

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Daytrana® safely and effectively. See full prescribing information for Daytrana.

DAYTRANA® (methylphenidate transdermal system)

Initial U.S. Approval: 2006

WARNING: DRUG DEPENDENCE

See full prescribing information for complete boxed warning

- Daytrana should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behavior.

-----RECENT MAJOR CHANGES-----

- Indications and Usage (1), September 2009
- Dosage and Administration (2), September 2009

-----INDICATIONS AND USAGE-----

Daytrana is a CNS stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

- Children (ages 6-12): the efficacy of Daytrana in ADHD was established in two 7-week controlled trials in children (1)
- Adolescents (ages 13-17): the efficacy of Daytrana in ADHD was established in one 7-week, controlled study in adolescents (1)

-----DOSAGE AND ADMINISTRATION-----

- The recommended starting dose for patients new to or converting from another formulation of methylphenidate is 10 mg. (2)
- Daytrana should be applied to the hip area (using alternating sites) 2 hours before an effect is needed and should be removed 9 hours after application. Daytrana may be removed earlier than 9 hours if a shorter duration of effect is desired or late day side effects appear. (2)
- Dosage should be titrated to effect. Dose titration, final dosage, and wear time should be individualized according to the needs and response of the patient. (2)
- Patients should be advised to follow the full instructions for patch use provided in the Medication Guide. (17)

-----DOSAGE FORM AND STRENGTHS-----

- Transdermal Patch: 10mg/9 hours (1.1 mg/hr), 15mg/9 hours (1.6 mg/hr), 20mg/9 hours (2.2 mg/hr), 30mg/9 hours (3.3 mg/hr)

-----CONTRAINDICATIONS-----

- Known hypersensitivity to methylphenidate (4.1)
- Marked anxiety, tension, or agitation (4.2)
- Glaucoma (4.3)
- Tics or a family history or diagnosis of Tourette's syndrome (4.4)
- Patients currently using or within 2 weeks of using an MAO inhibitor (4.5)

-----WARNINGS AND PRECAUTIONS-----

- Serious Cardiovascular Events: Sudden death has been reported in association with CNS stimulant treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. Sudden death, stroke, and myocardial infarction have been reported in adults taking stimulant drugs at usual doses for ADHD. Stimulant products generally should not be used in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious heart problems. (5.1)
- Increase in Blood Pressure: Monitor patients for changes in heart rate and blood pressure and use with caution in patients for whom an increase in blood pressure or heart rate would be problematic. (5.1)
- Psychiatric Adverse Events: Use of stimulants may cause treatment-emergent psychotic or manic symptoms in patients with no prior history, or exacerbation of symptoms in patients with pre-existing psychiatric illness. Clinical evaluation for Bipolar Disorder is recommended prior to stimulant use. Monitor for aggressive behavior. (5.2)
- Seizures: Stimulants may lower the convulsive threshold. Discontinue in the presence of seizures. (5.3)
- Long-Term Suppression of Growth: Monitor height and weight at appropriate intervals in pediatric patients. (5.4)

- Visual Disturbance: Difficulties with accommodation and blurring of vision have been reported with stimulant treatment. (5.5)
- Contact Sensitization: Use of Daytrana may lead to contact sensitization. Treatment should be discontinued if contact sensitization is suspected. Erythema is commonly seen with use of Daytrana and is not by itself an indication of sensitization. However, contact sensitization should be suspected if erythema is accompanied by evidence of a more intense local reaction (edema, papules, vesicles) that does not significantly improve within 48 hours or spreads beyond the patch site. (5.6)
- External Heat: Patients should be advised to avoid exposing the Daytrana application site to direct external heat sources. When heat is applied to Daytrana after patch application, both the rate and extent of absorption are significantly increased. (5.7)
- Hematologic monitoring: Periodic CBC, differential, and platelet counts are advised during prolonged therapy. (5.8)

-----ADVERSE REACTIONS-----

- Children (ages 6-12): The most commonly ($\geq 5\%$ and twice the rate of placebo) reported adverse reactions in a placebo-controlled trial in children aged 6-12 included appetite decreased, insomnia, nausea, vomiting, weight decreased, tic, affect lability, and anorexia (6.1).
- Adolescents (ages 13-17): The most commonly ($>5\%$ and twice the rate of placebo) reported adverse reactions in a placebo-controlled trial in adolescents aged 13-17 included appetite decreased, nausea, insomnia, weight decreased, dizziness, abdominal pain, and anorexia. The majority of subjects in these trials had erythema at the application site (6.1).
- The most common ($\geq 2\%$ of subjects) adverse reaction associated with discontinuations in controlled clinical trials in children or adolescents was application site reactions (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Shire US Inc. 1-800-828-2088 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----DRUG INTERACTIONS-----

- Do not use Daytrana in patients currently using or within 2 weeks of using an MAO inhibitor. (7.1)
- Daytrana may increase blood pressure; use cautiously with vasopressors. (7.2)
- Methylphenidate may decrease the effectiveness of drugs used to treat hypertension. (7.3)
- Methylphenidate may inhibit metabolism of coumarin anticoagulants, anticonvulsants, and some antidepressants. (7.4)
- Serious adverse events have been reported when using clonidine in combination with methylphenidate, although no causality has been established. (7.5)

-----USE IN SPECIFIC POPULATIONS-----

- Pregnancy and Nursing Mothers: Use only if the potential benefit justifies the potential risk to the fetus and/or child. Based on animal data, may cause fetal harm. (8.1, 8.3)
- Pediatric Use: has not been studied in children under 6 years of age (8.4)
- Geriatric Use: has not been studied in geriatric patients. (8.5)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

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FULL PRESCRIBING INFORMATION

WARNING: DRUG DEPENDENCE

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

1 INDICATIONS AND USAGE

Daytrana (methylphenidate transdermal system) is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

The efficacy of Daytrana in patients diagnosed with ADHD was established in two 7-week controlled clinical trials in children (ages 6-12) and one 7-week, controlled clinical trial in adolescents (ages 13-17).

A diagnosis of ADHD (DSM-IV-TR®) implies the presence of hyperactive-impulsive or inattentive symptoms that caused impairment and were present before age 7 years. The symptoms must cause clinically significant impairment, e.g., in social, academic, or occupational functioning, and be present in two or more settings, e.g., school (or work) and at home. The symptoms must not be better accounted for by another mental disorder. For the Inattentive Type, at least six of the following symptoms must have persisted for at least 6 months: lack of attention to details/careless mistakes; lack of sustained attention; poor listener; failure to follow through on tasks; poor organization; avoids tasks requiring sustained mental effort; loses things; easily distracted; forgetful. For the Hyperactive-Impulsive Type, at least six of the following symptoms must have persisted for at least 6 months: fidgeting/squirming; leaving seat; inappropriate running/climbing; difficulty with quiet activities; "on the go;" excessive talking; blurting answers; can't wait turn; intrusive. The Combined Type requires both inattentive and hyperactive-impulsive criteria to be met.

1.1 Special Diagnostic Considerations

The specific etiology of this syndrome is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use not only of medical but of special psychological, educational, and social resources. Learning may or may not be impaired. The diagnosis must be based upon a complete history and evaluation of the patient and not solely on the presence of the required number of DSM-IV-TR® characteristics.

1.2 Need for Comprehensive Treatment Program

Daytrana is indicated as an integral part of a total treatment program for ADHD that may include other measures (psychological, educational, social) for patients with this syndrome. Drug treatment may not be indicated for all patients with this syndrome. Stimulants are not intended for use in the patient who exhibits symptoms secondary to environmental factors and/or other primary psychiatric disorders, including psychosis. Appropriate educational placement is essential and psychosocial intervention is often helpful. When remedial measures alone are insufficient, the decision to prescribe stimulant medication will depend upon the physician's assessment of the chronicity and severity of the patient's symptoms.

2 DOSAGE AND ADMINISTRATION

It is recommended that Daytrana be applied to the hip area 2 hours before an effect is needed and should be removed 9 hours after application. Dosage should be titrated to effect. The recommended dose titration schedule is shown in the table below. Dose titration, final dosage, and wear time should be individualized according to the needs and response of the patient.

Table 1	Daytrana - Recommended Titration Schedule (Patients New to			Methylphenidate)
Upward Titration, if Response is Not Maximized				
	Week 1	Week 2	Week 3	Week 4
Patch Size	12.5 cm ²	18.75 cm ²	25 cm ²	37.5 cm ²
Nominal Delivered Dose* (mg/9 hours)	10 mg	15 mg	20 mg	30 mg
Delivery Rate*	(1.1 mg/hr)*	(1.6 mg/hr)*	(2.2 mg/hr)*	(3.3 mg/hr)*

*Nominal *in vivo* delivery rate children and adolescents when applied to the hip, based on a 9-hour wear period.

Patients converting from another formulation of methylphenidate should follow the above titration schedule due to differences in bioavailability of Daytrana compared to other products.

2.1 Application

The parent or caregiver should be encouraged to use the administration chart included with each carton of Daytrana to monitor application and removal time, and method of disposal. It is recommended that parents or caregivers apply and remove the patch for children; responsible adolescents may apply or remove the patch themselves if appropriate. The Medication Guide included at the end of this insert also includes a timetable to calculate when to remove Daytrana, based on the 9-hour application time.

The adhesive side of Daytrana should be placed on a clean, dry area of the hip. The area selected should not be oily, damaged, or irritated. Apply patch to the hip area, avoiding the waistline, since clothing may cause the patch to rub off. When applying the patch the next morning, place on the opposite hip at a new site if possible.

If patients or caregivers experience difficulty separating the patch from the release liner or observe transfer of adhesive to the liner, tearing and/or other damage to the patch during removal from the liner, the patch should be discarded according to the directions provided below, and a new patch should be applied. Patients or caregivers should inspect the release liner to ensure that no adhesive containing medication has transferred to the liner. If adhesive transfer has occurred, the patch should be discarded.

Daytrana should be applied immediately after opening the individual pouch and removing the protective liner. Do not use if the individual pouch seal is broken or if the patch appears to be damaged. Do not cut patches. Only intact patches should be applied. The patch should then be pressed firmly in place with the palm of the hand for approximately 30 seconds, making sure that there is good contact of the patch with the skin, especially around the edges. Exposure to water during bathing, swimming, or showering can affect patch adherence. Patches should not be applied or re-applied with dressings, tape, or other common adhesives. In the event that a patch does not fully adhere to the skin upon application, or becomes partially or fully detached during wear time, the patch should be discarded according to the directions provided in this label [see *Dosage and Administration* (2.3)] and a new patch may be applied at a different site. The total recommended wear time for that day should remain 9 hours regardless of the number of patches used [see *Patient Counseling Information* (17.1)].

All patients should be advised to avoid exposing the Daytrana application site to direct external heat sources, such as hair dryers, heating pads, electric blankets, heated water beds, etc., while wearing the patch [see *Warnings and Precautions* (5.7)]. When heat is applied to Daytrana™ after patch application, both the rate and the extent of absorption are significantly increased. The temperature-dependent increase in methylphenidate absorption can be greater than 2-fold (see **CLINICAL PHARMACOLOGY: Pharmacokinetics/Absorption**).

This increased absorption can be clinically significant and result in overdose of methylphenidate (see **OVERDOSAGE**).

Patches should not be stored in refrigerators or freezers.

2.2 Removal of Daytrana

Daytrana patches should be peeled off slowly. If necessary, patch removal may be facilitated by gently applying an oil-based product (i.e., petroleum jelly, olive oil, or mineral oil) to the patch edges, gently working the oil underneath the patch edges. If any adhesive remains on the skin following patch removal, an oil-based product may be applied to patch sites in an effort to gently loosen and remove any residual adhesive that remains following patch removal.

In the unlikely event that a patch remains tightly adhered despite these measures, the patient or caregiver should contact the physician or pharmacist. Nonmedical adhesive removers and acetone-based products (i.e., nail polish remover) should not be used to remove Daytrana patches or adhesive.

2.3 Disposal of Daytrana

Upon removal of Daytrana, used patches should be folded so that the adhesive side of the patch adheres to itself and should be flushed down the toilet or disposed of in an appropriate lidded container. If the patient stops using the prescription, each unused patch should be removed from its individual pouch, separated from the protective liner, folded onto itself, and disposed of in the same manner as used patches.

The parent or caregiver should be encouraged to record on the administration chart included with each carton the time that each patch was applied and removed. If a patch was removed without the parent or caregiver's knowledge, or if a patch is missing from the tray or outer pouch, the parent or caregiver should be encouraged to ask the child when and how the patch was removed.

2.4 Maintenance/Extended Treatment

There is no body of evidence available from controlled clinical trials to indicate how long the patient with ADHD should be treated with Daytrana. It is generally agreed, however, that pharmacological treatment of ADHD may be needed for extended periods. The effectiveness of Daytrana for long-term use, i.e., for more than 7 weeks, has not been systematically evaluated in controlled trials. The physician who elects to use Daytrana for extended periods should periodically re-evaluate the long-term usefulness of Daytrana for the individual patient with periods off medication to assess the patient's functioning without pharmacotherapy. Improvement may be sustained when the drug is either temporarily or permanently discontinued.

2.5 Dose/Wear Time Reduction and Discontinuation

Daytrana may be removed earlier than 9 hours if a shorter duration of effect is desired or late day side effects appear. Plasma concentrations of *d*-methylphenidate generally begin declining when the patch is removed, although absorption may continue for several hours. Individualization of wear time may help manage some of the side effects caused by methylphenidate. If aggravation of symptoms or other adverse events occur, the dosage or wear time should be reduced, or, if necessary, the drug should be discontinued. Residual methylphenidate remains in used patches when worn as recommended.

3 DOSAGE FORM AND STRENGTHS

Four dosage strengths are available:

Nominal Dose Delivered (mg) Over 9 Hours*	Dosage Rate* (mg/hr)	Patch Size (cm²)	Methylphenidate Content per Patch (mg)
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10	1.1	12.5	27.5
15	1.6	18.75	41.3
20	2.2	25	55
30	3.3	37.5	82.5

*Nominal *in vivo* delivery rate in children and adolescents when applied to the hip, based on a 9-hour wear period.

4 CONTRAINDICATIONS

4.1 Hypersensitivity to Methylphenidate

Daytrana is contraindicated in patients known to be hypersensitive to methylphenidate or other components of the product (polyester/ethylene vinyl acetate laminate film backing, acrylic adhesive, silicone adhesive, and fluoropolymer-coated polyester) [see *Description (11.1)*].

4.2 Agitation

Daytrana is contraindicated in patients with marked anxiety, tension, and agitation, since the drug may aggravate these symptoms.

4.3 Glaucoma

Daytrana is contraindicated in patients with glaucoma.

4.4 Tics

Daytrana is contraindicated in patients with motor tics or with a family history or diagnosis of Tourette's syndrome [see *Adverse Reactions (6.1)*].

4.5 Monoamine Oxidase Inhibitors

Daytrana is contraindicated during treatment with monoamine oxidase inhibitors, and also within a minimum of 14 days following discontinuation of treatment with a monoamine oxidase inhibitor (hypertensive crises may result).

5 WARNINGS and PRECAUTIONS

5.1 Serious Cardiovascular Events

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

Children and Adolescents

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

Adults

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

Hypertension and Other Cardiovascular Conditions

Stimulant medications cause a modest increase in average blood pressure (about 2-4 mmHg) and average heart rate (about 3-6 bpm), and individuals may have larger increases. While the mean changes alone would not be expected to have short-term consequences, all patients should be monitored for larger changes in heart rate and blood pressure. Caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate, e.g., those with pre-existing hypertension, heart failure, recent myocardial infarction, or ventricular arrhythmia [see *Adverse Reactions* (6.1)].

Assessing Cardiovascular Status in Patients Being Treated With Stimulant Medications

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

5.2 Psychiatric Adverse Events

Pre-Existing Psychosis

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

Bipolar Illness

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

Emergence of New Psychotic or Manic Symptoms

Treatment emergent psychotic or manic symptoms, e.g., hallucinations, delusional thinking, or mania in children and adolescents without a prior history of psychotic illness or mania can be caused by stimulants at usual doses. If such symptoms occur, consideration should be given to a possible causal role of the stimulant, and discontinuation of treatment may be appropriate. In a pooled analysis of multiple short term, placebo-controlled studies, such symptoms occurred in about 0.1% (4 patients with events out of 3,482 exposed to methylphenidate or amphetamine for several weeks at usual doses) of stimulant-treated patients compared to none in placebo-treated patients.

Aggression

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

patients beginning treatment for ADHD should be monitored for the appearance of or worsening of aggressive behavior or hostility.

5.3 Seizures

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

5.4 Long-Term Suppression of Growth

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

5.5 Visual Disturbance

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

5.6 Contact Sensitization

In an open-label study of 305 subjects conducted to characterize dermal reactions in children with ADHD treated with Daytrana using a 9-hour wear time, one subject (0.3%) was confirmed by patch testing to be sensitized to methylphenidate (allergic contact dermatitis). This subject experienced erythema and edema at Daytrana application sites with concurrent urticarial lesions on the abdomen and legs resulting in treatment discontinuation. This subject was not transitioned to oral methylphenidate.

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

Patients sensitized from use of Daytrana, as evidenced by development of an allergic contact dermatitis, may develop systemic sensitization or other systemic reactions if methylphenidate-containing products are taken via other routes, e.g., orally. Manifestations of systemic sensitization may include a flare-up of previous dermatitis or of prior positive patch-test sites, or generalized skin eruptions in previously unaffected skin. Other systemic reactions may include headache, fever, malaise, arthralgia, diarrhea, or vomiting. No cases of systemic sensitization have been observed in clinical trials of Daytrana.

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

5.7 Patients Using External Heat

Patients should be advised to avoid exposing the Daytrana application site to direct external heat sources, such as hair dryers, heating pads, electric blankets, heated water beds, etc., while wearing the patch. When heat is applied to Daytrana after patch application, both the rate and extent of absorption are significantly increased. The temperature-dependent increase in methylphenidate absorption can be greater than 2-fold [see *Clinical Pharmacology* (12.3)]. This increased absorption can be clinically significant and can result in overdose of methylphenidate [see *Overdosage* (10)].

5.8 Hematologic Monitoring

Periodic CBC, differential, and platelet counts are advised during prolonged therapy.

6 ADVERSE REACTIONS

Detailed information on serious and adverse reactions of particular importance is provided in the *Boxed Warning* and *Warnings and Precautions* (5) sections:

- Drug dependence [see *box Warning*]
- Hypersensitivity to Methylphenidate [see *Contraindications* (4.1)]
- Marked anxiety, tension, or agitation [see *Contraindications* (4.2)]
- Glaucoma [see *Contraindications* (4.3)]
- Tics or a family history of Tourette's syndrome [see *Contraindications* (4.4)]
- Monoamine Oxidase Inhibitors [see *Contraindications* (4.5) and *Drug Interactions* (7.1)]
- Serious Cardiovascular Events [see *Warnings and Precautions* (5.1)]
- Increase in Blood Pressure [see *Warnings and Precautions* (5.2)]
- Psychiatric Adverse Events [see *Warnings and Precautions* (5.2)]
- Seizures [see *Warnings and Precautions* (5.3)]
- Long-Term Suppression of Growth [see *Warnings and Precautions* (5.4)]
- Visual Disturbance [see *Warnings and Precautions* (5.5)]
- Contact Sensitization [see *Warnings and Precautions* (5.6)]
- External Heat [see *Warnings and Precautions* (5.7)]
- Hematologic Monitoring [see *Warnings and Precautions* (5.8)]

The most commonly reported (frequency $\geq 5\%$ and twice the rate of placebo) adverse reactions in a controlled trial in children aged 6-12 included appetite decreased, insomnia, nausea, vomiting, weight decreased, tic, affect lability, and anorexia. The most commonly reported (frequency $\geq 5\%$ and twice the rate of placebo) adverse reactions in a controlled trial in adolescents aged 13-17 were appetite decreased, nausea, insomnia, weight decreased, dizziness, abdominal pain, and anorexia [see *Adverse Reactions* (6.1)].

The most common ($\geq 2\%$ of subjects) adverse reaction associated with discontinuations in double-blind clinical trials in children or adolescents was application site reactions [see *Adverse Reactions* (6.3)].¹⁵

The overall Daytrana development program included exposure to Daytrana in a total of 2,152 participants in clinical trials, including 1,529 children aged 6-12, 223 adolescents aged 13-17, and 400 adults. The 1,752 child and adolescent subjects aged 6-17 years were evaluated in 10 controlled clinical studies, 7 open-label clinical studies, and 5 clinical pharmacology studies. In a combined studies pool of children using Daytrana with a wear time of 9 hours, 212 subjects were exposed for ≥ 6 months and 115 were exposed for ≥ 1 year; 85 adolescents have been exposed for ≥ 6 months. Most patients studied were exposed to Daytrana patch sizes of 12.5 cm², 18.75 cm², 25 cm² or 37.5 cm², with a wear time of 9 hours.

In the data presented below, the adverse reactions reported during exposure were obtained primarily by general inquiry at each visit, and were recorded by the clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals

experiencing adverse reactions without first grouping similar types of events into a smaller number of standardized event categories.

Throughout this section adverse reactions reported are events that were considered to be reasonably associated with the use of Daytrana based on comprehensive assessment of the available adverse event information. A causal association for Daytrana often cannot be reliably established in individual cases. Further, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not reflect the rates observed in clinical practice.

6.1 Clinical Trials Experience

Adverse Reactions Associated With Discontinuation of Treatment

In a 7-week double-blind, parallel-group, placebo-controlled study in children with ADHD conducted in the outpatient setting, 7.1% (7/98) of patients treated with Daytrana discontinued due to adverse events compared with 1.2% (1/85) receiving placebo. The most commonly reported (>1% and twice the rate of placebo) adverse reactions leading to discontinuation in the Daytrana group were application site reaction (2%), tics (1%), headache (1%), and irritability (1%).

In a 7-week double-blind, parallel-group, placebo-controlled study in adolescents with ADHD conducted in the outpatient setting, 5.5% (8/145) of patients treated with Daytrana discontinued due to adverse reactions compared with 2.8% (2/72) receiving placebo. The most commonly reported adverse reactions leading to discontinuation in the Daytrana group were application site reaction (2%) and decreased appetite/anorexia (1.4%).

Commonly Observed Adverse Reactions in Double-Blind, Placebo-Controlled Trials

Skin Irritation and Application Site Reactions

Daytrana is a dermal irritant. In addition to the most commonly reported adverse reactions presented in Table 2, the majority of subjects in those studies had minimal to definite skin erythema at the patch application site. This erythema generally caused no or minimal discomfort and did not usually interfere with therapy or result in discontinuation from treatment. Erythema is not by itself a manifestation of contact sensitization. However, contact sensitization should be suspected if erythema is accompanied by evidence of a more intense local reaction (edema, papules, vesicles) that does not significantly improve within 48 hours or spreads beyond the patch site [see *Warnings and Precautions* (5.6)].

Most Commonly Reported Adverse Reactions

Table 2 lists treatment-emergent adverse reactions reported in >1% Daytrana-treated children or adolescents with ADHD in two 7 week double-blind, parallel-group, placebo-controlled studies conducted in the outpatient setting. Overall, in these studies, 75.5% of children and 78.6% of adolescents experienced at least 1 adverse event.

Table 2 Number (%) of Subjects with Commonly Reported Adverse Reactions (≥1% in the Daytrana Group) in 7-Week Placebo-controlled Studies in Either Children or Adolescents- Safety Population						
System	Organ	Class	Adolescents		Children	
			Placebo N = 72	Daytrana N = 145	Placebo N = 85	Daytrana N = 98
		Cardiac Disorders				
		Tachycardia	0 (0)	1 (0.7)	0 (0)	1 (1.0)
		Gastrointestinal disorders				
		Abdominal pain	0 (0)	7 (4.8)	5 (5.9)	7 (7.1)
		Nausea	2 (2.8)	14 (9.7)	2 (2.4)	12 (12.2)
		Vomiting	1 (1.4)	5 (3.4)	4 (4.7)	10 (10.2)
		Investigations				
		Weight decreased	1 (1.4)	8 (5.5)	0 (0)	9 (9.2)
		Metabolism and nutrition disorders				
		Anorexia	1 (1.4)	7 (4.8)	1 (1.2)	5 (5.1)
		Decreased appetite	1 (1.4)	37 (25.5)	4 (4.7)	25 (25.5)
		Nervous system disorders				
		Dizziness	1 (1.4)	8 (5.5)	1 (1.2)	0 (0)
		Headache	9 (12.5)	18 (12.4)	10 (11.8)	15 (15.3)
		Psychiatric disorders				
		Affect lability	1 (1.4)	0 (0)	0 (0)	6 (6.1)*
		Insomnia	2 (2.8)	9 (6.2)	4 (4.7)	13 (13.3)
		Irritability	5 (6.9)	16 (11)	4 (4.7)	7 (7.1)
		Tic	0 (0)	0 (0)	0 (0)	7 (7.1)
* Six subjects had affect lability, all judged as mild and described as increased emotionally sensitive, emotionality, emotional instability, emotional lability, and intermittent emotional						

Adverse Reactions With the Long-Term Use of Daytrana

In a long-term open-label study of up to 12 months duration in 326 children wearing Daytrana 9 hours daily, the most common (≥10%) adverse reactions were decreased appetite, headache, and weight decreased. A total of 30 subjects (9.2%) were withdrawn from the study due to adverse events and 22 additional subjects (6.7%) discontinued treatment as the result of an application site reaction. Other than application site reactions, affect lability (5 subjects, 1.5%) was the only additional adverse reaction leading to discontinuation reported with a frequency of greater than 1%.

In a long-term open-label study of up to 6 months duration in 162 adolescents wearing Daytrana 9 hours daily, the most common (≥10%) adverse reactions were decreased appetite and headache. A total of 9 subjects (5.5%) were withdrawn from the study due to adverse events and 3 additional subjects (1.9%) discontinued treatment as the result of an application site reaction. Other adverse reactions leading to discontinuation that occurred with a frequency of greater than 1% included affect lability and irritability (2 subjects each, 1.2%).

6.2 Postmarketing Experience

In addition, the following adverse reactions have been identified during the postapproval use of Daytrana. 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.

Cardiac Disorders: palpitations

Eye Disorders: visual disturbances, blurred vision, mydriasis, accommodation disorder

General Disorders and Administration Site Disorders: application site reactions such as bleeding, bruising, burn, burning, dermatitis, discharge, discoloration, discomfort, dryness, eczema, edema, erosion, erythema, excoriation, exfoliation, fissure, hyperpigmentation, hypopigmentation, induration, infection, inflammation, irritation, pain, papules, paresthesia, pruritus, rash, scab, swelling, ulcer, urticaria, vesicles, and warmth.

Immune System Disorders: hypersensitivity reactions including generalized erythematous and urticarial rashes, allergic contact dermatitis, angioedema, and anaphylaxis

Investigations: blood pressure increased

Nervous System Disorders: convulsion, dyskinesia

Psychiatric Disorders: transient depressed mood, hallucination, nervousness

Skin and Subcutaneous Tissue Disorders: alopecia

6.3 Adverse Reactions With Oral Methylphenidate Products

Nervousness and insomnia are the most common adverse reactions reported with other methylphenidate products. In children, loss of appetite, abdominal pain, weight loss during prolonged therapy, insomnia, and tachycardia may occur more frequently; however, any of the other adverse reactions listed below may also occur.

Other reactions include:

Cardiac: angina, arrhythmia, pulse increased or decreased

Immune: hypersensitivity reactions including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura

Metabolism/Nutrition: anorexia, weight loss during prolonged therapy

Nervous System: drowsiness, rare reports of Tourette's syndrome, toxic psychosis

Vascular: blood pressure increased or decreased, cerebral arteritis and/or occlusion

Although a definite causal relationship has not been established, the following have been reported in patients taking methylphenidate:

Blood/Lymphatic: leukopenia and/or anemia

Hepatobiliary: abnormal liver function, ranging from transaminase elevation to hepatic coma

Psychiatric: transient depressed mood

Skin/Subcutaneous: scalp hair loss

Neuroleptic Malignant Syndrome: Very rare reports of neuroleptic malignant syndrome (NMS) have been received, and, in most of these, patients were concurrently receiving therapies associated with NMS. In a single report, a ten-year-old boy who had been taking methylphenidate for approximately 18 months experienced an NMS-like event within 45 minutes of ingesting his first dose of venlafaxine. It is uncertain whether this case represented a drug-drug interaction, a response to either drug alone, or some other cause.

7 DRUG INTERACTIONS

7.1 MAO Inhibitors

Daytrana should not be used in patients being treated (currently or within the preceding two weeks) with monoamine oxidase inhibitors [see *Contraindications* (4.5)].

7.2 Vasopressor Agents

Because of a possible effect on blood pressure, Daytrana should be used cautiously with pressor agents.

7.3 Hypotension Agents

Methylphenidate may decrease the effectiveness of drugs used to treat hypertension.

7.4 Coumarin Anticoagulants, Antidepressants, and Selective Serotonin Reuptake Inhibitors

Human pharmacologic studies have shown that methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (e.g., phenobarbital, phenytoin, primidone), and some tricyclic drugs (e.g., imipramine, clomipramine, desipramine) and selective serotonin reuptake inhibitors. Downward dose adjustments of these drugs may be required when given concomitantly with methylphenidate. It may be necessary to adjust the dosage and monitor plasma drug concentrations (or, in the case of coumarin, coagulation times), when initiating or discontinuing methylphenidate.

7.5 Clonidine

Serious adverse events have been reported in concomitant use of methylphenidate with clonidine, although no causality for the combination has been established. The safety of using methylphenidate in combination with clonidine or other centrally acting alpha-2-agonists has not been systematically evaluated.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C - Animal reproduction studies with transdermal methylphenidate have not been performed. In a study in which oral methylphenidate was given to pregnant rabbits during the period of organogenesis at doses up to 200 mg/kg/day no teratogenic effects were seen, although an increase in the incidence of a variation, dilation of the lateral ventricles, was seen at 200 mg/kg/day; this dose also produced maternal toxicity. A previously conducted study in rabbits showed teratogenic effects of methylphenidate at an oral dose of 200 mg/kg/day. In a study in which oral methylphenidate was given to pregnant rats during the period of organogenesis at doses up to 100 mg/kg/day, no teratogenic effects were seen although a slight delay in fetal skeletal ossification was seen at doses of 60 mg/kg/day and above; these doses caused some maternal toxicity.

In a study in which oral methylphenidate was given to rats throughout pregnancy and lactation at doses up to 60 mg/kg/day, offspring weights and survival were decreased at 40 mg/kg/day and above; these doses caused some maternal toxicity.

Adequate and well-controlled studies in pregnant women have not been conducted. Daytrana should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.2 Labor and Delivery

The effect of Daytrana on labor and delivery in humans is unknown.

8.3 Nursing Mothers

It is not known whether methylphenidate is excreted in human milk. Daytrana should be administered to a nursing woman only if the potential benefit justifies the potential risk to the child.

8.4 Pediatric Use

Daytrana should not be used in children under six years of age, since safety and efficacy in this age group have not been established. Long-term effects of methylphenidate in children have not been well established.

Studies with transdermal methylphenidate have not been performed in juvenile animals. In a study conducted in young rats, methylphenidate was administered orally at doses of up to 100 mg/kg/day for 9 weeks, starting early in the postnatal period (Postnatal Day 7) and continuing through sexual maturity (Postnatal Week 10). When these animals were tested as adults (Postnatal Weeks 13-14), decreased spontaneous locomotor activity was observed in males and females previously treated with 50 mg/kg/day or greater, and a deficit in the acquisition of a specific learning task was seen in females exposed to the highest dose. The no effect level for juvenile neurobehavioral development in rats was 5 mg/kg/day. The clinical significance of the long-term behavioral effects observed in rats is unknown.

8.5 Geriatric Use

Daytrana has not been studied in patients greater than 65 years of age.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Daytrana is classified as a Schedule II controlled substance by federal regulation.

9.2 Abuse

See warning containing drug abuse information [see *Boxed Warning*].

9.3 Dependence

See warning containing drug dependence information [see *Boxed Warning*].

10 OVERDOSAGE

10.1 Signs and Symptoms

Signs and symptoms of acute methylphenidate overdose, resulting principally from overstimulation of the CNS and from excessive sympathomimetic effects, may include the following: vomiting, agitation, tremors, hyperreflexia, muscle twitching, convulsions (may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitations, cardiac arrhythmias, hypertension, mydriasis, and dryness of mucous membranes.

10.2 Recommended Treatment

Remove all patches immediately and cleanse the area(s) to remove any remaining adhesive. The continuing absorption of methylphenidate from the skin, even after removal of the patch, should be considered when treating patients with overdose. Treatment consists of appropriate supportive measures. The patient must be protected against self-injury and against external stimuli that would aggravate overstimulation already present. Intensive care must be provided to maintain adequate circulation and respiratory exchange; external cooling procedures may be required for hyperpyrexia.

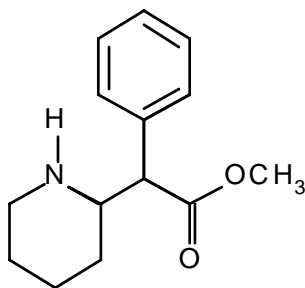
Efficacy of peritoneal dialysis or extracorporeal hemodialysis for Daytrana overdose has not been established.

10.3 Poison Control Center

As with the management of all overdoses, the possibility of multiple drug ingestion should be considered. The physician may wish to consider contacting a poison control center for up-to-date information on the management of overdose with methylphenidate.

11 DESCRIPTION

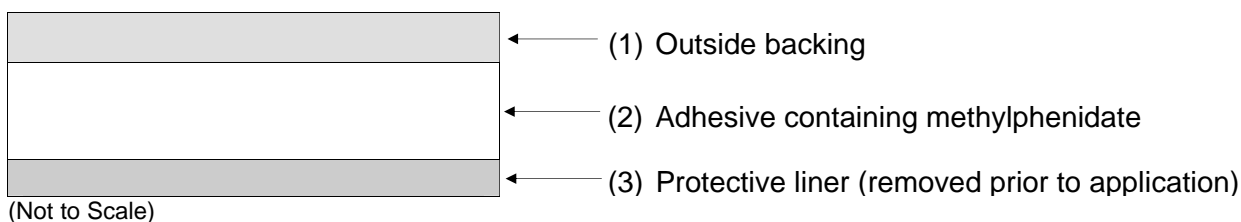
Daytrana is an adhesive-based matrix transdermal system (patch) that is applied to intact skin. The chemical name for methylphenidate is α -phenyl-2-piperidineacetic acid methyl ester. It is a white to off-white powder and is soluble in alcohol, ethyl acetate, and ether. Methylphenidate is practically insoluble in water and petrol ether. Its molecular weight is 233.31. Its empirical formula is $C_{14}H_{19}NO_2$. The structural formula of methylphenidate is:



11.1 Patch Components

Daytrana contains methylphenidate in a multipolymeric adhesive. The methylphenidate is dispersed in acrylic adhesive that is dispersed in a silicone adhesive. The composition per unit area of all dosage strengths is identical, and the total dose delivered is dependent on the patch size and wear time.

The patch consists of three layers, as seen in the figure below (cross-section of the patch).



Proceeding from the outer surface toward the surface adhering to the skin, the layers are (1) a polyester/ethylene vinyl acetate laminate film backing, (2) a proprietary adhesive formulation incorporating Noven Pharmaceuticals, Inc.'s DOT Matrix™ transdermal technology consisting of an acrylic adhesive, a silicone adhesive, and methylphenidate, and (3) a fluoropolymer-coated polyester protective liner which is attached to the adhesive surface and must be removed before the patch can be used.

The active component of the patch is methylphenidate. The remaining components are pharmacologically inactive.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Methylphenidate is a CNS stimulant. Its mode of therapeutic action in Attention Deficit Hyperactivity Disorder (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.

12.2 Pharmacodynamics

Methylphenidate is a racemic mixture comprised of the *d*- and *l*-enantiomers. The *d*-enantiomer is more pharmacologically active than the *l*-enantiomer.

12.3 Pharmacokinetics

The pharmacokinetics of Daytrana when applied to the hip for 9 hours have been studied in ADHD patients 6 to 17 years old.

Absorption

The amount of methylphenidate absorbed systemically is a function of both wear time and patch size. In patients with ADHD, peak plasma levels of methylphenidate are reached at about 10 hours after single application and 8 hours after repeat patch applications (12.5 cm² to 37.5 cm²) when worn up to 9 hours.

On single dosing with Daytrana to children or adolescents, there was a delay of, on average, 2 hours before *d*-methylphenidate was detectable in the circulation. On repeat dosing, low concentrations (1.2-3.0 ng/mL in children and 0.5-1.7ng/mL in adolescents, on average across the dose range) were observed earlier in the profile, due to carry-over effect. Following the application of Daytrana once daily with a 9 hour wear time, the mean pharmacokinetic parameters of *d*-methylphenidate in children and adolescents with ADHD after 4 weeks of therapy are summarized in Table 3.

Table 3
Mean Plasma *d*-Methylphenidate Pharmacokinetic Parameters After Repeated 9-Hour Applications of Daytrana or Oral ER-MPH for up to 28 days to Pediatric ADHD Patients (Aged 6 – 17 years)

<i>Children</i>				
Parameter	Daytrana ¹ 12.5 cm ² (N=12)	Daytrana ² 37.5 cm ² (N=10)	Oral ER-MPH ³ 18 mg	Oral ER-MPH ³ 54 mg
C _{ssmax} (ng/mL)	15.7 ± 9.39	42.9 ± 22.4	8.37 ± 4.14	26.1 ± 11.2

C_{ssmin} (ng/mL)	1.04 ± 1.17	1.96 ± 1.73	0.708 ± 1.08	1.19 ± 1.54
AUC_{ss} (ng·hr/mL)	163 ± 101	447 ± 230	97.7 ± 67.0	317 ± 160
t_{lag} (h) ⁴	0 (0 – 2.0)	0 (0 – 1.0)	0	0
<i>Adolescents</i>				
C_{ssmax} (ng/mL)	8.32 ± 4.60	16.5 ± 6.94	5.23 ± 1.72	18.0 ± 6.97
C_{ssmin} (ng/mL)	0.544 ± 0.383	1.02 ± 0.629	0.360 ± 0.478	1.50 ± 0.937
AUC_{ss} (ng·hr/mL)	85.7 ± 50.0	167 ± 66.0	59.7 ± 19.1	216 ± 80.8
t_{lag} (h) ⁴	0 (0 – 2.0)	0 (0 – 2.0)	0	0

¹Dose maintained fixed for 28 days;

²Dose escalated at 7 day intervals from 12.5 cm² through 18.75 cm² and 25 cm² to 37.5 cm²;

³Dose escalated at 7 day intervals from 18 mg through 27 mg and 36 mg to 54 mg; ⁴Median (minimum – maximum); t_{lag} = Last Sampling Time Prior to Time of First Quantifiable Plasma Concentration

Following administration of Daytrana 12.5 cm² to pediatric and adolescent ADHD patients daily for 7 days, there were 13% and 14% increases, respectively, in steady state area under the plasma concentration-time curve (AUC_{ss}) relative to that anticipated on the basis of single dose pharmacokinetics ($AUC_{0-\infty}$); after 28 days administration, these increments increased to 64% and 76%, respectively. C_{max} increased by nearly 69% and 100% within 4 weeks of daily administration of the starting dose in children and adolescents, respectively.

The observed exposures with Daytrana could not be explained by drug accumulation predicted from observed single dose pharmacokinetics, and there was no evidence that clearance or rate of elimination changed between single and repeat dosing. Neither were they explainable by differences in dosing patterns between treatments, age, race, or gender. This suggests that transdermal absorption of methylphenidate may increase with repeat dosing with Daytrana; on average, steady-state is likely to have been achieved by approximately 14 days of dosing.

In the single- and multiple-dose study described above, exposure to *l*-methylphenidate was 46% of the exposure to *d*-methylphenidate in children and 40% in adolescents. *l*-methylphenidate is less pharmacologically active than *d*-methylphenidate [see *Pharmacodynamics* (12.2)].

In a phase 2 PK/PD study in children aged 6-12 years, 2/3 of patients had 2-hour *d*-MPH concentrations < 5 ng/mL on chronic dosing, and at 3 hours 40% of patients had *d*-MPH concentrations < 5 ng/mL [see *Clinical Studies* (14)].

When Daytrana is applied to inflamed skin, both the rate and extent of absorption are increased as compared with intact skin. When applied to inflamed skin, lag time is no greater than 1 hour, T_{max} is 4 hours, and both C_{max} and AUC are approximately 3-fold higher.

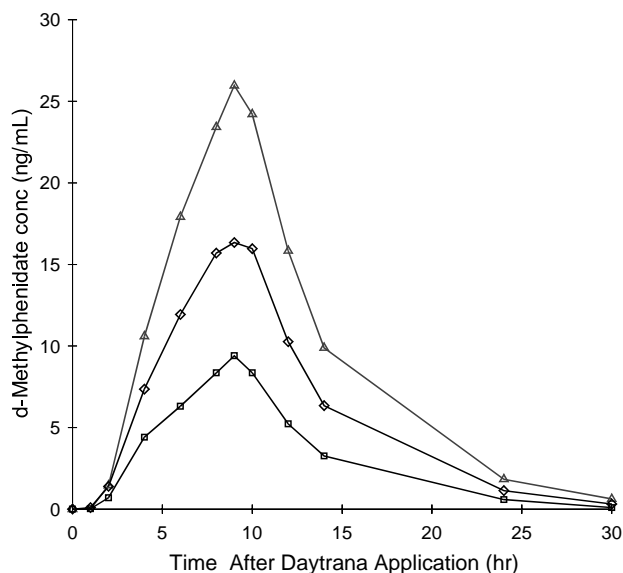
When heat is applied to Daytrana after patch application, both the rate and the extent of absorption are significantly increased. Median T_{lag} occurs 1 hour earlier, T_{max} occurs 0.5 hours earlier, and median C_{max} and AUC are 2-fold and 2.5-fold higher, respectively.

Application sites other than the hip can have different absorption characteristics and have not been adequately studied in safety or efficacy studies.

Dose Proportionality

Following a single 9-hour application of Daytrana patch doses of 10 mg / 9 hours to 30 mg / 9 hours patches to 34 children with ADHD, C_{max} and AUC_{0-t} of *d*-methylphenidate were proportional to the patch dose. Mean plasma concentration-time plots are shown in Figure 1. C_{max} of *l*-methylphenidate was also proportional to the patch dose. AUC_{0-t} of *l*-methylphenidate was only slightly greater than proportional to patch dose.

FIGURE 1
Mean Concentration-time Profiles for *d*-Methylphenidate in all Patients (N=34) Following Administration of Single Applications (9-Hour Wear Time) of *d,l*-Methylphenidate Using Daytrana 10 mg (□), 20 mg (◇) and 30 mg (△) per 9-Hour Patches



Distribution

Upon removal of Daytrana, methylphenidate plasma concentrations in children with ADHD decline in a biexponential manner. This may be due to continued distribution of MPH from the skin after patch removal.

Metabolism and Excretion

Methylphenidate is metabolized primarily by de-esterification to alpha-phenyl-piperidine acetic acid (ritalinic acid), which has little or no pharmacologic activity.

Transdermal administration of methylphenidate exhibits much less first pass effect than oral administration. Consequently, a much lower dose of Daytrana on a mg/kg basis, compared to oral dosages, may still produce higher exposures of *d*-MPH with transdermal administration compared to oral administration. In addition, very little, if any, *l*-methylphenidate is systemically available after oral administration due to first pass metabolism, whereas after transdermal administration of racemic methylphenidate, exposure to *l*-methylphenidate is nearly as high as to *d*-methylphenidate.

The mean elimination $t_{1/2}$ from plasma of *d*-methylphenidate after removal of Daytrana in children aged 6 to 12 years and adolescents aged 13-17 years was approximately 4 to 5 hours. The $t_{1/2}$ of *l*-methylphenidate was shorter than for *d*-methylphenidate and ranged from 1.4 to 2.9 hours, on average.

The C_{max} 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 accumulation index of methylphenidate was 1.1 based on the mean steady state area under the plasma concentration-time curve (AUC_{ss}) relative to that anticipated on the basis of single dose pharmacokinetics ($AUC_{0-\infty}$).

Food Effects

The pharmacokinetics or the pharmacodynamic food effect performance after application of Daytrana has not been studied, but because of the transdermal route of administration, no food effect is expected.

Special Populations

Gender

The pharmacokinetics of methylphenidate after single and repeated doses of Daytrana were similar between boys and girls with ADHD, after allowance for differences in body weight.

Race

The influence of race on the pharmacokinetics of methylphenidate after administration of Daytrana has not been defined.

Age

The pharmacokinetics of methylphenidate after administration of Daytrana have not been studied in children less than 6 years of age.

Renal Impairment

There is no experience with the use of Daytrana in patients with renal insufficiency.

Hepatic Impairment

There is no experience with the use of Daytrana in patients with hepatic insufficiency.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis/Mutagenesis and Impairment of Fertility

Carcinogenesis

Carcinogenicity studies of transdermal methylphenidate have not been performed. In a lifetime carcinogenicity study of oral methylphenidate carried out in B6C3F1 mice, methylphenidate caused an increase in hepatocellular adenomas and, in males only, an increase in hepatoblastomas, at a daily dose of approximately 60 mg/kg/day. Hepatoblastoma is a relatively rare rodent malignant tumor type. There was no increase in total malignant hepatic tumors. The mouse strain used is sensitive to the development of hepatic tumors and the significance of these results to humans is unknown.

Orally administered methylphenidate did not cause any increases in tumors in a lifetime carcinogenicity study carried out in F344 rats; the highest dose used was approximately 45 mg/kg/day.

In a 24-week oral carcinogenicity study in the transgenic mouse strain p53^{+/-}, which is sensitive to genotoxic carcinogens, there was no evidence of carcinogenicity. In this study, male and female mice were fed diets containing the same concentration of methylphenidate as in the lifetime carcinogenicity study; the high-dose groups were exposed to 60 to 74 mg/kg/day of methylphenidate.

Mutagenesis

Methylphenidate was not mutagenic in the *in vitro* Ames reverse mutation assay or in the *in vitro* mouse lymphoma cell forward mutation assay, and was negative *in vivo* in the mouse bone marrow micronucleus assay. Sister chromatid exchanges and chromosome aberrations were increased, indicative of a weak clastogenic response, in an *in vitro* assay in cultured Chinese hamster ovary cells.

Impairment of Fertility

Methylphenidate did not impair fertility in male or female mice that were fed diets containing the drug in an 18-week Continuous Breeding study. The study was conducted at doses up to 160 mg/kg/day.

14 CLINICAL STUDIES

Daytrana was demonstrated to be effective in the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in two (2) randomized double-blind, placebo-controlled studies in children aged 6 to 12 years and one (1) randomized, double-blind, placebo-controlled study in adolescents aged 13 to 17 years who met Diagnostic and Statistical Manual (DSM-IV-TR®) criteria for ADHD. The patch wear time was 9 hours in all three (3) studies.

In Study 1, conducted in a classroom setting, symptoms of ADHD were evaluated by school teachers and observers using the Department Subscale from the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) rating scale which assesses behavior symptoms in the classroom setting. Daytrana was applied for 9 hours before removal. There was a 5-week open-label Daytrana dose optimization phase using dosages of 10, 15, 20, and 30 mg / 9 hours, followed by a 2-week randomized, double-blind, placebo-controlled crossover treatment phase using the optimal patch dose for each patient or placebo. The mean differences between Daytrana and placebo in change from baseline in SKAMP Department Scores were statistically significant in favor of Daytrana beginning at 2 hours and remained statistically significant at all subsequent measured time points through 12 hours after application of the Daytrana patch.

In Study 2, 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 to achieve an optimal regimen over 5 weeks, followed by a 2-week maintenance period using the optimal patch dose for each patient. Symptoms of ADHD were evaluated by the ADHD-Rating Scale (RS)-IV. Daytrana was statistically significantly superior to placebo as measured by the mean change from baseline for the ADHD-RS-IV total score. Although this study was not designed specifically to evaluate dose response, in general there did not appear to be any additional effectiveness accomplished by increasing the patch dose from 20 mg / 9 hours to 30 mg / 9 hours.

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 (RS)-IV. Daytrana was statistically significantly superior to placebo as measured by the mean change from baseline in the ADHD-RS-IV total score.

15 REFERENCES

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Washington, DC: American Psychiatric Association 1994.

16 HOW SUPPLIED/STORAGE AND HANDLING

Daytrana is supplied in a sealed tray or outer pouch containing 30 individually pouched patches. See the chart below for information regarding available strengths.

	Nominal Dose Delivered (mg) Over 9 Hours	Dosage Rate* (mg/hr)	Patch Size (cm²)	Methylphenidate Content per Patch** (mg)	Patches Per Carton	NDC Number
10		1.1	12.5	27.5	30	54092-552-30
15		1.6	18.75	41.3	30	54092-553-30
20		2.2	25	55	30	54092-554-30
30		3.3	37.5	82.5	30	54092-555-30

*Nominal *in vivo* delivery rate in children and adolescents when applied to the hip, based on a 9-hour wear period.

**Methylphenidate content in each patch.

Store at 25° C (77° F); excursions permitted to 15-30° C (59-86° F) [see USP Controlled Room Temperature]. Do not store patches unpouched. Do not store patches in refrigerators or freezers.

Once the sealed tray or outer pouch is opened, use contents within 2 months. Apply the patch immediately upon removal from the individual protective pouch. **For transdermal use only.**

17 PATIENT COUNSELING INFORMATION

See *Medication Guide*

17.1 Information for Patients

Parents and patients should be informed to apply Daytrana to a clean, dry site on the hip, which is not oily, damaged, or irritated. The site of application must be alternated daily. The patch should not be applied to the waistline, or where tight clothing may rub it.

If patients or caregivers experience difficulty separating the patch from the release liner or observe tearing and/or other damage to the patch during removal from the liner, the patch should be discarded according to the directions provided in this label, and a new patch should be applied [see *Dosage and Administration (2.3)*]. Patients or caregivers should inspect the release liner to ensure that no adhesive containing medication has transferred to the liner. If adhesive transfer has occurred, the patch should be discarded.

Daytrana should be applied 2 hours before the desired effect. Daytrana should be removed approximately 9 hours after it is applied, although the effects from the patch will last for several more hours. Daytrana may be removed earlier than 9 hours if a shorter duration of effect is desired or late day side effects appear.

The parent or caregiver should be encouraged to use the administration chart included with each carton of Daytrana to monitor application and removal time, and method of disposal. The Medication Guide included at the end of this insert also includes a timetable to calculate when to remove Daytrana, based on the 9 hour application time.

Patients or caregivers should avoid touching the adhesive side of the patch during application, in order to avoid absorption of methylphenidate. If they do touch the adhesive side of the patch, they should immediately wash their hands after application.

In the event that a patch does not fully adhere to the skin upon application, or is partially or fully detached during wear time, the patch should be discarded according to the directions provided in this label, and a new patch should be applied (*see Dosage and Administration (2.3)*). If a patch is replaced, the total recommended wear time for that day should remain 9 hours, regardless of the number of patches used.

Patches should not be applied or re-applied with dressings, tape, or other common adhesives.

Exposure to water during bathing, swimming, or showering can affect patch adherence.

Do not cut patches. Only intact patches should be applied.

If there is an unacceptable duration of appetite loss or insomnia in the evening, taking the patch off earlier may be attempted before decreasing the patch dose.

Skin redness or itching is common with Daytrana and small bumps on the skin may also occur in some patients. If any swelling or blistering occurs the patch should not be worn and the patient should be seen by the prescriber. Patients or caregivers should not apply hydrocortisone or other solutions, creams, ointments, or emollients immediately prior to patch application, since the effect on patch adhesion and methylphenidate absorption has not been established. The potential adverse effects of topical corticosteroid use during treatment with Daytrana are unknown.

Stimulants may impair the ability of the patient to operate potentially hazardous machinery or vehicles. Patients should be cautioned accordingly until they are reasonably certain that Daytrana does not adversely affect their ability to engage in such activities.

Patches should be stored at 25 degrees Celsius (77 degrees Fahrenheit) with excursions permitted that do not exceed 15 to 30 degrees Celsius (59 to 86 degrees Fahrenheit) [*see How Supplied/Storage and Handling (16)*]. Patients or caregivers should be advised not to store Daytrana in the refrigerator or freezer.

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with Daytrana and should counsel them in its appropriate use. A patient Medication Guide is available for Daytrana. 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.

Manufactured for Shire US Inc., Wayne, PA 19087 by Noven Pharmaceuticals, Inc., Miami, FL 33186.

For more information call 1-800-828-2088 or visit www.daytrana.com.

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This product is covered by US patents including 5,958,446; 6,210,715; 6,348,211.

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