HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use SYNDROS safely and effectively. See full prescribing information for SYNDROS.

SYNDROS (dronabinol) oral solution, CX
Initial U.S. Approval: 1985

INDICATIONS AND USAGE

SYNDROS is a cannabinoid indicated in adults for the treatment of:

- anorexia associated with weight loss in patients with AIDS (1); and
- nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments. (1)

DOSAGE AND ADMINISTRATION

Administration (2.1):

- Always use the enclosed calibrated oral dosing syringe.
- The calibrated oral syringe measures a maximum SYNDROS dose of 5 mg. If the prescribed dose is greater than 5 mg, the total dose will need to be divided and drawn up in two or more portions using the oral syringe.
- Take SYNDROS with a full glass of water (6 to 8 ounces).

Anorexia Associated with Weight Loss in Adult Patients with AIDS (2.2):

- The recommended starting dosage is 2.1 mg orally twice daily, one hour before lunch and dinner.
- See the full prescribing information for dosage titration to manage adverse reactions and to achieve desired therapeutic effect

Nausea and Vomiting Associated with Chemotherapy in Adult Patients Who Failed Conventional Antiemetics (2.3):

- The recommended starting dosage is 4.2 mg/m^2, administered 1 to 3 hours prior to chemotherapy, then every 2 to 4 hours after chemotherapy for a total of 4 to 6 doses per day. Administer the first dose on an empty stomach at least 30 minutes prior to eating; subsequent doses can be taken without regard to meals.
- See the full prescribing information for dosage titration to manage adverse reactions and to achieve desired therapeutic effect.

DOSAGE FORMS AND STRENGTHS

Oral Solution: 5 mg/ mL (3)

CONTRAINDICATIONS

Patients:

- with a sensitivity to dronabinol or alcohol. (4)
- with a history of hypersensitivity reaction to alcohol. (4)
- who are receiving, or have received, disulfiram- or metronidazole-containing products within the past 14 days. (4, 5.3, 7.1)

WARNINGS AND PRECAUTIONS

- Neurological Adverse Reactions: May cause psychiatric and cognitive effects and impair mental and/or physical abilities. Avoid use in patients with a psychiatric history. Monitor for symptoms and avoid concomitant use of drugs with similar effects. Inform patients not to operate motor vehicles or other dangerous machinery until they are reasonably certain that SYNDROS does not affect them adversely. (5.1)
- Hemodynamic Instability: Patients with cardiac disorders may experience hypotension, hypertension, syncope or tachycardia. Avoid concomitant use of drugs with similar effects and monitor for hemodynamic changes after initiating or increasing the dosage of SYNDROS. (5.2)
- Interaction with Disulfiram and Metronidazole: May cause disulfiram-like reaction. Discontinue products containing disulfiram or metronidazole at least 14 days before and do not administer 7 days after treatment with SYNDROS. (4, 5.3, 7.1)
- Seizures and Seizure-like Activity: Weigh the potential risk versus benefits before prescribing SYNDROS to patients with a history of seizures, including those requiring anti-epileptic medication or with other factors that lower the seizure threshold. Monitor patients and discontinue if seizures occur. (5.4)
- Multiple Substance Abuse: Assess risk for abuse or misuse in patients with a history of substance abuse or dependence, prior to prescribing SYNDROS and monitor for the development of associated behaviors or conditions (5.5)
- Paradoxical Nausea, Vomiting, or Abdominal Pain: Consider dose reduction or discontinuation, if worsening of symptoms while on treatment. (5.6)
- Toxicities Related to Propylene Glycol in Preterm Neonates: The safety and effectiveness of SYNDROS have not been established in pediatric patients. Avoid use in preterm neonates in the immediate postnatal period. (5.7)

ADVERSE REACTIONS

Most common adverse reactions are dizziness, euphoria, paranoid reaction, somnolence, thinking abnormal, abdominal pain, nausea and vomiting. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Insys Therapeutics, Inc. at 1-855-978-2797 or FDA at MedWatch phone number 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- Inhibitors and Inducers of CYP2C9 and CYP3A4: May alter dronabinol systemic exposure; monitor for dronabinol-related adverse reactions or loss of efficacy. (7.2)
- Highly Protein-Bound Drugs: Potential for displacement of other drugs from plasma proteins; monitor for adverse reactions to concomitant narrow therapeutic index drugs (e.g., warfarin, cyclosporine, or amphotericin B) when initiating or increasing the dosage of SYNDROS. (7.3)

USE IN SPECIFIC POPULATIONS

- Pregnancy: May cause fetal harm. (8.1)
- Lactation: Advise HIV infected women not to breastfeed and women with nausea and vomiting associated with cancer chemotherapy not to breastfeed during treatment with SYNDROS and for 9 days after the last dose. (8.2)
- Geriatric Use: Elderly patients may be more sensitive to the neurological, psychoactive, and postural hypotensive effects. Consider a lower starting dose in elderly patients. (2.2, 2.3, 5.1, 5.2, 8.5)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 07/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

Reference ID: 3954181

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

SYNDROS is indicated in adults for the treatment of:

- anorexia associated with weight loss in patients with Acquired Immune Deficiency Syndrome (AIDS); and
- nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

- Always use the enclosed calibrated oral dosing syringe when administering SYNDROS to ensure the dose is measured and administered accurately.
- The calibrated oral syringe measures a maximum SYNDROS dose of 5 mg. If the prescribed dose is greater than 5 mg, the total dose will need to be divided and drawn up in two or more portions using the oral syringe.
- Take each dose of SYNDROS with a full glass of water (6 to 8 ounces).
- For information on dosing SYNDROS with regard to meals, *see Dosage and Administration 2.2 and 2.3.*

2.2 Anorexia Associated with Weight Loss in Adult Patients with AIDS

Adults

Starting Dosage

The recommended adult starting dosage of SYNDROS is 2.1 mg orally twice daily, one hour before lunch and one hour before dinner.

In elderly patients, consider initiating SYNDROS at 2.1 mg once daily one hour before dinner or at bedtime to reduce the risk of central nervous system (CNS) symptoms *[see Use in Specific Populations (8.5)]*.

Dosing later in the day may reduce the frequency of Central Nervous System (CNS) adverse reactions. CNS adverse reactions are dose-related *[see Warnings and Precautions (5.1)]*; therefore monitor patients and reduce the dosage as needed. If CNS adverse reactions of feeling high, dizziness, confusion, and somnolence occur, they usually resolve in 1 to 3 days and usually do not require dosage reduction. If CNS adverse reactions are severe or persistent, reduce the dose to 2.1 mg once daily one hour before dinner or in the evening at bedtime.

Dosage Titration

- If tolerated and further therapeutic effect is desired, the dosage may be increased gradually to 2.1 mg one hour before lunch and 4.2 mg one hour before dinner. Increase the dose of SYNDROS gradually in order to reduce the frequency of dose-related adverse reactions *[see Warnings and Precautions (5.1)]*.
- Most patients respond to 2.1 mg twice daily, but the dose may be further increased to 4.2 mg one hour before lunch and 4.2 mg one hour before dinner, as tolerated to achieve a therapeutic effect.
- Maximum Dosage: 8.4 mg twice daily.

2.3 Nausea and Vomiting Associated with Cancer Chemotherapy in Adult Patients Who Failed Conventional Antiemetics

Adults

Starting Dosage

The recommended starting dosage of SYNDROS is 4.2 mg/m^2 orally administered 1 to 3 hours prior to chemotherapy and then every 2 to 4 hours after chemotherapy for a total of 4 to 6 doses per day.

- Calculate the starting dose by following the steps below:
  - Starting dose (mg) = Patient body surface area (BSA) in m^2 multiplied by 4.2 mg/m^2
  - Round dose to the nearest 0.1 mg increment
  - To correspond with the calibrated oral dosing syringe, the dose may need to be rounded to the nearest 0.1 mL increment

In elderly patients, consider initiating SYNDROS at 2.1 mg/m^2 once daily 1 to 3 hours prior to chemotherapy to reduce the risk of CNS symptoms *[see Use in Specific Populations (8.5)]*.

Because food delays the absorption of SYNDROS, administer the first dose on an empty stomach at least 30 minutes before eating. Subsequent doses can be taken without regard to meals.

Because food can substantially change the systemic exposure to dronabinol and its active metabolite, the timing of dosing in relation to meal times should be kept consistent for each chemotherapy cycle, once the dosage has been determined from the titration process.

Dosage Titration

- The dosage can be titrated to clinical response during a chemotherapy cycle or subsequent cycles, based upon initial effect, as tolerated to achieve a clinical effect, in increments of 2.1 mg/m^2.
- Maximum Dosage: 12.6 mg/m^2 per dose for 4 to 6 doses per day.
- Adverse reactions are dose-related and psychiatric symptoms increase significantly at the maximum dosage *[see Warnings and Precautions (5.1)]*.

Monitor patients for adverse reactions and consider decreasing the dose to 2.1 mg once daily 1 to 3 hours prior to chemotherapy to reduce the risk of CNS adverse reactions.

3 DOSAGE FORMS AND STRENGTHS

Oral Solution: 5 mg/mL, a clear, pale yellow to brown solution.

4 CONTRAINDICATIONS

SYNDROS is contraindicated in patients:

- with a history of a hypersensitivity reaction to dronabinol. Reported hypersensitivity reactions to dronabinol include lip swelling, hives, disseminated rash, oral lesions, skin burning, flushing, throat tightness *[see Adverse Reactions (6.2)]*.
- with a history of a hypersensitivity reaction to alcohol.
- who are receiving, or have recently received, disulfiram- or metronidazole-containing products within 14 days *[see Warning and Precautions (5.3)]*. SYNDROS contains 50% (w/w) dehydrated alcohol and 5.5% (w/w) propylene glycol.

5 WARNINGS AND PRECAUTIONS

5.1 Neurological Adverse Reactions

Psychiatric Adverse Reactions

Dronabinol has been reported to exacerbate mania, depression, or schizophrenia. Prior to initiating treatment with SYNDROS, screen patients for a history of these illnesses. Avoid use in patients with a psychiatric history or, if the drug cannot be avoided, monitor patients for new or worsening psychiatric symptoms during treatment. Also, avoid concomitant use with other drugs that are associated with similar psychiatric effects.

Cognitive Adverse Reactions

Use of SYNDROS has been associated with cognitive impairment and altered mental state. Reduce the dose of SYNDROS or discontinue use of SYNDROS if signs or symptoms of cognitive impairment develop. Elderly and pediatric patients may be more sensitive to the neurological and psychoactive effects of SYNDROS *[see Use in Specific Populations (8.4, 8.5)]*.

Hazardous Activities

SYNDROS can cause and may impair the mental and/or physical abilities required for the performance of hazardous tasks such as driving a motor vehicle or operating machinery. Concomitant use of other drugs that cause dizziness, confusion, sedation, or somnolence such as CNS depressants may increase this effect (e.g., barbiturates, benzodiazepines, lithium, opioids, buspirone, antihistamines, and muscle relaxants). Inform patients not to operate motor vehicles or other dangerous machinery until they are reasonably certain that SYNDROS does not affect them adversely.

5.2 Hemodynamic Instability

Patients may experience occasional hypotension, possible hypertension, syncope, or tachycardia while taking SYNDROS *[see Clinical Pharmacology (12.2)]*. Patients with cardiac disorders may be at higher risk. Avoid concomitant use of other drugs that are also associated with similar cardiac effects (e.g., amphetamines, other sympathomimetic agents, atropine, amoxapine, antihistamines, other anticholinergic agents, amitriptyline, desipramine, other tricyclic antidepressants). Monitor patients for changes in blood pressure, heart rate, and syncope after initiating or increasing the dosage of SYNDROS.

5.3 Interaction with Disulfiram and Metronidazole

SYNDROS contains 50% (w/w) dehydrated alcohol and 5.5% (w/w) propylene glycol. Use of SYNDROS may cause a disulfiram-like reaction, characterized by abdominal cramps, nausea, vomiting, headaches, and flushing, in patients receiving disulfiram or other drugs that produce this reaction (e.g., metronidazole). Discontinue products containing disulfiram or metronidazole at least 14 days before starting treatment with SYNDROS and do not administer these products within 7 days of completing treatment with SYNDROS *[see Contraindications (4), Drug Interactions (7.3)]*.

When administered concomitantly with propylene glycol, ethanol competitively inhibits the metabolism of propylene glycol, which may lead to elevated concentrations of propylene glycol. However, the contribution of propylene glycol, if any, to the interaction between disulfiram and SYNDROS is unknown.

5.4 Seizures

Seizures and seizure-like activity have been reported in patients receiving dronabinol.

Weigh this potential risk against the benefits before prescribing SYNDROS to patients with a history of seizures, including those receiving anti-epileptic medication or with other factors that can lower the seizure

threshold. Monitor patients with a history of seizure disorders for worsened seizure control during SYNDROS therapy.

If a seizure occurs, advise patients to discontinue SYNDROS and contact a healthcare provider immediately.

5.5 Multiple Substance Abuse

Patients with a history of substance abuse or dependence, including marijuana or alcohol, may be more likely to abuse SYNDROS as well. SYNDROS contains 50% (w/w) dehydrated alcohol.

Assess each patient's risk for abuse or misuse prior to prescribing SYNDROS and monitor patients with a history of substance abuse during treatment with SYNDROS for the development of these behaviors or conditions.

5.6 Paradoxical Nausea, Vomiting, or Abdominal Pain

New or worsening nausea, vomiting, or abdominal pain can occur during treatment with synthetic delta-9 tetrahydrocannabinol (delta-9-THC), the active ingredient in SYNDROS. In some cases, these adverse reactions were severe (e.g., dehydration, electrolyte abnormalities) and required dose reduction or drug discontinuation. Symptoms are similar to cannabinoid hyperemesis syndrome (CHS), which is described as cyclical events of abdominal pain, nausea, and vomiting in chronic, long-term users of delta-9-THC products.

Because patients may not recognize these symptoms as abnormal, it is important to specifically ask patients or their caregivers about the development of worsening of nausea, vomiting, or abdominal pain while being treated with SYNDROS. Consider dose reduction or discontinuing SYNDROS if a patient develops worsening nausea, vomiting, or abdominal pain while on treatment.

5.7 Toxicity in Preterm Neonates

SYNDROS contains the excipients dehydrated alcohol (50%, w/w) and propylene glycol (5.5%, w/w). When administered concomitantly with propylene glycol, ethanol competitively inhibits the metabolism of propylene glycol, which may lead to elevated concentrations of propylene glycol. Preterm neonates may be at increased risk of propylene glycol-associated adverse reactions due to a diminished ability to metabolize propylene glycol, thereby, leading to accumulation

The safety and effectiveness of SYNDROS have not been established in pediatric patients. Avoid SYNDROS in preterm neonates in the immediate postnatal period because of possible propylene glycol-associated toxicities including: hyperosmolarity, with or without lactic acidosis, renal toxicity, CNS depression (including stupor, coma, and apnea), seizures, hypotonia, cardiac arrhythmias, and electrocardiogram (EEG) changes, and hemolysis.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The following serious adverse reactions are described below and elsewhere in the labeling.

- Neurological Adverse Reactions *[see Warnings and Precautions (5.1)]*
- Hemodynamic Instability *[see Warnings and Precautions (5.2)]*

- Seizures *[see Warnings and Precautions (5.4)]*
- Paradoxical Nausea, Vomiting, and Abdominal Pain *[see Warnings and Precautions (5.6)]*
- Toxicity in Preterm Neonates *[see Warnings and Precautions (5.7)]*

The safety of SYNDROS has been established based on studies of dronabinol capsules. Studies of AIDS-related weight loss included 157 patients receiving dronabinol capsules and 67 receiving placebo. Studies of nausea and vomiting related to cancer chemotherapy included 317 patients receiving dronabinol capsules and 68 receiving placebo. In the tables below is a summary of the adverse reactions in 474 patients exposed to dronabinol capsules in studies.

Studies of different durations were combined by considering the first occurrence of adverse reactions during the first 28 days.

A cannabinoid dose-related "high" (easy laughing, elation and heightened awareness) has been reported by patients receiving dronabinol capsules in both the antiemetic (24%) and the lower dose appetite stimulant clinical trials (8%). The most frequently reported adverse experiences in patients with AIDS during placebo-controlled clinical trials involved the CNS and were reported by 33% of patients receiving dronabinol capsules. About 25% of patients reported a CNS adverse reaction during the first 2 weeks and about 4% reported such a reaction each week for the next 6 weeks thereafter.

Common Adverse Reactions

The following adverse reactions were reported in clinical trials of dronabinol capsules at an incidence greater than 1%.

System Organ Class	**Adverse Reactions**
General	Asthenia
Cardiovascular	Palpitations, tachycardia, vasodilation/facial flush
Gastrointestinal	Abdominal pain*, nausea*, vomiting*
Central Nervous System	dizziness*, euphoria*, paranoid reaction*, somnolence*, thinking abnormal*, amnesia, anxiety/nervousness, ataxia, confusion, depersonalization,

*Actual Incidence 3% to 10%

Less Common Adverse Reactions

The following adverse reactions were reported in clinical trials of dronabinol capsules at an incidence less than or equal to 1%.

System Organ Class	**Adverse Reactions**
General	Chills, headache, malaise
Cardiovascular	Hypotension, conjunctival injection *[see Clinical Pharmacology (12.2)]*
Gastrointestinal	Diarrhea, fecal incontinence, anorexia, hepatic enzyme elevation
Musculoskeletal	Myalgias
Central Nervous System	Depression, nightmares, speech difficulties, tinnitus

How to prepare a dose of SYNDROS oral solution after the adapter is inserted:

Step 1: Open the bottle by pushing down firmly on the child-resistant cap and turning it counter-clockwise (See Figure D). Do not throw away the child-resistant cap.

Figure D

Step 2: If you are using the oral syringe for the first time, remove the oral syringe from the plastic wrap. You may need to use a pair of scissors.

Step 3: Hold the oral syringe in one hand. With your other hand, fully push down (depress) the plunger (See Figure E).

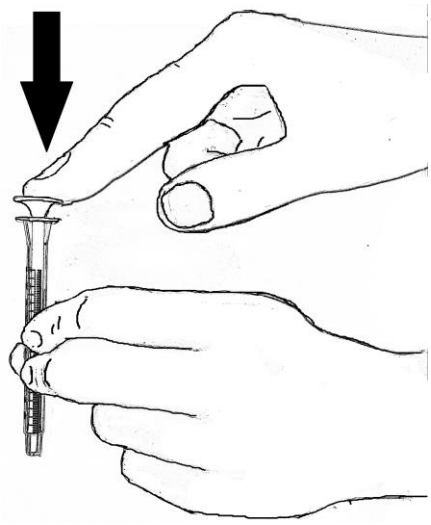

Figure E

Step 4: Keeping the bottle in an upright position, insert the syringe tip firmly into the adapter (See Figure F).

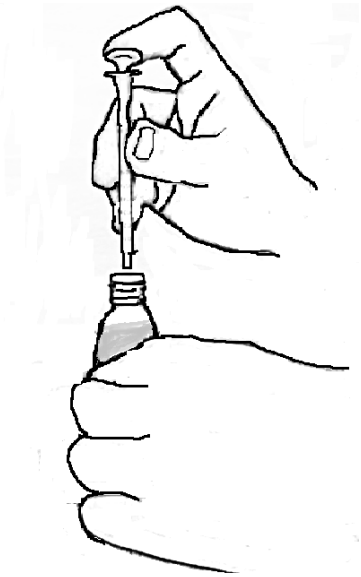

Figure F

Step 5: Carefully turn the bottle upside down with the syringe tip firmly inserted into the adapter (See Figure G).

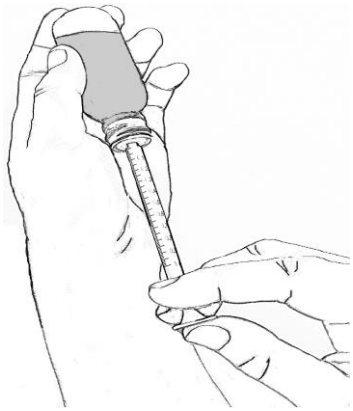

Figure G

Step 6: Slowly pull back on the plunger until the measuring ring is at the line marking for the dose prescribed by your doctor. The measuring ring is the widest part of the plunger at the bottom of the tip of plunger. (See Figures H(a) and H(b)). Figure H(a) shows a dose of 0.4 mL as an example.

If you see air bubbles in the oral syringe, fully push in the plunger so that the oral solution flows back into the bottle. Then, withdraw your prescribed dose of oral solution.

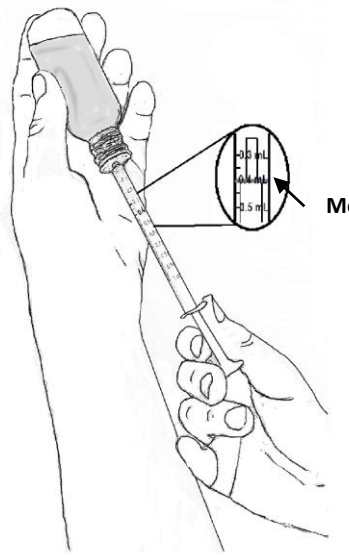

Figure H(a)

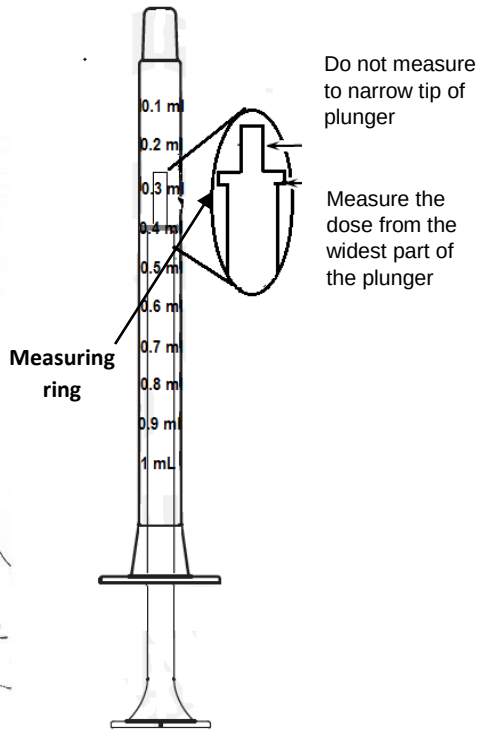

Figure H(b)

If your prescribed dose is more than 1 mL, you will need to draw up two or more doses.

For example, if your dose is 1.2 mL, you will need to draw up a 1 mL dose followed by a 0.2 mL dose.

Step 7: Leave the oral syringe in the adapter and turn the bottle to an upright position. Place the bottle onto a flat surface. Remove the oral syringe from the bottle adapter by gently pulling straight up on the oral syringe (See Figure I).

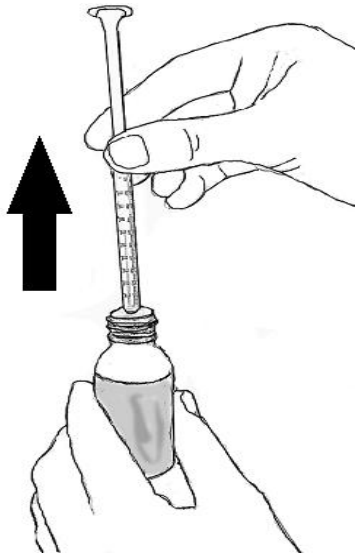

Figure I

Step 8: Check that the correct dose of SYNDROS oral solution was drawn up into the oral syringe. If the dose is not correct, insert the syringe tip firmly into the bottle adapter. Fully push in the plunger so that the oral solution flows back into the bottle (See Figure J).

Repeat Steps 5-8.

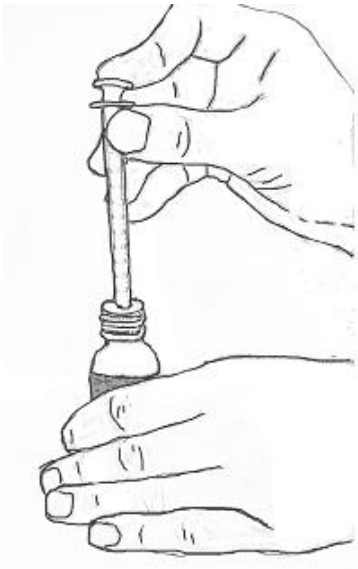

Figure J

Step 9: Open your mouth. Place the oral syringe tip in the back of your mouth on top of your tongue. Tilt your head back

slightly and close your lips around the barrel of the oral syringe. Slowly push down the plunger until the oral syringe is empty (See Figure K).

Swallow the oral solution.

If your prescribed dose is more than 1 mL, repeat Steps 4-8 to draw up the remaining dose until the prescribed dose is given. For example, if your prescribed dose is 1.6 mL, take a 1 mL dose first, then an additional dose of 0.6 mL.

Figure K

Take your SYNDROS oral solution right away after it is drawn up into the oral syringe.

Step 10: Drink a full glass of water (6 to 8 ounces) right after you take your prescribed dose of SYNDROS oral solution (See Figure L).

Figure L

Step 11: **Leave the adapter in the bottle.** Put the child-resistant cap back on the bottle (See Figure M).

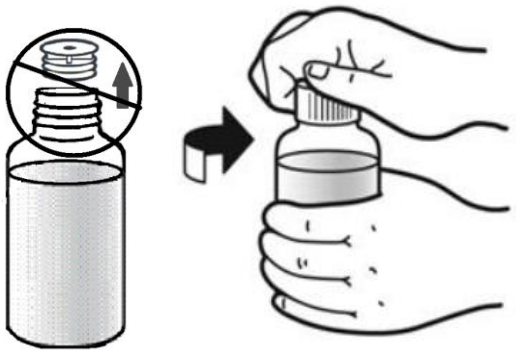

Figure M

Step 12: Remove the plunger from the oral syringe barrel. Rinse the oral syringe barrel and plunger with warm water after each use and let them air dry. When the oral syringe barrel and plunger are dry, put the plunger back into the oral syringe barrel for the next use. Keep SYNDROS oral solution and the oral syringe in the carton that it comes in. **Do not throw away the oral syringe**.

How should I store SYNDROS?

- Store SYNDROS in the refrigerator between 36°F to 46°F (2°C to 8°C).
- After the bottle is opened, SYNDROS can be stored at room temperature, between 68°F to 77°F (20°C to 25°C), for up to 28 days.
- Do not use SYNDROS that has been stored in the refrigerator or at room temperature 28 days after opening the bottle. Write the date that you open the bottle of SYNDROS on the bottle and carton it comes in. See "**How should I dispose of unused SYNDROS?**"

Keep SYNDROS and all medicines out of the reach of children.

How should I dispose of unused SYNDROS?

- Dispose of unused SYNDROS as soon as you no longer need it or 28 days after opening the bottle.

Talk to your doctor or pharmacist if you have questions about how to use SYNDROS oral solution.

For more information, go to www.syndros.com or call 1-855-978-2797.

This Patient Information and Instructions for Use have been approved by the U.S. Food and Drug Administration.

Manufactured by:
DPT Lakewood LLC, Lakewood, NJ, 08701

Manufactured for:
Insys Therapeutics, Inc., Chandler, AZ 85286

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