

## Daytrana™ (methylphenidate transdermal system)

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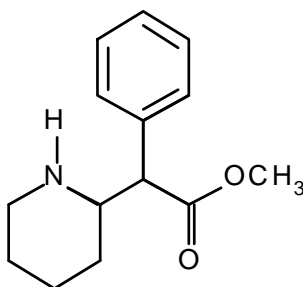
Rx Only

## Daytrana™ (day-TRON-ah)

### Prescribing Information

#### DESCRIPTION

Daytrana™ (methylphenidate transdermal system) is an adhesive-based matrix transdermal system (patch) that is applied to intact skin. The chemical name for methylphenidate is  $\alpha$ -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<sub>14</sub>H<sub>19</sub>NO<sub>2</sub>. The structural formula of methylphenidate is:



#### Patch Components

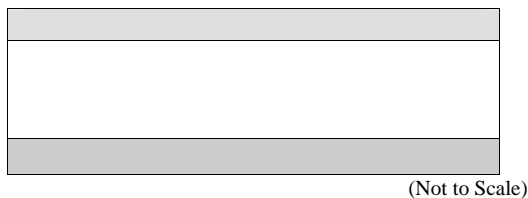
Daytrana™ contains methylphenidate in a multipolymeric adhesive. The methylphenidate is dispersed in acrylic adhesive that is dispersed in a silicone adhesive. The composition per unit area of all dosage strengths is identical, and the total dose delivered is dependent on the patch size and wear time.

Four dosage strengths are available:

Nominal Dose Delivered (mg) Over 9 Hours*	Dosage Rate* (mg/hr)	Patch Size (cm <sup>2</sup> )	Methylphenidate Content per Patch (mg)
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 pediatric subjects aged 6-12 when applied to the hip, based on a 9-hour wear period.

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



- (1) Outside backing
- (2) Adhesive containing methylphenidate
- (3) Protective liner (removed prior to application)

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.

## CLINICAL PHARMACOLOGY

### Pharmacodynamics

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

### Pharmacokinetics

The pharmacokinetics of Daytrana™ when applied to the hip for 9 hours have been studied in ADHD patients 6 to 12 years old.

### Absorption

When Daytrana™ was titrated to effect in the pivotal phase III clinical efficacy study, after at least 6 weeks of therapy with 9 hour wear times when applied to alternating hips, the mean peak *d*-methylphenidate (*d*-MPH) plasma concentration was 39 ng/mL with a range of 0 – 114 ng/mL. These mean peak concentrations varied inversely by age ranging from 25 ng/mL, (range 2 – 80 ng/mL) in 12 year olds, to 53 ng/mL (range 18 – 83 ng/mL) in 6 year olds.

Daytrana™ mean peak *d*-MPH concentrations were approximately 1.9-fold higher than the highest observed concentrations after a once-daily oral methylphenidate formulation over a period of 7.5 to 10.5 hours, when  $T_{max}$  typically occurs. These higher concentrations were observed for all children 6 – 12 years of age, both overall and when grouped by age. The Daytrana™ peak concentrations on chronic dosing were also higher than  $C_{maxs}$  seen with Daytrana™ after single dosing, or 4 days of multiple dosing. With single doses of

Daytrana™, peak concentrations were comparable to  $C_{\max}$  from single doses of the once daily oral MPH formulation.

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 chronic therapy with the methylphenidate transdermal system.

On multiple dosing of the transdermal system, exposure to *l*-methylphenidate was 27% to 45% lower, on average, than exposures to *d*-methylphenidate. For comparison, little if any *l*-methylphenidate was detectable after administration of a once daily oral MPH formulation. *l*-methylphenidate is less pharmacologically active than *d*-methylphenidate.

The average lag time (i.e., the time until any *d*-MPH is detectable in the circulation) was 3.1 hours, (range 1- 6 hours) with Daytrana™ in the single dose study. In the phase II PK/PD study, 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** - Study 1).

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.

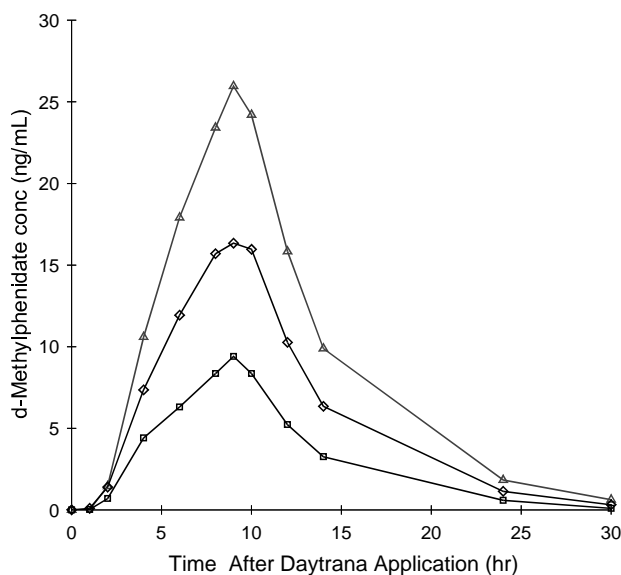
When heat is applied to Daytrana™ after patch application, both the rate and the extent of absorption are significantly increased. Median  $T_{\text{lag}}$  occurs 1 hour earlier and  $T_{\max}$  occurs 0.5 hours earlier, and median  $C_{\max}$  and AUC are 2-fold and 2.5-fold higher, respectively.

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 hour to 30 mg / 9 hour 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 was approximately 3 to 4 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.

### **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.

### **Adhesion**

In a study of 20 mg / 9 hour (25 cm<sup>2</sup>) transdermal systems > 95% of patches were greater than 90% adhered, and the remainder were 75% - 90% adhered. No patients discontinued therapy during clinical trials due to adhesion failure.

In the event 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 (see **DOSAGE AND ADMINISTRATION -- Disposal of Daytrana™**), and a new patch should be applied. If a patch is replaced, the total recommended wear time for that day should remain 9 hours. (see **DOSAGE AND ADMINISTRATION – Application**).

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

### **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 Insufficiency**

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

#### **Hepatic Insufficiency**

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

### **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 old who met Diagnostic and Statistical Manual (DSM-IV-TR®) criteria for ADHD. The patch wear time was 9 hours in both 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.

## **INDICATION AND USAGE**

### **Attention Deficit Hyperactivity Disorder (ADHD)**

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

The efficacy of Daytrana™ was established in two controlled clinical trials in children with ADHD.

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.

### **Special Diagnostic Considerations**

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 child and not solely on the presence of the required number of DSM-IV-TR® characteristics.

### **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 children with this syndrome. Stimulants are not intended for use in the child 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 child’s symptoms.

### **Long-Term Use**

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 (see **DOSAGE AND ADMINISTRATION**).

## **CONTRAINDICATIONS**

### **Agitation**

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

### **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**).

### **Glaucoma**

Daytrana™ is contraindicated in patients with glaucoma.

### **Tics**

Daytrana™ is contraindicated in patients with motor tics or with a family history or diagnosis of Tourette’s syndrome (see **ADVERSE REACTIONS**).

### **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).

### **WARNINGS**

#### **Serious Cardiovascular Events**

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

##### Children and Adolescents

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

##### Adults

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

#### ***Hypertension and Other Cardiovascular Conditions***

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

#### ***Assessing Cardiovascular Status in Patients Being Treated With Stimulant Medications***

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

### Contact Sensitization

Use of Daytrana™ may lead to contact sensitization. Daytrana™ should be discontinued if contact sensitization is suspected. Erythema is commonly seen with use of Daytrana™ and is not by itself an indication of sensitization. However, 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.

A study designed to provoke skin sensitization revealed a signal for Daytrana™ to be an irritant and also a contact sensitizer. This study involved an induction phase consisting of continuous exposure to the same skin site for 3 weeks, followed by a 2 week rest period, and then challenge/rechallenge. Under conditions of the study, Daytrana™ was more irritating than both the placebo patch control and the negative control (saline). Of 133 adult subjects who participated in the challenge phase of the sensitization study, at least 18 (13.5%) were confirmed to have been sensitized to Daytrana™ based on the results of the challenge and/or rechallenge phases of the study. This evaluation methodology employed continuous irritant induction exposure. This evaluation methodology may not be predictive of dermal sensitization in actual clinical use with recommended 9-hour wear times and alternating application sites on the hip.

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.

## **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 0 in placebo-treated patients.

### ***Aggression***

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

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

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

## Seizures

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

## Visual Disturbance

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

## Use in Children Under Six Years of Age

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

## Drug Dependence

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

## PRECAUTIONS

### 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: Pharmacokinetics/Absorption**). This increased absorption can be clinically significant and can result in overdose of methylphenidate (see **OVERDOSAGE**).

### Hematologic Monitoring

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

### Information for Patients

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 (see **DOSAGE AND ADMINISTRATION: Disposal of Daytrana™**), 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 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.

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 (see **DOSAGE AND ADMINISTRATION: Disposal of Daytrana™**), and a new patch should be applied. 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.

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**). 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<sup>TM</sup> (methylphenidate transdermal system) and should counsel them in its appropriate use. A patient Medication Guide is available for Daytrana<sup>TM</sup>. 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.

### **Drug Interactions**

Daytrana<sup>TM</sup> should not be used in patients being treated (currently or within the preceding two weeks) with monoamine oxidase inhibitors (see **CONTRAINDICATIONS-Monoamine Oxidase Inhibitors**).

Because of a possible effect on blood pressure, Daytrana<sup>TM</sup> should be used cautiously with pressor agents.

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

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.

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.

### **Carcinogenesis, Mutagenesis, and Impairment of Fertility**

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<sup>+/-</sup>, 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.

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.

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.

## **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<sup>TM</sup> should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

## **Nursing Mothers**

It is not known whether methylphenidate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised if Daytrana<sup>TM</sup> is administered to a nursing woman.

## **Pediatric Use**

The safety and efficacy of Daytrana™ in children under 6 years old have not been established. Long-term effects of methylphenidate in children have not been well established (see **WARNINGS**).

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.

## **ADVERSE REACTIONS**

The pre-marketing clinical development program for Daytrana™ included exposures in a total of 1,158 participants in clinical trials (758 pediatric patients and 400 healthy adult subjects). These participants received Daytrana™ in patch sizes ranging from 6.25 cm<sup>2</sup> to 50 cm<sup>2</sup>. The 758 pediatric patients (age 6 to 16 years) were evaluated in 9 controlled clinical studies, 2 open-label clinical studies, and 4 clinical pharmacology studies. Adverse reactions were assessed by collecting adverse events data, the results of physical examinations, vital signs, weights, laboratory analyses, and ECGs.

Adverse events 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 events without first grouping similar types of events into a smaller number of standardized event categories. The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

### **Adverse Findings in Clinical Trials With Daytrana™**

#### ***Adverse Events 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 reasons for discontinuation among the patients treated with Daytrana™ were application site erythema, application site reaction, confusional state, crying, tics, headaches, irritability, infectious mononucleosis, and viral infection.

**Adverse Events Occurring at an Incidence of 5% or More Among Patients Treated With Daytrana™**

Table 1 enumerates the incidence of treatment-emergent adverse events reported in a 7 week double-blind, parallel-group, placebo-controlled study in children with ADHD conducted in the outpatient setting.

The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with those obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

**TABLE 1**  
**Most Commonly Reported Treatment-Emergent Adverse Events**  
**(≥ 5% and 2x Placebo) in a 7-week Placebo-controlled Study**

System Organ Class	Number (%) of Subjects Reporting Adverse Events	
Adverse Event	Daytrana™ (N = 98)	Placebo (N = 85)
Number of Subjects With ≥ 1 Adverse Event	74 (76)	49 (58)
<b>Gastrointestinal Disorders</b>		
Nausea	12 (12)	2 (2)
Vomiting	10 (10)	4 (5)
<b>Infections and Infestations</b>		
Nasopharyngitis	5 (5)	2 (2)
<b>Investigations</b>		
Weight decreased	9 (9)	0 (0)
<b>Metabolism and Nutrition Disorders</b>		
Anorexia	5 (5)	1 (1)
Decreased appetite	25 (26)	4 (5)
<b>Psychiatric Disorders</b>		
Affect lability*	6 (6)	0 (0)
Insomnia	13 (13)	4 (5)
Tic	7 (7)	0 (0)
<b>Respiratory</b>		
Nasal congestion	6 (6)	1 (1)

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

### **Skin Irritation**

Daytrana™ is a dermal irritant. The majority of subjects in the pivotal phase III clinical efficacy study had minimal to definite erythema. 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 an indication 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.

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. The subject was not transitioned to oral methylphenidate. Confirmation of a diagnosis of allergic contact dermatitis may require further diagnostic testing (see **WARNINGS – Contact Sensitization**).

### **Adverse Events With the Long-Term Use of Daytrana™**

In a long-term open-label study of up to 40-month duration in 191 children with ADHD, the most frequently reported treatment-emergent adverse events in pediatric patients treated with Daytrana™ for 12 hours daily were anorexia (87 subjects, 46%), insomnia (57 subjects, 30%), viral infection (54 subjects, 28%), and headache (53 subjects, 28%). A total of 45 (24%) subjects were withdrawn from the study because of treatment-emergent adverse events. The most common events leading to withdrawal were application site reaction (12 subjects, 6%), anorexia (7 subjects, 4%), and insomnia (7 subjects, 4%).

### **Adverse Events 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, palpitations, pulse increased or decreased, tachycardia

**Gastrointestinal:** abdominal pain, nausea

**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:*** dizziness, drowsiness, dyskinesia, headache, 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.

## **Postmarketing Reports**

Postmarketing reports of the following events have been reported. 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<sup>TM</sup> exposure.

*Cardiac Disorders:* palpitation

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

*Gastrointestinal Disorders:* abdominal pain

*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:* heart rate increased, blood pressure increased

*Nervous System Disorders:* convulsion, dizziness

*Psychiatric Disorders:* transient depressed mood, hallucination, nervousness

*Skin and Subcutaneous Tissue Disorders:* alopecia

## **DRUG ABUSE AND DEPENDENCE**

### **Controlled Substance Class**

Daytrana<sup>TM</sup> (methylphenidate transdermal system), like other methylphenidate products, is classified as a Schedule II controlled substance by federal regulation.

### **Abuse, Dependence, and Tolerance**

See **WARNINGS-Drug Dependence** for boxed warning containing drug abuse and dependence information.

## **OVERDOSAGE**

### **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.

## 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.

## 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.

## 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 2**  
**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 <sup>2</sup>	18.75 cm <sup>2</sup>	25 cm <sup>2</sup>	37.5 cm <sup>2</sup>
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 in pediatric subjects aged 6-12 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.

## 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. 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. Avoid 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 pouch and removing the protective liner. Do not use if the 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 falls off, a new patch may be applied at a different site, and the total recommended wear time for that day should remain 9 hours regardless of the number of patches used.

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. 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.

## 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.

### **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 pouch, separated from the protective liner, folded onto itself, and flushed down the toilet or disposed of in an appropriate lidded container.

The parent 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, the parent or caregiver should be encouraged to ask the child when and how the patch was removed.

### **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. Nevertheless, the physician who elects to use Daytrana™ for extended periods in patients with ADHD should periodically re-evaluate the long-term usefulness of the drug 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.

### **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.

### **HOW SUPPLIED**

Daytrana™ (methylphenidate transdermal system) is supplied in a sealed tray containing 30 or 10 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 (cm <sup>2</sup> )	Methylphenidate Content per Patch** (mg)	Patches Per Tray	NDC Number
10	1.1	12.5	27.5	30	54092-552-30
				10	54092-552-10
15	1.6	18.75	41.3	30	54092-553-30
				10	54092-553-10
20	2.2	25	55	30	54092-554-30
				10	54092-554-10
30	3.3	37.5	82.5	30	54092-555-30
				10	54092-555-10

\*Nominal *in vivo* delivery rate per hour in pediatric subjects aged 6-12 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 tray is opened, use contents within 2 months. Apply the patch immediately upon removal from the protective pouch. **For transdermal use only.**

## REFERENCE

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

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](http://www.daytrana.com).

**Dot Matrix™ is a trademark of Noven Pharmaceuticals, Inc.**  
**Daytrana™ is a trademark of Shire Pharmaceuticals Ireland Limited.**

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**Rx Only**

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

**Important: Only Use on Skin**

Read the Medication Guide that comes with Daytrana™ before you or your child starts using 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 your or your child's treatment with Daytrana™.

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

**Daytrana™ is a stimulant medicine. The following have been reported with use of Daytrana™ (methylphenidate transdermal system) or 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 has 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 your or your child's blood pressure and heart rate regularly during treatment with Daytrana™.

**Remove patch immediately and 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 using 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 has, or about a family history of suicide, bipolar illness, or depression.

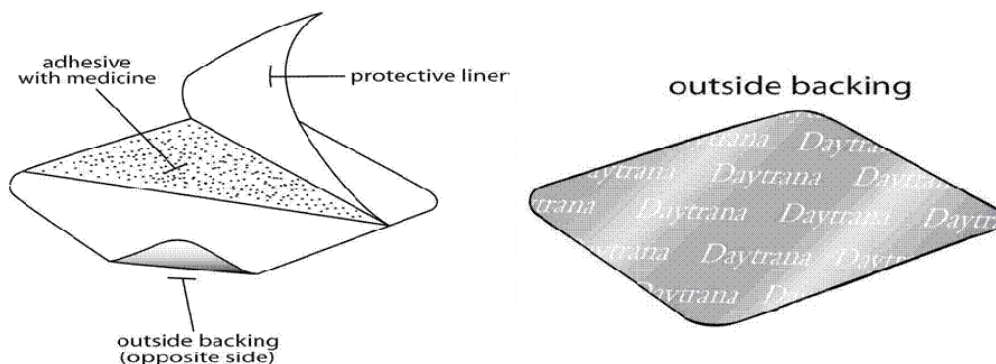
**Call your doctor right away if you or your child has any new or worsening mental symptoms or problems while using Daytrana™, especially seeing or hearing things that are not real, believing things that are not real, or are suspicious.**

**What Is Daytrana™?**

Daytrana™ is a central nervous system (CNS) 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 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.

The Daytrana™ patch has 3 layers. The 3 layers are displayed and described in the figures below. The figures below display both sides of a patch:



- **Protective liner:** the layer that is removed prior to applying the patch to the skin.
- **Adhesive with medicine:** After the protective liner is removed, this is the side of the patch that sticks to the skin.
- **Outside backing:** This is what you will see after the patch is put on the skin. The word “Daytrana™” is printed on this side.

**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 has (or has a family history of) ever abused or been dependent on alcohol, prescription medicines or street drugs.

### Who should not use Daytrana™?

**Daytrana™ should not be used if you or your child:**

- is very anxious, tense, or agitated
- has an eye problem called glaucoma
- has tics or Tourette’s syndrome, or a family history of Tourette’s syndrome. Tics are hard to control repeated movements or sounds.
- is taking or has taken within the past 14 days an anti-depression medicine called a monoamine oxidase inhibitor or MAOI.
- is 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
- 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 used with other medicines?

**Tell your doctor about all of the medicines that you or your child takes 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 using Daytrana™.

Your doctor will decide whether Daytrana™ can be used 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 using Daytrana™ without talking to your doctor first.**

**How should Daytrana™ be used?**

**Do not use hair dryers, heating pads, electric blankets, heated water beds or other heat sources while wearing a Daytrana™ patch. Too much medicine can pass into your 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 a while to check ADHD symptoms.
- Your doctor may do regular checks of the blood, heart, and blood pressure while using Daytrana™. Children should have their height and weight checked often while using 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, remove all patches and 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 is common. 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. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088

### **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.
- Do not store Daytrana™ in the refrigerator or freezer.
- **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.daytrana.com](http://www.daytrana.com).

### **Skin care information about Daytrana™**

Skin redness or itching is common with Daytrana™, and small bumps on the skin may also occur in some patients. If you have any swelling or blistering, the patch should not be worn and you should consult your doctor. Do not apply any medicine, cream, or lotion on the skin at the Daytrana patch site before applying the patch, since this might affect how the patch sticks to the skin and how the medicine is absorbed from the patch.

## **INSTRUCTIONS FOR APPLYING DAYTRANA™ (methylphenidate transdermal system)**

### **1. 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.

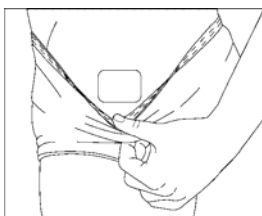
To use the administration chart, follow these instructions:

- 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

If you applied the patch at:	Remove the patch at:
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™

The patch should separate easily from the protective liner. Do not use the patch if the protective liner is difficult to remove.

Look at the patch to make sure it is not damaged or defective in any way. After the protective liner is removed, there should not be any adhesive (glue) sticking to the liner.

**If the patch is damaged, or you have problems removing it from the liner, discard the patch according to the instructions provided below (see How to Remove and Discard Daytrana™), and apply a new one to the child's skin.**

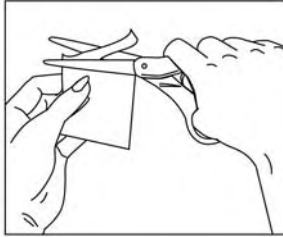
Do not use patches that have been stored in the refrigerator or freezer.

Make sure the child's skin is:

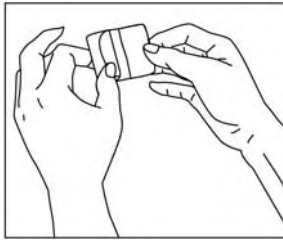
- Clean (freshly washed), dry, and cool.
- Free of any powder, oil, or lotion.
- Free of cuts and irritation (rashes, inflammation, redness, or other skin problems).

#### 4. HOW TO APPLY DAYTRANA™

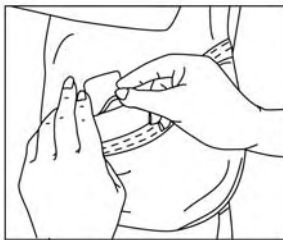
- Open the tray containing Daytrana™ and discard the small packet (drying agent) included in the tray.
- Each patch is sealed in its own protective pouch.
- Carefully cut the protective pouch open with scissors, being careful not to cut the patch. **Do not use patches that have been cut or damaged in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



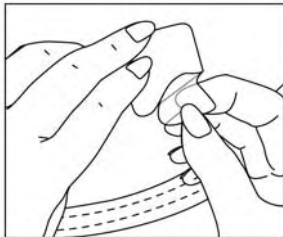
- **Apply the patch right away after removing from pouch.**
- Hold the patch with the rigid protective liner facing you – **the word Daytrana™ will appear backwards.**
- **Gently** bend the patch along the faint line and **slowly peel** half the liner, which covers the sticky surface of the patch.
- Avoid touching the sticky side of the patch with your fingers.
- If you accidentally touch the sticky side of the patch, apply the patch, then wash your hands right away so that you do not absorb the medicine.



- 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, gently fold back the other half of the patch.
- Grasp an edge of the remaining protective liner and **slowly peel** it off.



- Avoid touching the sticky side of the patch with your fingers.
- If you do touch the sticky side of the patch, wash your hands immediately after application.



- **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 the 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 can make the patch not stick well or make it fall off. If a patch falls off, do not touch the sticky side of the patch with your fingers. A new patch may be applied to a different area of the same hip. Patches that fall off should not be re-applied. Do not use bandages, tape, or other household adhesives (glue) to hold the patch on the skin. 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.
- **Do not use hair dryers, heating pads, electric blankets, heated water beds or other heat sources while wearing a Daytrana™ patch. Too much medicine can pass into your or your child's body and cause serious side effects.**

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

- When you remove the patch, peel it off slowly. If needed, patch removal may be helped by gently applying an oil-based product (petroleum jelly, olive oil, or mineral oil) to the patch edges, gently working the oil underneath the patch edges. If any adhesive (glue) remains on the skin after the patch is removed, an oil based product may be applied to patch sites in an effort to gently loosen and remove any leftover adhesive that remains following patch removal.
- In the unlikely event that a patch remains tightly adhered despite these measures, ask your doctor or pharmacist about what to do for this problem.
- 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 it 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<sup>TM</sup> 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 them in a lidded container.**

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

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

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