Clinical Team Leader Review Memo

Date	June 6, 2010
From	Robert L. Levin, M.D.
Subject	Cross-Discipline Team Leader Review
NDA# / Supp #	21514 / S-010
Sponsor	Shire Pharmaceuticals
Proprietary / Established name	DAYTRANA (methylphenidate transdermal system)
Submission date	September 4, 2009
Dosage forms / strengths	10 mg (12.5 cm^2), 15 mg (18.75 cm^2), 20 mg (25 cm^2), and 30 mg (37.5 cm^2) transdermal patches
Proposed Indication	Attention Deficit-Hyperactivity Disorder in Adolescents (ages 13 to 17 years)
Recommendation:	Approval

1. Introduction

Daytrana (methylphenidate transdermal system) is an adhesive-based matrix transdermal system (patch) that is applied to the skin daily for the treatment of Attention Deficit-Hyperactivity Disorder (ADHD) in children (ages 6-12 years). It is the only transdermal system stimulant formulation currently approved for the treatment of ADHD.

2. Background/Regulatory History

Daytrana was approved for the treatment of ADHD in children (ages 6-12) on April 6, 2006. The original NDA was submitted on June 27, 2002, and the Division of Neuropharmacologic Drug Products took a non-approvable action on April 25, 2003, due to concerns about excessive exposures and adverse events. In the studies supporting the original NDA, the daily wear time (12 hours) that had been studied and proposed was longer than the currently approved daily wear time (9 hours) that was used in subsequent studies that supported the approval of Daytrana. In the initial NDA review, the primary adverse reactions of concern were gastrointestinal adverse effects, decreased appetite, weight loss, insomnia, and anxiety.

The sponsor submitted a non-approvable response on June 28, 2005. The studies supporting the resubmission included two new efficacy and safety trials in children (ages 6-12) with ADHD. The doses used were 10 mg (12.5 cm^2), 15 mg (18.75 cm^2), 20 mg (25 cm^2), and 30 mg (37.5 cm^2) transdermal patches with a wear time of 9 hours. Both studies demonstrated the efficacy of Daytrana in ADHD in children. In addition, treatment with Daytrana was reasonably safe and well tolerated. The Division took an approvable action on December 23, 2005; the sponsor submitted an approvable response on February 9, 2006; and the Division took an approval action on April 6, 2006.

In the April 6, 2006 approval letter, the Division requested a Phase 4 postmarketing commitment. Under section 2 of the Pediatric Research Equity Act (PREA), the sponsor would

be required to conduct an adequate and well controlled trial of Daytrana in the treatment of ADHD in pediatric patients (ages 13 to 17 years). The final report submission date would be 3 years form the date of approval of the NDA (April 2009). On October 9, 2006, the sponsor submitted a Proposed Pediatric Study Request for a pivotal study of Daytrana in adolescents with ADHD. The review of the study was filed in November 2006.

3. CMC

There was no new Chemistry, Manufacturing, and Controls information submitted in this application. There are no unresolved CMC issues that would affect an action on this application.

4. Nonclinical Pharmacology/Toxicology

There are no unresolved Pharmacology/Toxicology issues.

5. Clinical Pharmacology/Biopharmaceutics

Andre Jackson, Ph.D. conducted the clinical pharmacology/biopharmaceutics review. Dr. Jackson concluded that the clinical pharmacology data submitted for this application are acceptable. The sponsor submitted data from Study SPD485-106, which was a clinical pharmacology study of Daytrana in pediatric subjects between the ages of 6 and 17 years-old with a diagnosis of ADHD. The objective of the study was to evaluate the pharmacokinetics of methylphenidate when Daytrana was administered as fixed single-doses and fixed multiple-doses. The doses used were 10 mg/day (12.5 cm^2 patch) and 30 mg/day (37.5 cm^2 patch), which are the lowest and highest Daytrana strengths, respectively. A specific objective was to evaluate the degree of accumulation of methylphenidate with multiple-dosing of Daytrana.

Compared to children (ages 6-12), the C_{max} and AUC_{inf} of methylphenidate in adolescents treated with single doses of Daytrana 10 mg/9 hours were decreased by 55% and 51%, respectively. After 7 days of dosing with 10 mg/9 hours, the Css_{max} and AUC_{ss} of methylphenidate in adolescents (compared to children) were decreased by 56% and 50%, respectively. Thus, the exposure differences between adolescents and children were comparable following single and multiple doses. Following fixed, multiple doses of Daytrana for 7 and 28 days, the accumulation index (based on AUC_{ss}) in children was 1.12 and 1.64, respectively. Following fixed, multiple doses of Daytrana for 7 and 28 days, the accumulation index in adolescents was 1.14 and 1.75, respectively.

Dr. Jackson also noted that since the efficacy studies of Daytrana in children and adolescents used flexible dosing, one cannot formally assess whether there is a dose/response relationship:

> "The efficacy data presented by the firm for weeks 1-7 for the 13-14 and 15-17 yr olds did not exhibit any dose response. Therefore the decreased exposure in adolescents compared to children does not warrant any adjustment in dose based upon dose response. Due to the study design, a true exposure response could not be assessed. In addition, the label recommends that the dosage be titrated to effect."

Based on his analysis of the PK data, Dr. Jackson has recommended specific additions in labeling for the clinical pharmacology sections.

6. Clinical Microbiology

There are no clinical microbiology issues regarding this application.

7. Clinical/Statistical

The Division and the sponsor prospectively agreed that one adequate and well controlled study of Daytrana in adolescents with ADHD would be adequate to: 1) meet the requirements of the written request, and 2) support the addition of labeling language describing the study results. In addition, the Division and the sponsor prospectively agreed on the specific design of the pivotal study (SPD485-409).

7.1. Efficacy

7.1.1. Dose identification/selection and limitations

The flexible doses used in adolescent study SPD485-409 were identical to those used in the controlled ADHD studies in children (ages 6 to 12). The sponsor conducted single-dose and multiple-dose pharmacokinetic studies in children and adolescents with the various Daytrana dose strengths, in order to select the doses in this controlled study. The choice of doses was also based on the controlled efficacy data in children.

7.1.2. Phase 3 clinical studies essential to regulatory decisions, including design, analytic features, and results

7.1.2.1 Study Design

Study SPD485-409 was conducted in 32 U.S. centers between June 28, 2007 and May 19, 2008. This was a randomized, double-blind, placebo-controlled, outpatient, flexible-dose study of methylphenidate transdermal system (Daytrana) in adolescents (ages 13-17) with Attention Deficit-Hyperactivity Disorder. The primary objective was to evaluate the efficacy of Daytrana compared to placebo transdermal patches. The primary endpoint was the change in mean ADHD-RS-IV score at the end of Week 7.

7.1.2.2 Subject Selection Criteria

Subjects were outpatient male and female adolescents between the ages of 13 and 17 years with a primary diagnosis of ADHD. The diagnosis was based on a structured Kiddie-Schedule for Affective Disorders-Present and Lifetime-Diagnostic Interview (K-SADS-PL). Subjects must have had a baseline ADHD-RS-IV total score of > 26. They must have had an IQ score > 80 as measured by the Kaufman Brief Intelligence Test. In addition, subjects had to have normal blood pressure values for their age, gender, and height and must have had no significant comorbid illnesses, significant ECG findings, or history of dermatologic disorders.

Exclusion criteria included a current (controlled or uncontrolled) comorbid psychiatric diagnosis (except Oppositional Defiant Disorder) that, in the opinion of the investigator, would contraindicate MTS treatment or confound the interpretation of the efficacy or safety findings. Overweight adolescents (BMI > 95th percentile) and those who had a history of non-response to psychostimulant treatment were also excluded.

7.1.2.3 Demographic Features

A total of 217 subjects participated in the study. Subjects were randomized to Daytrana (n= 145) or placebo (n= 72) in a 2:1 ratio. The study population was 75% male and 25% female, which is consistent with the gender distribution of ADHD in the pediatric population. The age subgroups were well represented (52.5% were 13-14 years-old, and 47.5% were 15-17 years-old). The distribution of ethnicities in the study subjects was as follows: Caucasian (77%), African American (18%), Asian (0.5%), Native American (0.5%), and Other (4%). The mean weight, height, and BMI were 130 lbs., 65 inches, and 21.2 kg/m2, respectively. These demographic features were well balanced between treatment groups.

7.1.2.4 Dose Optimization and Maintenance Phases of the Study

After a screening and drug washout period, subjects entered the randomized, double-blind, placebo-controlled treatment phase (7 weeks). Subjects were randomized to treatment with either Daytrana or placebo (in a 2:1 ratio) and began a 5-week dose optimization phase. All subjects in the Daytrana group began treatment with 10 mg/9 hour (12.5 cm^2). After one week, the dose could be increased to 15 mg/9 hour (18.75 cm^2), depending on response and tolerability. At the end of Weeks 2 and 3, the dose could be increased to 20 mg (25 cm^2) and 30 mg (37.5 cm^2), respectively. The dose could be decreased by one dose level during the 5-week dose-optimization phase. During a 2-week double-blind, placebo-controlled maintenance phase, the subjects' doses remained constant. The primary efficacy assessment was conducted at the end of the 2-week maintenance phase (at the end of Week 7).

7.1.2.5 Efficacy findings and Statistical Analysis

Christina Burkhart, M.D. performed the clinical review. As Dr. Burkhart notes, the results of Study 409 demonstrated the efficacy of Daytrana in the treatment of ADHD in an adolescent study population. The primary efficacy results are illustrated in the table below (adapted from the sponsor's Table 19 in the clinical study report). The primary efficacy instrument was the Attention Deficit-Hyperactivity Rating Scale-IV (ADHD-RS-IV), which is a well validated and widely used efficacy measure for assessing ADHD symptoms in children and adolescents with a diagnosis of ADHD.

The primary endpoint was the mean change in ADHD-RS-IV total score at the end of Week 7. The primary statistical analysis was a comparison between the Daytrana and placebo groups in the mean change from baseline in ADHD-RS-IV total score at endpoint using an ANCOVA model with treatment as a factor and baseline ADHD-RS-IV total score as a covariate. The least square mean difference (95% CI) between Daytrana and placebo was -9.96 (-13.39, -6.53). At endpoint, the least square mean change from baseline in ADHD-RS-IV total score

was statistically significantly greater ($p < 0.001$) for the MTS group (-18.8) compared with the placebo group (-8.8). This magnitude of difference in ADHD-RS score is clinically significant.

Sponsor's Table 19: Analysis of LS Mean (SE) Change from Baseline ADHD-RS-IV Total Score (ANCOVA model-ITT Population)

ADHD-RS-IV Total	**Placebo N= 72**	**MTS N= 143**	**95% CI LS Mean Difference**	**p-value**
Endpoint- LS mean (SE) Difference (MTS – PLA)	-8.8 (1.42)	-18.8 (1.01) -9.96	(-13.39, -6.53)	<0.001

The key secondary efficacy endpoint was the change in mean total score on the Conners' Parent Rating Scale-Revised Short Version (CPRS-R) at the end of Week 7. This key secondary endpoint was positive, and it supports the primary efficacy findings. The LS mean difference (95% CI) between the Daytrana and placebo groups in the change from baseline CPRS-R total score was -13.48 (-18.48, -8.47). The difference between groups was statistically significant ($p < 0.001$).

Sponsor's Table 23: Analysis of LS Mean (SE) Change from Baseline CPRS-R Total Score (ANCOVA model)-ITT Population

	Placebo N= 72	**MTS** N= 143	**95% CI LS Mean Difference**	**p-value**
Endpoint- LS mean (SE) Difference (MTS – placebo)	-7.5 (2.08)	-20.9 (1.45) -13.48	(-18.48, -8.47)	<0.001

Yeh-Fong Chen, Ph.D. conducted the statistical review. Essentially, Dr. Chen replicated the sponsor's analysis results for the primary and secondary endpoints, and she concluded that Study 409 demonstrated the efficacy of Daytrana in this study:

> "After evaluation, the statistical reviewer agreed with the sponsor that the data from Study SPD485-409 supported the efficacy of Methylphenidate Transdermal System (MTS) as a treatment of attention deficit/hyperactivity disorder (ADHD) for adolescent patients."

7.1.3. Discussion of primary and secondary reviewers' comments and conclusions

7.1.3.1. Clinical Review

Dr. Burkhart has concluded that the clinical data demonstrate that Daytrana was efficacious in the treatment of ADHD in adolescents. She concluded that Study 409 was an adequate and well controlled study. I agree with her conclusions.

7.1.3.2. Statistical Review

Dr. Chen replicated the sponsor's efficacy analysis, and she concluded that the results demonstrated the efficacy of treatment with Daytrana in Study 409. I agree with her conclusions.

7.1.4. Pediatric use/PREA waivers/deferrals

In the April 6, 2006 Daytrana approval letter, the Division requested a phase 4 postmarketing commitment for the studies currently under review. Under section 2 of the Pediatric Research Equity Act (PREA), the sponsor would be required to conduct an adequate and well controlled trial of Daytrana in the treatment of ADHD in pediatric patients (ages 13 to 17 years). The final report submission date would be 3 years form the date of approval of the NDA (April 2009). On October 9, 2006, the sponsor submitted a Proposed Pediatric Study Request for a pivotal study of Daytrana in adolescents with ADHD. The review of the study was filed in November 2006. There are no other outstanding commitments under PREA.

7.2. Safety

7.2.1. General safety considerations

The safety database was adequate for this application. The safety monitoring was appropriate and adequate for a study of methylphenidate in pediatric subjects. The number of subjects exposed to Daytrana and the duration of exposure were adequate for assessing the safety parameters. There were 145 subjects exposed to Daytrana for a total exposure of 16.4 subject-years in the short-term, controlled study. The median duration of Daytrana exposure was 48 days. In the open-label extension study (410), the median exposure was 168 days, and the total exposure was 57.6 subject-years.

7.2.2. Safety findings from the clinical studies

There were no new or unexpected safety findings related to treatment with Daytrana, compared to previous experience with Daytrana or other methylphenidate formulations. There were no deaths in the study, and there were two serious adverse events.

One subject treated with Daytrana had two serious adverse events (syncope), which led to discontinuation from the study. The subject recovered from the episodes. Subject 33-011 had episodes of dizziness followed by syncope on Day 8 and Day 11 after beginning treatment with Daytrana. On Day 13, the subject reported these episodes. Both episodes of syncope occurred approximately 1 hour after removal of the patch and lasted less than 30 seconds. The subject's dose had been 15 mg/d (18.75 cm^2 patch). The subject's screening, baseline, and early termination visit ECGs were reviewed by a pediatric cardiologist. Reportedly, there was no evidence of structural heart disease or aberrant conduction.

There were no other serious adverse events in the study. Drug-related adverse events leading to discontinuation included: decreased appetite, irritability, dizziness, dry mouth, syncope, and

application site dermatitis. In the methylphenidate group, 6% of subjects discontinued due to an adverse event. In the placebo group, 3% of subjects discontinued due to an adverse event. Commonly reported adverse reactions included decreased appetite (26%), weight loss (6%), irritability (11%), insomnia (6%), nausea (10%), abdominal discomfort (5%), vomiting (2%), dizziness (6%), and application site reactions (6%).

The mean change in weight in the Daytrana group was -0.86 kg (-1.9 lbs.). In the placebo group, the mean change in weight was +0.804 kg (+1.77 lbs). There were small increases in pulse rate and blood pressure in the Daytrana. The mean pulse, SBP, and DBP increased by 6.7 bpm, 2 mm Hg, and 1.7 mm Hg, respectively.

7.2.3. Safety update

The sponsor submitted the Four Month Safety Update Report on January 4, 2010. The sponsor reported that during the period of September 4, 2009 to January 4, 2010, no clinical studies with Daytrana had been initiated or ongoing. The sponsor stated that there were no significant safety findings that would change the assessment of the safety profile of Daytrana. Daytrana is not currently marketed in any countries other than the U.S.

The sponsor submitted the results of two non-clinical safety studies in juvenile rats (January 4, 2010) as part of the Four Month Safety Update. As Dr. Burkhart notes, the results of the two studies do not change the interpretation of safety profile of Daytrana.

7.2.4. Discussion of primary reviewer's comments and conclusions

Dr. Burkhart conducted a thorough and thoughtful review of the safety data. She has concluded that treatment with Daytrana in the adolescent ADHD study was generally safe and well tolerated. Dr. Burkhart also concluded that there were no new safety findings in this study, compared to those in previous Daytrana studies or with methylphenidate studies in general. I agree with Dr. Burkhart's conclusions.

8. Advisory Committee Meeting

There was no advisory committee meeting regarding this application, because there were no unique or controversial features of the application. Daytrana is approved for the treatment of ADHD in children (ages 6-12).

9. Financial Disclosure

There are no concerns about the financial disclosure of investigators who participated in the studies supporting this submission.

10. Labeling

10.1 Physician labeling

As part of the review of this submission, the Division converted approved Daytrana labeling into the Physician Labeling Rule labeling format. All relevant disciplines conducted the labeling review.

10.2 Clinical Pharmacology Section - Pharmacokinetics

Dr. Jackson (OCP) recommends adding the following language to the pharmacokinetics section:

> The Cmax and AUC of d-methylphenidate were approximately 50% lower in adolescents, compared to children, following either a 1-day or 7-day administration of Daytrana (10mg/9 hr). Multiple-dose administration of Daytrana did not result in significant accumulation of methylphenidate; following 7 days of Daytrana administration (10 mg/ 9 hr) in children and adolescents, the average accumulation index of methylphenidate was 1.1.

10.3 Clinical Studies Section

The Division has proposed the following additional language to describe the efficacy results of Study 409:

> In Study 3, conducted in the outpatient setting, Daytrana or placebo was blindly administered in a flexible-dose design using doses of 10, 15, 20, and 30 mg / 9 hours during a 5-week dose-optimization phase, followed by a 2-week maintenance period using the optimal patch dose for each patient. Symptoms of ADHD were evaluated using the ADHD-Rating Scale (ADHD-RS-IV). Daytrana was statistically significantly superior to placebo as measured by the mean change from baseline in the ADHD-RS-IV total score.

10.4 Patient labeling/Medication guide

We have proposed substantial changes to the medication guide, in order to make it more consistent with labeling and to use more accessible language for patients and families.

11. DSI Audits

Anthony Orencia, M.D. conducted the DSI review. The Division recommended auditing two U.S. clinical sites which were relatively high enrollers of subjects in Study 409. The investigators are: 1) Robert Findling, M.D. at University Hospitals Case Medical Center, Division of Child and Adolescent Psychiatry, and 2) Keith Saylor, Ph.D. at NeuroScience Inc., Herndon, Virginia. There were no significant concerns about the data from these two sites. Dr. Orencia concluded that the study was conducted adequately at the sites, and he found the data to be acceptable. Dr. Orencia recommended that there was no action indicated for both sites.

12. Conclusions and Recommendations

12. 1 Recommended regulatory action

I recommend approval of this supplemental NDA for Daytrana in the treatment of ADHD in adolescents (ages 13-17). The sponsor conducted an adequate and well controlled trial of Daytrana that clearly demonstrated efficacy in the treatment of ADHD in adolescents. The study demonstrated that treatment with Daytrana was reasonably safe and well tolerated. There were no new or unexpected safety concerns related to treatment, compared to previous experience with Daytrana or other methylphenidate formulations.

12.2 Safety concerns to be followed postmarketing

We and the sponsor will continue routine pharmacovigilance for Daytrana.

12.3 Risk Minimization Action Plan

There is no specific risk minimization action plan for Daytrana.

12.4 Postmarketing studies

Other than the studies under review, there are no outstanding required postmarketing studies.

12.5 Comments to be conveyed to the applicant in the regulatory action letter

There are no specific comments to convey to the sponsor. We have sent our proposed labeling.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21514	SUPPL-10	SHIRE DEVELOPMENT INC	Daytrana System

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/s/

ROBERT L LEVIN
06/06/2010