Daytrana™ (methylphenidate transdermal system) **C II**

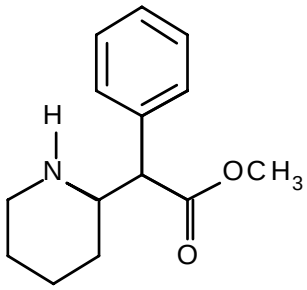
Rx Only

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 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:



Patch Components

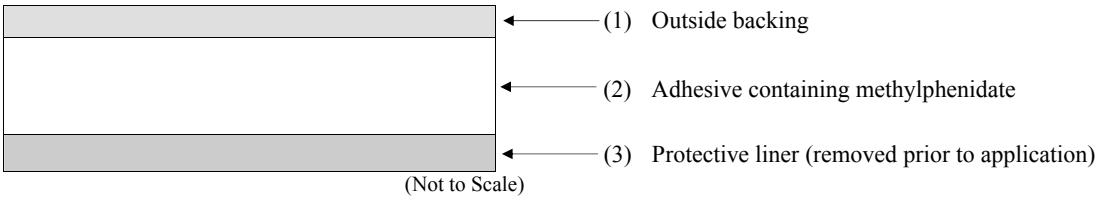
Daytrana™ contains methylphenidate in a multipolymeric adhesive. The methylphenidate is dispersed in acrylic adhesive that is dispersed in a silicone adhesive. The composition per unit area of all dosage strengths is identical, and the total dose delivered is dependent on the patch size and wear time.

Four dosage strengths are available:

Nominal Dose Delivered (mg) Over 9 Hours*	Dosage Rate* (mg/hr)	Patch Size (cm^2)	Methylphenidate Content per Patch (mg)
10	1.1	12.5	27.5
15	1.6	18.75	41.3
20	2.2	25	55.0
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).



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_{maxs} 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.

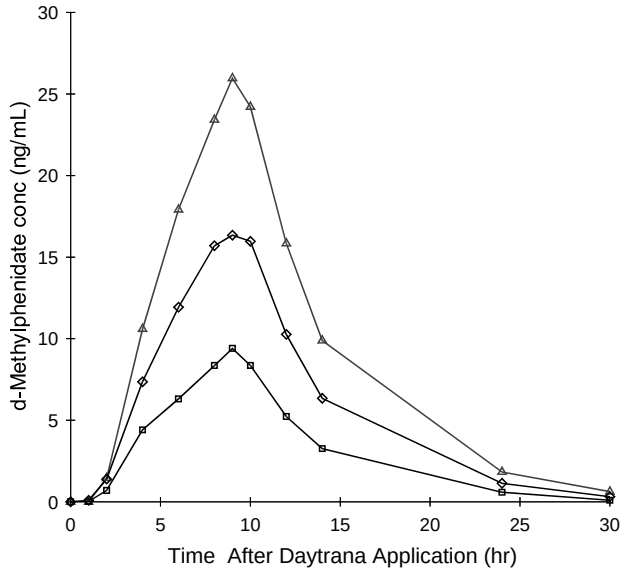
When heat is applied to Daytrana™ after patch application, both the rate and the extent of absorption are significantly increased. Median T_{lag} occurs 1 hour earlier and T_{max} occurs 0.5 hours earlier, and median C_{max} and AUC are 2-fold and 2.5-fold higher, respectively.

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^2) 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.

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 Deportment 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 Deportment Scores were statistically significant in favor of Daytrana™ beginning at 2 hours and remained statistically significant at all subsequent measured timepoints 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

~~Sudden Death and Pre-existing Structural Cardiac Abnormalities~~

~~Sudden death has been reported in association with CNS stimulant treatment at usual doses in children with structural cardiac abnormalities. Although some structural cardiac abnormalities alone may carry an increased risk of sudden death, stimulant products generally~~

~~should not be used in children, adolescents, or adults with known structural cardiac abnormalities.~~

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, sensitization should be suspected if erythema is accompanied by evidence of a more intense local reaction (edema, papules, vesicles) that does not significantly improve within 48 hours or spreads beyond the patch site. Diagnosis of allergic contact dermatitis should be corroborated by appropriate diagnostic testing.

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

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

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

Using Daytrana™ as prescribed, alternating application sites on the hip, no cases of contact sensitization were reported. However, since patients were not specifically assessed for sensitization in the clinical effectiveness studies, it is unknown what the true incidence of sensitization is when Daytrana™ is used as directed.

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.

~~Depression~~

~~Daytrana™ should not be used to treat severe depression.~~

~~Fatigue~~

~~Daytrana™ should not be used for the prevention or treatment of normal fatigue states.~~

Long-Term Suppression of Growth

~~Data are inadequate to determine whether chronic use of stimulants in children, including methylphenidate and amphetamine, may cause suppression of growth. Therefore, growth should be monitored during treatment, and patients who are not growing or gaining weight as expected should have their treatment re-evaluated.~~ 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.

~~Psychosis~~

~~Clinical experience suggests that in psychotic patients, administration of methylphenidate may exacerbate symptoms of behavior disturbance and thought disorder.~~

Seizures

There is some clinical evidence that ~~methylphenidate~~ stimulants may lower the convulsive threshold in patients with prior history of seizures, in patients with prior EEG abnormalities in ~~the~~ absence ~~of a history~~ of seizures, and, very rarely, in patients without a history of seizures and no prior EEG evidence of seizures. ~~Safe concomitant use of anticonvulsants and methylphenidate has not been established.~~ In the presence of seizures, ~~Daytrana™~~ the drug should be discontinued.

~~Hypertension and Other Cardiovascular Disorders~~

~~Use cautiously in patients with hypertension. Blood pressure should be monitored at appropriate intervals in patients using Daytrana™, especially patients with hypertension. Studies of methylphenidate have shown modest increases of resting pulse and systolic and diastolic blood pressure. Therefore, 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 hyperthyroidism.~~

Visual Disturbance

~~Symptoms of visual disturbances have been encountered in rare cases.~~ 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

All patients should be advised to avoid exposing the Daytrana™ application site to direct external heat sources, such as heating pads, electric blankets, heated water beds, etc., while wearing the patch. There is a potential for temperature-dependent increases in methylphenidate release of greater than 2-fold from the patch.

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.

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 patient information included at the end of this insert also includes a timetable to calculate when to remove Daytrana™, based on the 9 hour application time.

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 size.

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.

Patient information is printed at the end of this insert. To assure safe and effective use of Daytrana™, the patient information should be discussed with patients.

Drug Interactions

Daytrana™ 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™ 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 $p53^{+/-}$, 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™ 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™ 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^2 to 50 cm^2. 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)
Gastrointestinal Disorders		
Nausea	12 (12)	2 (2)
Vomiting	10 (10)	4 (5)
Infections and Infestations		
Nasopharyngitis	5 (5)	2 (2)
Investigations		
Weight decreased	9 (9)	0 (0)
Metabolism and Nutrition Disorders		
Anorexia	5 (5)	1 (1)
Decreased appetite	25 (26)	4 (5)
Psychiatric Disorders		
Affect lability*	6 (6)	0 (0)
Insomnia	13 (13)	4 (5)
Tic	7 (7)	0 (0)
Respiratory		
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. If erythema, edema, and/or papules do not resolve or significantly reduce within 24 hours after patch removal, further evaluation should be sought. Erythema is not by itself an indication of contact sensitization. However, sensitization should be considered if erythema is accompanied by edema, papules, vesicles, or other evidence of more intense local reactions. Diagnosis of allergic contact dermatitis should be corroborated by appropriate 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.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

Daytrana™ (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 overdosage, 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™ overdosage has not been established.

Poison Control Center

As with the management of all overdosages, 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 overdosage 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^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 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 patient information 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.

Daytrana™ should be applied immediately after opening the pouch and removing the protective liner. Do not use if the pouch seal is broken. 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. After proper application, bathing, swimming, or showering have not been shown to affect patch adherence. In the unlikely event that a patch should fall off, a new patch may be applied at a different site, but the total recommended wear time for that day should remain 9 hours.

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^2)	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	55.0	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.

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

Once the tray is opened, use contents within 2 months. Apply the patch immediately upon removal from the protective pouch. Do not store patches unpouched. **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.shire.com.

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INFORMATION FOR PARENTS OR CAREGIVERS USING DAYTRANA™ (METHYLPHENIDATE TRANSDERMAL SYSTEM) ON A CHILD FOR THE TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)

INTRODUCTION

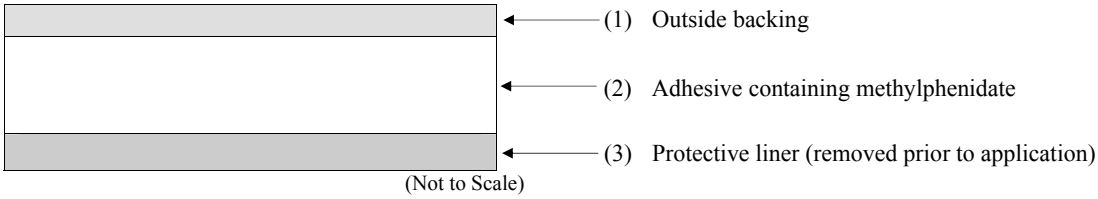
This information is for parents or caregivers using Daytrana™ on a child for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

Please read this before using Daytrana™. Remember, this information does not take the place of your doctor's instructions. If you have any questions about this information or about Daytrana™, talk to your doctor or pharmacist.

WHAT IS DAYTRANA™?

Daytrana™ is a once daily treatment for ADHD containing the drug methylphenidate, a central nervous system (CNS) stimulant. Daytrana™ is applied to the hip area in the morning and is worn for approximately 9 hours. It can be removed earlier if a shorter duration of effect is desired or late day side effects appear.

The patch system consists of three layers, as seen in the figure below (cross-section of the patch). The protective liner is removed prior to application of the patch.



(Not to Scale)

WHAT IS ATTENTION DEFICIT HYPERACTIVITY DISORDER?

ADHD is a condition that affects approximately 3% to 7% of school-aged children.

The three main symptoms of ADHD are inattention, hyperactivity, and impulsivity. Those with ADHD may have difficulty in school or at work, troubled relationships with family and peers, and low self-esteem.

If you have any questions, please see your doctor.

HOW DOES DAYTRANA™ WORK?

Daytrana™ contains methylphenidate. When applied to the skin as directed below, Daytrana™ releases methylphenidate, which flows through the skin and into the bloodstream.

WHO SHOULD NOT USE DAYTRANA™?

Daytrana™ should not be used if the child:

- Has significant anxiety, tension, or agitation, since methylphenidate may make these conditions worse.
- Has allergies to methylphenidate or other ingredients in Daytrana™.
- Has glaucoma, an eye disease.
- Is currently taking a monoamine oxidase inhibitor (MAOI), a treatment for depression, or has discontinued a MAOI in the last 14 days.
- Has motion or verbal tics or Tourette's syndrome, or a family history of Tourette's syndrome.

A Daytrana™ patch should not be placed on an open wound or cut or skin that is red or irritated.

Daytrana™ may be irritating to the skin of some individuals (including those with eczema, psoriasis, seborrheic dermatitis, or sensitivities to the ingredients in soaps, lotions, cosmetics, or adhesives). Your doctor will decide if the child should continue treatment if skin irritation occurs.

Talk to your doctor if you believe any of the above conditions apply to the child.

WHAT ARE THE POSSIBLE SIDE EFFECTS OF DAYTRANA™?

In the clinical studies with patients using Daytrana™, the most common side effects were decreased appetite, sleeplessness, sadness/crying, twitching, weight loss, nausea, vomiting, nasal congestion, inflammation of the nasal passages, and irritation (redness, itching) at site of application. Other side effects seen with methylphenidate, the active ingredient of Daytrana™, include dizziness, headache, fever, drowsiness, nervousness, allergic reactions, increased blood pressure, and psychosis (abnormal thinking or hallucinations).

Dependence

Abuse of methylphenidate can lead to dependence. Tell your doctor if the child has ever abused or been dependent on alcohol or drugs, or if the child is now abusing or dependent on alcohol or drugs.

Blurred Vision

Tell your doctor if the child has blurred vision when taking Daytrana™. This could be a sign of a serious problem.

Slower Growth

Slower growth (weight gain and/or height) has been reported with long-term use of methylphenidate in children. Your doctor will be carefully watching the child's height and weight. If the child is not growing or gaining weight as your doctor expects, your doctor may re-evaluate the child's Daytrana™ treatment.

Skin Irritation and Skin Rash

The majority of patients in the clinical trials experienced no or mild skin irritation at the application site. Mild irritation was defined as slight redness. For the majority, this mild irritation dissipated over time.

Daytrana™ may be irritating to the skin or cause an allergic skin rash. Tell your doctor about any skin rash that develops in areas where Daytrana™ has been applied. Your doctor will need to determine if the rash is irritation or an allergic skin rash. Your doctor will decide if treatment should continue if a skin rash occurs, either with Daytrana™ or methylphenidate in oral form. It is possible that some patients who develop an allergic sensitivity to methylphenidate as a result of taking Daytrana™ may not be able to take methylphenidate in any form.

This is not a complete list of possible side effects. Ask your doctor about other side effects. If the child develops any side effects, talk to your doctor.

WHAT MUST I DISCUSS WITH MY DOCTOR BEFORE USING DAYTRANA™?

Tell your doctor about any heart conditions the child or a family member of the child may have. Inform your doctor ***immediately*** if the child develops symptoms that suggest heart problems, such as chest pain or fainting.

Also tell ~~Talk to~~ your doctor ***before*** using Daytrana™ if the child:

- Is being treated for depression or has symptoms of depression, such as feelings of sadness, worthlessness, and hopelessness.
- Is being treated for or has symptoms of bipolar disorder.
- Has motion tics (hard-to-control, repeated twitching of any parts of his or her body) or verbal tics (hard-to-control, repeating sounds or words).
- Has someone in his or her family with motion tics, verbal tics, or Tourette's syndrome.
- Has abnormal thoughts or visions, hears abnormal sounds, or has been diagnosed with psychosis.
- Has had seizures (convulsions, epilepsy) or abnormal electroencephalograms (EEGs).
- Has high blood pressure or a history of high blood pressure.
- Exhibits aggressive behavior or hostility.

Tell your doctor ***immediately*** if the child develops any of the above conditions or symptoms while using Daytrana™.

CAN DAYTRANA™ BE USED WITH OTHER MEDICINES?

Before starting Daytrana™, be sure to tell your doctor about any and all medications being taken by the child while using Daytrana™, including herbal and over-the-counter products. Your physician will decide whether or not Daytrana™ can be used with other medications.

Make sure you tell your physician about:

- Other medications that have been prescribed.
- Medications that are bought without a prescription, such as those used for colds, allergies, or a stuffy nose.
- Any herbal medications.

Tell your physician if the child is sexually active, is pregnant, or plans to breast feed.

MONOAMINE OXIDASE INHIBITORS (MAOI)

Daytrana™ should not be taken while using a prescription monoamine oxidase inhibitor (MAOI) or within 14 days of stopping a MAOI. If you do not know if the child's prescription contains an MAOI, ask your physician or pharmacist before applying Daytrana™ on the child.

OTHER IMPORTANT SAFETY INFORMATION

Pregnancy and Nursing

Before using Daytrana™, tell your doctor if the child is pregnant or is sexually active. If the child takes methylphenidate, it may be in her breast milk. Tell the doctor if the child is nursing a baby.

External Heat

Avoid applying heating pads or any external heat to Daytrana™.

Overdose

Call your doctor ***immediately*** if the child uses more Daytrana™ than prescribed by your doctor.

HOW LONG SHOULD DAYTRANA™ BE USED?

Daytrana™ is a once-daily patch for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). It is applied in the morning and should be worn by the child for approximately 9 hours. Your doctor may change the amount of time Daytrana™ is worn to help manage how long the medication works each day and some of the side effects that may

be caused by methylphenidate. If the patch is worn for longer than the recommended 9 hours, methylphenidate-induced side effects such as insomnia may occur with greater frequency in some children.

WHAT ELSE SHOULD I KNOW ABOUT DAYTRANA™?

Daytrana™ has not been studied in children under 6 years of age.

Daytrana™ may be a part of an overall treatment for ADHD. Your doctor may also recommend that the child have counseling or other therapy.

As with all medicines, never share Daytrana™ with anyone else and use only the number of patches prescribed by your doctor for the child.

Daytrana™ should be stored at room temperature (about 25º C [77º F]). Once the tray has been opened, use patches within 2 months. Discard unused patches as described above.

Keep this and all medicines out of reach of children. In case of overdose, remove the patch(es) and call your doctor, hospital, or poison control center immediately.

APPLICATION INSTRUCTIONS FOR 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 approximately 9 hours.

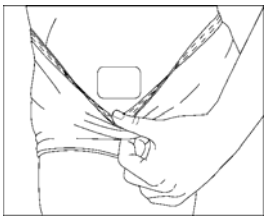
To use the administration chart, follow these instructions:

- 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 (see additional instructions in this insert), 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 opposite hip. Make sure there is no irritation at the site where the patch is going to be applied.

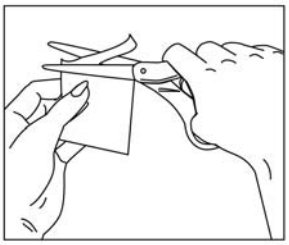
3. BEFORE YOU APPLY DAYTRANA™

Make sure the child's skin is:

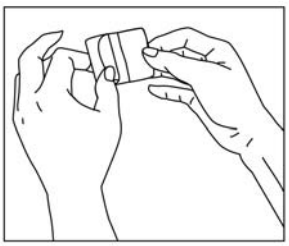
- Clean (freshly washed), dry, and cool.
- Free of any powder, oil, or lotion.
- Free of cuts and/or irritation (rashes, inflammation, redness, or other skin problems).

4. HOW TO APPLY DAYTRANA™

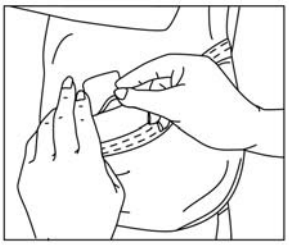
- Open the tray containing Daytrana™ and discard the desiccant (drying agent) included in the tray.
- Each patch is individually sealed in a protective pouch.
- Carefully cut the protective pouch open with scissors, being careful not to cut the patch. Do not use patches that have been cut or damaged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



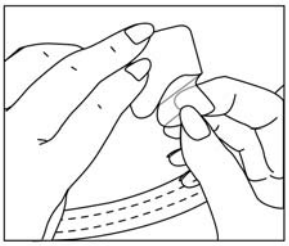
- **Apply the patch immediately after removing from pouch**.
- Holding the patch with the rigid protective liner facing you, remove **half** of the liner, which covers the sticky surface of the patch.
- Avoid touching the sticky side of the patch with your fingers.



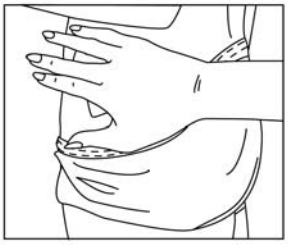
- Using the other half of the protective liner as a handle, apply the sticky side of the patch to the selected area of the child's hip.
- Press the sticky side of the patch firmly into place and smooth it down.



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



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



- Press the entire patch firmly into place with the palm of your hand over the patch, for approximately 30 seconds.
- Make sure that the patch is firmly adhered 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:

- After proper application, contact with water while bathing, swimming, or showering should not affect the patch or make it fall off.
- In the unlikely event that a patch should fall off, avoid touching the sticky side of the patch with your fingers. If this occurs, a new patch may be applied to a different area of the same hip. If a new patch is applied it is recommended that it be removed 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 possibility of later day side effects. You can use the timetable above to know when to remove the patch.

5. HOW TO REMOVE AND DISCARD DAYTRANA™

- When you remove the patch, peel it off slowly.
- Fold the used Daytrana™ patch in half and press firmly so that the sticky side sticks to itself. **Flush the used patch down the toilet or dispose of in an appropriate lidded container right away.**
- Do not flush the pouches or the protective liners down the toilet. These items should be thrown away in an appropriate lidded container.
- If any adhesive residue 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

- **PLEASE KEEP PATCHES OUT OF REACH OF CHILDREN**.
- Throw away any unused Daytrana™ patches that are left over from the prescription as soon as they are no longer needed. Remove the leftover patches from their protective pouches and remove the protective liners. **Fold the patches in half with the sticky sides together, and flush the patches down the toilet or dispose of in an appropriate lidded container.**

This leaflet provides a summary of the most important information about Daytrana™ and methylphenidate. If you want more information, ask your doctor or pharmacist to show you the professional labeling.

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.shire.com.

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