transdermal patch: 10 mg/9 hr; 15 mg/9 hr; 20 mg/9 hr; 30 mg/9 hr

### I. Background & Description of Compound

Daytrana (methylphenidate transdermal system) has been approved (April 6, 2006) for the treatment of Attention Deficit-Hyperactivity Disorder (ADHD) in children (ages 6-12). The sponsor proposes an efficacy and safety study in adolescents (ages 13-19) with a diagnosis of ADHD, in order to fulfill a post-approval commitment. The sponsor has requested a 75-Day expedited review of the Proposed Pediatric Study Request.

### II. Proposed Clinical Study

This is a Phase 3b, multicenter (20), randomized, double-blind, placebo-controlled, parallel-group, dose-optimization study designed to evaluate the efficacy and safety of Daytrana (methylphenidate transdermal system) in adolescent patients (ages 13-17) with a diagnosis of Attention Deficit/Hyperactivity Disorder (ADHD). The primary objective is to evaluate the efficacy of Daytrana (compared to placebo), as measured by the change from baseline in the clinician-rated ADHD-RS-IV. Secondary objectives include the assessment of: 1) the safety and tolerability of Daytrana; 2) the efficacy of Daytrana in the home environment as rated by parent/caregiver using the Connors' Parent Scale-Revised: Short Form (CPRS-R); 3) global impression ratings (clinician and parent/caregiver); 4) skin tolerance and potential skin sensitization to Daytrana, as measured by the Dermal Response Scale; and 5) the relationship between plasma methylphenidate exposure and safety and efficacy measurement results (through sparse sampling).

## **Subjects**

The sponsor has proposed appropriate psychiatric and medical subject selection criteria. Subjects will include approximately 210 male and female ADHD patients between the ages of 13 and 17, inclusive. Female subjects of child-bearing potential must have a negative bHCG test at screening and a negative urine pregnancy test at baseline. Such subjects must agree to use an acceptable method of contraception throughout the study and for 30 days after the last dose of study medication. Those who are pregnant or lactating will be excluded. Patients with particular cardiovascular and neurological disorders will be excluded. Patients with skin-sensitive syndrome or significant signs or symptoms of skin irritation will be excluded. Patients with allergy, hypersensitivity, or clinically significant intolerance to methylphenidate or any component of Daytrana will be excluded.

## **Treatment with Study Drug**

Approximately 210 subjects will be randomized to methylphenidate transdermal system (Daytrana) or placebo transdermal system (PTS) in a 2:1 ratio for the 5-week, double-blind, stepwise, dose-optimization phase of the study. Daytrana dosages will include 10 mg/9 hr, 15 mg/9 hr, 20 mg/9 hr, and 30 mg/9 hr. All subjects will begin treatment with Daytrana or matching PTS 10 mg/9 hr per day. A new patch will be applied each morning. Subjects will be evaluated on Day 7 for safety, tolerability, and efficacy. On Day 7, and at each 7-day interval, the dose may be increased to the next dosage strength, depending on clinical response and tolerability of the drug. Subjects may be titrated back down to the previous dose to optimize tolerability. The sponsor has specified appropriate criteria for evaluating a subject's response, based on ADHD-RS-IV scores.

In the maintenance phase, subjects will continue treatment with their optimal dose for an additional 2 weeks. They will continue to undergo double-blind efficacy and safety assessments. Thirty (30) days after discontinuing study treatment, subjects will have a follow-up telephone interview to assess new or ongoing adverse events. Subjects who have developed an application site reaction may be contacted up to a year after the last dose of study medication, to obtain information about any subsequent medication treatment for ADHD and tolerability of such medication.

## **Safety Assessments**

Safety assessments will include the following:

- Medical history and physical examination
- Concomitant medication history
- Vital sign monitoring
- ECG monitoring
- Adverse events monitoring
- Clinical laboratory testing
- Pregnancy testing

- Dermatologic monitoring using: 1) Dermal Response Scale; and 2) Experience of Discomfort and Pruritus

### **III. Conclusions and Recommendations**

The proposed study is reasonably safe to proceed as currently written. The proposed daily doses and duration of study drug exposure are identical to those used in the studies in children between the ages of 6 and 12 years-old. The Daytrana NDA was approved based on those studies. The plan for dermatological monitoring and treatment is reasonable.

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Robert L. Levin, M.D.,  
Medical Reviewer, November 28, 2006  
FDA CDER ODE1 DNDP HFD 130

cc: IND  
HFD 130  
T Laughren  
M Mathis  
N Khin  
F Curtis

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Robert Levin  
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## Review and Evaluation of Clinical Data

IND: 54,732

Protocol: SPD485-409

<b>Sponsor:</b>	Shire
<b>Drug:</b>	Methylphenidate Transdermal System
<b>Material Submitted:</b>	Proposed Pediatric Study Request
<b>Correspondence Date:</b>	October 9, 2006
<b>Drug Category:</b>	Stimulant
<b>Forms available for study:</b>	Methylphenidate transdermal patch 25 cm <sup>2</sup> ;

### I. Background & Description of Compound

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### II. Proposed Clinical Study (Protocol: SPD485-409)

This is a Phase 3b, multicenter (20), randomized, double-blind, placebo-controlled, parallel-group, dose-optimization study designed to evaluate the efficacy and safety of Daytrana (methylphenidate transdermal system) in adolescent patients (ages 13-17) with a diagnosis of Attention Deficit/Hyperactivity Disorder (ADHD). The primary objective is to evaluate the efficacy of Daytrana (compared to placebo), as measured by the change from baseline in the clinician-rated ADHD-RS-IV. Secondary objectives include the assessment of: 1) the safety and tolerability of Daytrana; 2) the efficacy of Daytrana in the home environment as rated by parent/caregiver using the Connors' Parent Scale-Revised: Short Form (CPRS-R); 3) global impression ratings (clinician and parent/caregiver); 4) skin tolerance and potential skin sensitization to Daytrana, as measured by the Dermal Response Scale; and 5) the relationship between plasma methylphenidate exposure and safety and efficacy measurement results (via sparse sampling).

#### Subjects

The sponsor has proposed appropriate psychiatric and medical subject selection criteria. Subjects will include approximately 210 male and female ADHD patients between the ages of 13 and 17, inclusive. Female subjects of child-bearing potential must have a negative bHCG test at screening and a negative urine pregnancy test at baseline. Such subjects must agree to use an acceptable method of contraception throughout the study and for 30 days after the last dose of study medication. Those who are pregnant or lactating will be excluded. Patients with particular cardiovascular and neurological disorders will be excluded. Patients with skin-sensitive syndrome or significant signs or

symptoms of skin irritation will be excluded. Patients with allergy, hypersensitivity, or clinically significant intolerance to methylphenidate or any component of Daytrana will be excluded.

#### **Treatment with Study Drug**

Subjects will be randomized (in a 2:1 ratio) to treatment with either Daytrana (methylphenidate transdermal system) or placebo transdermal system. Clinicians will titrate the dose according to response, in order to reach an optimal dose. Daily dosages (mg of methylphenidate per patch) will include: 10 mg/9 hours; 15 mg/9hr; 20 mg/9hr; and 30 mg/9hr. Clinicians will review ratings from the clinic as well as from the home in deciding upon the dose of study drug. The duration of the titration/dose-optimization period will be five (5) weeks. Subjects will wear each patch for nine (9) hours each day; a new patch will be applied to the hip each morning. All subjects will initiate treatment with 10 mg/9hr/day. Subjects will be evaluated after 7 days, and they may have their dose increased to 15 mg/9hr/day if needed. After subsequent intervals of 7 days, subjects may have their daily dose increased or decreased as needed. The dose may be reduced, if the subject has difficulty tolerating a particular dose. At the end of five (5) weeks, subjects who have had an adequate response and have tolerated treatment may enter a two-week maintenance phase.

#### **Safety Assessments**

Safety assessments will include the following:

- 1) Medical history; 2) physical examinations; 3) concomitant medication history;
- 4) vital sign monitoring; 5) ECG monitoring; 6) serum and urine pregnancy testing;
- 7) clinical laboratory testing; 8) urine drug screening; and 9) dermal evaluations (Dermal Response Scale; and Experience of Discomfort and Pruritus Scale).

#### **Conclusions and Recommendations**

In my opinion, the proposed study is reasonably safe to proceed as currently written. The protocol is essentially identical to those used in previous Daytrana studies. The doses and duration of treatment proposed are identical to those used in previous studies of pediatric ADHD subjects between the ages of 6 and 12 years old. Treatment with Daytrana in these studies was reasonably safe and well-tolerated. The sponsor has proposed a reasonable plan for safety monitoring, including dermatologic assessments for potential skin sensitivity to methylphenidate.