

Key Prescription Stimulant Label Updates

The following tables provide comparisons of the more significant updates FDA is requiring to ensure that the prescribing information concerning the serious risks of misuse, abuse, addiction, and sharing of these medications with those for whom they are not prescribed is consistent across the entire class of prescription stimulant medicines. These updates will align labels with recent labeling language, address diversion and stigmatization, and incorporate recent safety changes. The “Former” column contains current language, with removals shown by red-lined text. The “New” column shows updated language in **bold in the “New” column** and will be added to the Boxed Warning (Table 1), Warnings and Precautions (Table 2), Drug Abuse and Dependence (Table 3), Overdosage (Table 4), and Patient Counseling Information (Table 5).

*NOTE: There are different versions of the example language across the stimulant class. Other minor updates were incorporated within this action but are not listed below and will be available once the label updates for each product are approved by FDA.

Table 1. Boxed Warning	
Former*	New
<p>POTENTIAL for ABUSE AND DEPENDENCE</p> <p>CNS stimulants, including [DRUG-X], other amphetamine-containing products, and methylphenidate, have high potential for abuse and dependence. Assess the risk of abuse prior to prescribing and monitor for signs of abuse and dependence while on therapy [see WARNING AND PRECAUTIONS (5.1) and DRUG ABUSE AND DEPENDENCE (9.2, 9.3)].</p>	<p>WARNING: ABUSE, MISUSE, AND ADDICTION</p> <p>DRUG-X has a high potential for abuse and misuse, which can lead to the development of a substance use disorder, including addiction. Misuse and abuse of CNS stimulants, including DRUG-X, can result in overdose and death [see Overdosage (10)], and this risk is increased with higher doses or unapproved methods of administration, such as snorting or injection.</p> <p>Before prescribing DRUG-X, assess each patient’s risk for abuse, misuse, and addiction. Educate patients and their families about these risks, proper storage of the drug, and proper disposal of any unused drug. Throughout DRUG-X treatment, reassess each patient’s risk of abuse, misuse, and addiction and frequently monitor for signs and symptoms of abuse, misuse, and addiction [see Warnings and Precautions (5.1) and Drug Abuse and Dependence (9.2)].</p>

Table 2. Warnings and Precautions	
Former*	New
<p>Potential for Abuse and Dependence</p> <p>CNS stimulants, including DRUG-X, other methylphenidate-containing products, and amphetamines, have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing, and monitor for signs of abuse and</p>	<p>Abuse, Misuse, and Addiction</p> <p>DRUG-X has a high potential for abuse and misuse. The use of DRUG-X exposes individuals to the risks of abuse and misuse, which can lead to the development of a substance use disorder, including addiction. DRUG-X can be diverted for</p>

<p>dependence while on therapy [see Boxed Warning, Drug Abuse and Dependence (9.2, 9.3)].</p>	<p>non-medical use into illicit channels or distribution [see Drug Abuse and Dependence (9.2)]. Misuse and abuse of CNS stimulants, including DRUG-X, can result in overdose and death [see Overdosage (10)], and this risk is increased with higher doses or unapproved methods of administration, such as snorting or injection.</p> <p>Before prescribing DRUG-X, assess each patient’s risk for abuse, misuse, and addiction. Educate patients and their families about these risks and proper disposal of any unused drug. Advise patients to store DRUG-X in a safe place, preferably locked, and instruct patients to not give DRUG-X to anyone else. Throughout DRUG-X treatment, reassess each patient’s risk of abuse, misuse, and addiction and frequently monitor for signs and symptoms of abuse, misuse, and addiction.</p>
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Table 3. Drug Abuse and Dependence

Former*	New
<p>CNS stimulants, including DRUG-X, other amphetamines, and methylphenidate-containing products have a high potential for abuse. Abuse is the intentional non-therapeutic use of a drug, even once, to achieve a desired psychological or physiological effect. Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use (e.g., continuing drug use despite harmful consequences, giving a higher priority to drug use than other activities and obligations), and possible tolerance or physical dependence. Both abuse and misuse may lead to addiction, and some individuals may develop addiction even when taking [DRUG-X] as prescribed.</p> <p>Signs and symptoms of CNS stimulant abuse may include increased heart rate, respiratory rate, blood pressure, and/or sweating, dilated pupils, hyperactivity, restlessness, insomnia, decreased appetite, loss of coordination, tremors, flushed skin, vomiting, and/or abdominal pain. Anxiety, psychosis, hostility, aggression, and suicidal or homicidal ideation have also been observed.</p>	<p>DRUG-X has a high potential for abuse and misuse which can lead to the development of a substance use disorder, including addiction [see Warnings and Precautions (5.1)]. DRUG-X can be diverted for non-medical use into illicit channels or distribution.</p> <p>Abuse is the intentional non-therapeutic use of a drug, even once, to achieve a desired psychological or physiological effect. Misuse is the intentional use, for therapeutic purposes, of a drug by an individual in a way other than prescribed by a health care provider or for whom it was not prescribed. Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use (e.g., continuing drug use despite harmful consequences, giving a higher priority to drug use than other activities and obligations), and possible tolerance or physical dependence.</p> <p>Misuse and abuse of [insert active ingredient] may cause increased heart rate, respiratory rate, or blood pressure; sweating; dilated pupils;</p>

<p>Individuals who abuse CNS stimulants may chew, snort, inject, or use other unapproved routes of administration, which can result in overdose and death [see OVERDOSAGE (10)].</p> <p>To reduce the abuse of [DRUG-X], assess the risk of abuse prior to prescribing. After prescribing, keep careful prescription records, educate patients and their families about abuse and on proper storage and disposal of CNS stimulants, monitor for signs of abuse while on therapy, and re-evaluate the need for [DRUG-X] use.</p>	<p>hyperactivity; restlessness; insomnia; decreased appetite; loss of coordination; tremors; flushed skin; vomiting; and/or abdominal pain. Anxiety, psychosis, hostility, aggression, and suicidal or homicidal ideation have also been observed with CNS stimulants abuse and/or misuse. Misuse and abuse of CNS stimulants, including DRUG-X, can result in overdose and death [see Overdosage (10)], and this risk is increased with higher doses or unapproved methods of administration, such as snorting or injection.</p>
<p><u>Physical Dependence</u> [DRUG-X] may produce physical dependence from continued therapy. Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug.</p> <p>Withdrawal symptoms after abrupt cessation following prolonged high-dosage administration of CNS stimulants include dysphoric mood; depression; fatigue; vivid, unpleasant dreams; insomnia or hypersomnia; increased appetite; and psychomotor retardation or agitation.</p> <p><u>Tolerance</u> [DRUG-X] may produce tolerance from continued therapy. Tolerance is a physiological state characterized by a reduced response to a drug after repeated administration (i.e., a higher dose of a drug is required to produce the same effect that was once obtained at a lower dose).</p>	<p><u>Physical Dependence</u> DRUG-X may produce physical dependence. Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug.</p> <p>Withdrawal signs and symptoms after abrupt discontinuation or dose reduction following prolonged use of CNS stimulants including DRUG-X include dysphoric mood; depression; fatigue; vivid, unpleasant dreams; insomnia or hypersomnia; increased appetite; and psychomotor retardation or agitation.</p> <p><u>Tolerance</u> DRUG-X may produce tolerance. Tolerance is a physiological state characterized by a reduced response to a drug after repeated administration (i.e., a higher dose of a drug is required to produce the same effect that was once obtained at a lower dose).</p>

Table 4. Overdosage

Former*	New (reordered information)
<p>Manifestations of amphetamine overdose include restlessness, tremor, hyperreflexia, rapid respiration, confusion, assaultiveness, hallucinations, panic states, hyperpyrexia, and rhabdomyolysis. Fatigue and depression usually follow the central nervous system stimulation. Serotonin syndrome has been reported with amphetamine use.</p>	<p><u>Clinical Effects of Overdose</u> Overdose of CNS stimulants is characterized by the following sympathomimetic effects: <ul style="list-style-type: none"> • Cardiovascular effects including tachyarrhythmias, and hypertension or hypotension. Vasospasm, myocardial infarction, or aortic dissection may precipitate sudden </p>

<p>Cardiovascular effects include arrhythmias, hypertension or hypotension and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning is usually preceded by convulsions and coma.</p> <p>Remove all transdermal systems immediately and cleanse the area(s) to remove any remaining adhesive. The continuing absorption of dextroamphetamine from the skin, even after removal of the transdermal system, should be considered when treating patients with overdose.</p> <p>Dextroamphetamine is not dialyzable. (<i>moved to Overdose Management</i>)</p> <p><u>Management of Overdose</u> Consult with a Certified Poison Control Center (1-800-222-1222) for up-to-date guidance and advice on the management of overdosage with methylphenidate. Provide supportive care, including close medical supervision and monitoring. Treatment should consist of those general measures employed in the management of overdosage with any drug. Consider the possibility of multiple drug overdoses. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. Use supportive and symptomatic measures. Individual patient response to amphetamines varies widely. Toxic symptoms may occur idiosyncratically at low doses.</p>	<p>cardiac death. Takotsubo cardiomyopathy may develop.</p> <ul style="list-style-type: none"> •CNS effects including psychomotor agitation, confusion, and hallucinations. Serotonin syndrome, seizures, cerebral vascular accidents, and coma may occur. •Life-threatening hyperthermia (temperatures greater than 104°F) and rhabdomyolysis may develop. <p><u>Overdose Management</u> Treatment for CNS stimulant overdose should consist of those general measures employed in the management of overdose with any drug. Consider the possibility of multiple drug ingestion. [[for amphetamines state: D-amphetamine is not dialyzable] [for methylphenidate state: Because methylphenidate has a large volume of distribution and is rapidly metabolized, dialysis is not useful]]. Consider contacting the Poison Help line (1-800-222-1222) or a medical toxicologist for additional overdose management recommendations.</p>
<p><u>Disposal</u> Comply with local laws and regulations on drug disposal of CNS stimulants. Dispose of remaining, unused, or expired [DRUG-X] by a medicine take-back program or at authorized collector registered with the Drug Enforcement Administration. If no take-back program or authorized collector is available, each unused system should be removed from its individual pouch, separated from the protective liner, folded in half, and disposed of in the same manner as used systems.</p>	<p>(Disposal text removed)</p>

Table 5. Patient Counseling Information

Former*	New (added misuse and diversion information)
<p data-bbox="203 233 740 296">Advise the patient to read the FDA-approved patient labeling (Medication Guide).</p> <p data-bbox="203 342 776 405"><u>Controlled Substance Status/High Potential for Abuse and Dependence</u></p> <p data-bbox="203 411 797 867">Advise patients that [DRUG-X] are controlled substances, and they can be abused and lead to dependence. Instruct patients that they should not give [DRUG-X] to anyone else. Advise patients to store [DRUG-X] in a safe place, preferably locked, to prevent abuse. Advise patients to comply with laws and regulations on drug disposal. Advise patients to dispose of remaining, unused, or expired [DRUG-X] by a medicine take-back program if available [see Boxed Warning, Warnings and Precautions (5.1), Drug Abuse and Dependence (9.1, 9.2, 9.3), How Supplied/Storage and Handling (16)].</p>	<p data-bbox="821 233 1359 296">Advise the patient to read the FDA-approved patient labeling (Medication Guide).</p> <p data-bbox="821 342 1183 369"><u>Abuse, Misuse, and Addiction</u></p> <p data-bbox="821 375 1406 688">Educate patients and their families about the risks of abuse, misuse, and addiction of DRUG-X, which can lead to overdose and death, and proper disposal of any unused drug [see Warnings and Precautions (5.1), Drug Abuse and Dependence (9.2), and Overdosage (10)]. Advise patients to store DRUG-X in a safe place, preferably locked, and instruct patients to not give DRUG-X to anyone else.</p>

NOTE: FDA defines *misuse* as the intentional use, for therapeutic purposes, of a drug in a manner other than as prescribed or by an individual for whom it was not prescribed. FDA defines *abuse* as the intentional, nontherapeutic use of a drug for its desirable psychological or physiological effects. The term *abuse* is used in this document to describe a specific behavior that confers a risk of adverse health outcomes; it is not intended to imply moral judgment. FDA is committed to reducing stigma, expanding therapeutic options, and ensuring access to evidence-based treatment for individuals with substance use disorders.