2.7 Dosage Adjustments in Patients with Hepatic Impairment

ONFI is hepatically metabolized; however, there are limited data to characterize the effect of hepatic impairment on the pharmacokinetics of ONFI. For this reason, proceed slowly with dosing escalations. For patients with mild to moderate hepatic impairment (Child-Pugh score 5-9), the starting dose should be 5 mg/day in both weight groups. Then titrate patients according to weight, but to half the dose presented in Table 1, as tolerated. If necessary and based upon clinical response, start an additional titration on day 21 to the maximum dose (20 mg/day or 40 mg/day, depending on the weight group). There is inadequate information about metabolism of ONFI in patients with severe hepatic impairment. Therefore no dosing recommendation in those patients can be given *[see Use in Specific Populations (8.8), Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

Tablets: 10 mg and 20 mg with a functional score for oral administration.
Each ONFI tablet is a white to off-white, oval tablet with a functional score on one side and either a “1” and “0” or a “2” and “0” debossed on the other side.

Oral Suspension: 2.5 mg/mL for oral administration. Each bottle contains 120 mL of an off-white suspension.

4 CONTRAINDICATIONS

ONFI is contraindicated in patients with a history of hypersensitivity to the drug or its ingredients. Hypersensitivity reactions have included serious dermatological reactions *[see Warnings and Precautions (5.5)].*

5 WARNINGS AND PRECAUTIONS

5.1 Risks from Concomitant Use with Opioids

Concomitant use of benzodiazepines, including ONFI, and opioids may result in profound sedation, respiratory depression, coma, and death. Because of these risks, reserve concomitant prescribing of benzodiazepines and opioids for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. If a decision is made to prescribe ONFI concomitantly with opioids, prescribe the lowest effective dosages and minimum durations of concomitant use, and follow patients closely for signs and symptoms of respiratory depression and sedation. Advise both patients and caregivers about the risks of respiratory depression and sedation when ONFI is used with opioids *[see Drug Interactions (7.1)].*

5.2 Potentiation of Sedation from Concomitant Use with Central Nervous System Depressants

Since ONFI has a central nervous system (CNS) depressant effect, patients or their caregivers should be cautioned against simultaneous use with other CNS depressant drugs or alcohol, and cautioned that the effects of other CNS depressant drugs or alcohol may be potentiated *[see Drug Interactions (7.2)]*.

5.3 Somnolence or Sedation

ONFI causes somnolence and sedation. In clinical trials, somnolence or sedation was reported at all effective doses and was dose-related.

In general, somnolence and sedation begin within the first month of treatment and may diminish with continued treatment. Prescribers should monitor patients for somnolence and sedation, particularly with concomitant use of other central nervous system depressants. Prescribers should caution patients against engaging in hazardous activities requiring mental alertness, such as operating dangerous machinery or motor vehicles, until the effect of ONFI is known.

5.4 Withdrawal Symptoms

Abrupt discontinuation of ONFI should be avoided. ONFI should be tapered by decreasing the dose every week by 5-10 mg/day until discontinuation *[see Dosage and Administration (2.2)]*.

Withdrawal symptoms occurred following abrupt discontinuation of ONFI; the risk of withdrawal symptoms is greater with higher doses.

As with all antiepileptic drugs, ONFI should be withdrawn gradually to minimize the risk of precipitating seizures, seizure exacerbation, or status epilepticus.

Withdrawal symptoms (e.g., convulsions, psychosis, hallucinations, behavioral disorder, tremor, and anxiety) have been reported following abrupt discontinuance of benzodiazepines. The more severe withdrawal symptoms have usually been limited to patients who received excessive doses over an extended period of time, followed by an abrupt discontinuation. Generally milder withdrawal symptoms (e.g., dysphoria, anxiety, and insomnia) have been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic doses for several months.

5.5 Serious Dermatological Reactions

Serious skin reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported with ONFI in both children and adults during the post-marketing period. Patients should be closely monitored for signs or symptoms of SJS/TEN, especially during the first 8 weeks of treatment initiation or when re-introducing therapy. ONFI should be discontinued at the first sign of rash, unless the rash is clearly not drug-related. If signs or symptoms suggest SJS/TEN, use of this drug should not be resumed and alternative therapy should be considered *[see Contraindications (4)].*

hormonal forms of contraception are recommended when using ONFI *[see Clinical Pharmacology (12.3), Patient Counseling Information (17)]*.

Drugs Metabolized by CYP2D6
ONFI inhibits CYP2D6. Dose adjustment of drugs metabolized by CYP2D6 may be necessary *[see Clinical Pharmacology (12.3)]*.

7.4 Effect of Other Drugs on ONFI

Strong and moderate inhibitors of CYP2C19
Strong and moderate inhibitors of CYP2C19 may result in increased exposure to N-desmethylclobazam, the active metabolite of clobazam. This may increase the risk of dose-related adverse reactions. Dosage adjustment of ONFI may be necessary when co-administered with strong CYP2C19 inhibitors (e.g., fluconazole, fluvoxamine, ticlopidine) or moderate CYP2C19 inhibitors (e.g., omeprazole) *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C.

Risk Summary

There are no adequate and well-controlled studies of ONFI in pregnant women. In animal studies, administration of clobazam during pregnancy resulted in developmental toxicity, including increased incidences of fetal malformations, at plasma exposures for clobazam and its major active metabolite, N-desmethylclobazam, below those expected at therapeutic doses in patients. ONFI should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Available human data on the risk of teratogenicity associated with benzodiazepines are inconclusive. There is insufficient evidence in humans to assess the effect of benzodiazepine exposure during pregnancy on neurodevelopment. Administration of benzodiazepines immediately prior to or during childbirth can result in a syndrome of hypothermia, hypotonia, respiratory depression, and difficulty feeding. In addition, infants born to mothers who have taken benzodiazepines during the later stages of pregnancy can develop dependence, and subsequently withdrawal, during the postnatal period.

Data for other benzodiazepines suggest the possibility of adverse developmental effects (including long-term effects on neurobehavioral and immunological function) in animals following prenatal exposure to benzodiazepines at clinically relevant doses.

Data

Animal

In a study in which clobazam (150, 450, or 750 mg/kg/day) was orally administered to pregnant rats throughout the period of organogenesis, embryofetal mortality and incidences of fetal skeletal variations were increased at all doses. The low-effect dose for embryofetal developmental toxicity in rats (150 mg/kg/day) was associated with plasma exposures (AUC) for clobazam and its major active metabolite, N-desmethylclobazam, lower than those in humans at the maximum recommended human dose (MRHD) of 40 mg/day.

Oral administration of clobazam (10, 30, or 75 mg/kg/day) to pregnant rabbits throughout the period of organogenesis resulted in decreased fetal body weights, and increased incidences of fetal malformations (visceral and skeletal) at the mid and high doses, and an increase in embryofetal mortality at the high dose. Incidences of fetal variations were increased at all doses. The highest dose tested was associated with maternal toxicity (ataxia and decreased activity). The low-effect dose for embryofetal developmental toxicity in rabbits (10 mg/kg/day) was associated with plasma exposures for clobazam and N-desmethylclobazam lower than those in humans at the MRHD.

Oral administration of clobazam (50, 350, or 750 mg/kg/day) to rats throughout pregnancy and lactation resulted in increased embryofetal mortality at the high dose, decreased pup survival at the mid and high doses and alterations in offspring behavior (locomotor activity) at all doses. The low-effect dose for adverse effects on pre- and postnatal development in rats (50 mg/kg/day) was associated with plasma exposures for clobazam and N-desmethylclobazam lower than those in humans at the MRHD.

Pregnancy Registry

To provide information regarding the effects of *in utero* exposure to ONFI, physicians are advised to recommend that pregnant patients taking ONFI enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. This can be done by calling the toll free number 1-888-233-2334, and must be done by patients themselves or their caregiver. Information on the registry can also be found at the website http://www.aedpregnancyregistry.org/.

8.3 Nursing Mothers

ONFI is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from ONFI, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness in patients less than 2 years of age have not been established.

In a study in which clobazam (4, 36, or 120 mg/kg/day) was orally administered to rats during the juvenile period of development (postnatal days 14 to 48), adverse effects on growth (decreased bone density and bone length) and behavior (altered motor activity and auditory startle response; learning deficit) were observed at the high dose. The

NDC 67386-315-01: 20 mg scored tablet, Bottles of 100

ONFI oral suspension is a berry flavored off-white liquid supplied in a bottle with child-resistant closure. The oral suspension is packaged with a dispenser set which contains two calibrated oral dosing syringes and a bottle adapter.

Store and dispense ONFI oral suspension in its original bottle in an upright position. Use within 90 days of first opening the bottle, then discard any remainder.

NDC 67386-313-21: 2.5 mg/mL supplied in a bottle containing 120 mL of suspension.

Store tablets and oral suspension at 20°C to 25°C (68°F to 77°F). See USP controlled room temperature.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Risks from Concomitant Use with Opioids

Inform patients and caregivers that potentially fatal additive effects may occur if ONFI is used with opioids and not to use such drugs concomitantly unless supervised by a healthcare provider *[see Warnings and Precautions (5.1), Drug Interactions (7.1)]*.

Somnolence or Sedation

Advise patients or caregivers to check with their healthcare provider before ONFI is taken with other CNS depressants such as other benzodiazepines, opioids, tricyclic antidepressants, sedating antihistamines, or alcohol *[see Warnings and Precautions (5.2, 5.3)]*.

If applicable, caution patients about operating hazardous machinery, including automobiles, until they are reasonably certain that ONFI does not affect them adversely (e.g., impair judgment, thinking or motor skills).

Increasing or Decreasing the ONFI Dose

Inform patients or caregivers to consult their healthcare provider before increasing the ONFI dose or abruptly discontinuing ONFI. Advise patients or caregivers that abrupt withdrawal of AEDs may increase their risk of seizure *[see Dosage and Administration (2.2), Warnings and Precautions (5.4)].*

Hypersensitivity

Inform patients or caregivers that ONFI is contraindicated in patients with a history of hypersensitivity to the drug or its ingredients *[see Warnings and Precautions (5.5)].*

Interactions with Hormonal Contraceptives
Counsel women to also use non-hormonal methods of contraception when ONFI is used with hormonal contraceptives and to continue these alternative methods for 28 days after discontinuing ONFI to ensure contraceptive reliability *[see Drug Interactions (7.3), Clinical Pharmacology (12.3)].*

Serious Dermatological Reactions
Advise patients or caregivers that serious skin reactions have been reported in patients taking ONFI. Serious skin reactions, including SJS/TEN, may need to be treated in a hospital and may be life-threatening. If a skin reaction occurs while taking ONFI, patients or caregivers should consult with healthcare providers immediately *[see Warnings and Precautions (5.5)].*

Suicidal Thinking and Behavior
Counsel patients, their caregivers, and their families that AEDs, including ONFI, may increase the risk of suicidal thoughts and behavior and advise them of the need to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts of self-harm. Patients should report behaviors of concern immediately to healthcare providers *[see Warnings and Precautions (5.7)].*

Use in Pregnancy
Instruct patients to notify their healthcare provider if they become pregnant or intend to become pregnant during therapy.

Encourage patients to enroll in the NAAED Pregnancy Registry if they become pregnant. This registry is collecting information about the safety of antiepileptic drugs during pregnancy. To enroll, patients can call the toll-free number 1-888-233-2334. Information on the registry can also be found at the website http://www.aedpregnancyregistry.org *[see Use in Specific Populations (8.1)]*.

Use in Nursing
Instruct patients to notify their physician if they are breast feeding or intend to breast feed during therapy *[see Use in Specific Populations (8.3)]*.

Tablets manufactured by: Catalent Pharma Solutions, LLC
Winchester, KY 40391, U.S.A.

Oral suspension manufactured by: Rosemont Pharmaceuticals, Ltd.
Leeds, West Yorkshire LS11 9XE, U.K.

For: Lundbeck
Deerfield, IL 60015, U.S.A.

ONFI is a registered trademark of Lundbeck

MEDICATION GUIDE
ONFI® *(ON-fee)*
(clobazam)
Tablets and Oral Suspension, CIV

What is the most important information I should know about ONFI?

- **Do not stop taking ONFI without first talking to your healthcare provider.** Stopping ONFI suddenly can cause serious side effects.
- **ONFI is a benzodiazepine medicine. Benzodiazepines can cause severe drowsiness, breathing problems (respiratory depression), coma, and death when taken with opioid medicines.**
- **ONFI can make you sleepy or dizzy and can slow your thinking and motor skills. This may get better over time.**
  - Do not drive, operate heavy machinery, or do other dangerous activities until you know how ONFI affects you.
  - ONFI may cause problems with your coordination, especially when you are walking or picking things up.
- **Do not drink alcohol or take other drugs that may make you sleepy or dizzy while taking ONFI until you talk to your healthcare provider.** When taken with alcohol or drugs that cause sleepiness or dizziness, ONFI may make your sleepiness or dizziness much worse.
- **ONFI can cause withdrawal symptoms.**
  - Do not stop taking ONFI all of a sudden without first talking to a healthcare provider. Stopping ONFI suddenly can cause seizures that will not stop (status epilepticus), hearing or seeing things that are not there (hallucinations), shaking, nervousness, and stomach and muscle cramps.
  - Talk to your healthcare provider about slowly stopping ONFI to avoid withdrawal symptoms.
- **ONFI can be abused and cause dependence.**
  - Physical dependence is not the same as drug addiction. Your healthcare provider can tell you more about the differences between physical dependence and drug addiction.
- **ONFI is a federal controlled substance (CIV) because it can be abused or lead to dependence**. Keep ONFI in a safe place to prevent misuse and abuse. Selling or giving away ONFI may harm others, and is against the law. Tell your healthcare provider if you have ever abused or been dependent on alcohol, prescription medicines or street drugs.
- **Serious skin reactions have been seen when ONFI is taken with other medicines and may require stopping its use.** Do not stop taking ONFI without first talking to your healthcare provider.
  - A serious skin reaction can happen at any time during your treatment with ONFI, but is more likely to happen within the first 8 weeks of treatment. These skin reactions may need to be treated right away.
  - Call your healthcare provider immediately if you have skin blisters, rash, sores in the mouth, hives or any other allergic reaction.
- **Like other antiepileptic drugs, ONFI may cause suicidal thoughts or actions in a very small number of people, about 1 in 500.**

Call your healthcare provider right away if you have any of these symptoms, especially if they are new, worse, or worry you:

- thoughts about suicide or dying
- new or worse anxiety
- trouble sleeping (insomnia)
- acting on dangerous impulses
- attempts to commit suicide
- feeling agitated or restless
- new or worse irritability
- an extreme increase in activity and talking (mania)
- new or worse depression
- panic attacks
- acting aggressive, being angry, or violent
- other unusual changes in behavior or mood

How can I watch for early symptoms of suicidal thoughts and actions?

- Pay attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings.
- Keep all follow-up visits with your healthcare provider as scheduled.

Call your healthcare provider between visits as needed, especially if you are worried about symptoms.
Suicidal thoughts or actions can be caused by things other than medicines. If you have suicidal thoughts or actions, your healthcare provider may check for other causes.

What is ONFI?

ONFI is a prescription medicine used along with other medicines to treat seizures associated with Lennox-Gastaut syndrome in people 2 years of age or older.

It is not known if ONFI is safe and effective in children less than 2 years old.

Do not take ONFI if you:

- are allergic to clobazam or any of the ingredients in ONFI. See the end of this Medication Guide for a complete list of ingredients in ONFI.

Before you take ONFI, tell your healthcare provider about all your medical conditions, including if you:

- have liver or kidney problems
- have lung problems (respiratory disease)
- have or have had depression, mood problems, or suicidal thoughts or behavior
- use birth control medicine. ONFI may cause your birth control medicine to be less effective. Talk to your healthcare provider about the best birth control method to use.
- are pregnant or plan to become pregnant. **ONFI may harm your unborn baby.**
  - Tell your healthcare provider right away if you become pregnant while taking ONFI. You and your healthcare provider will decide if you should take ONFI while you are pregnant.
  - Babies born to mothers receiving benzodiazepine medications (including ONFI) late in pregnancy may be at some risk of experiencing breathing problems, feeding problems, dangerously low body temperature, and withdrawal symptoms.
- If you become pregnant while taking ONFI, talk to your healthcare provider about registering with the North American Antiepileptic Drug Pregnancy Registry. You can register by calling 1-888-233-2334. For more information about the registry go to http://www.aedpregnancyregistry.org. The purpose of this registry is to collect information about the safety of antiepileptic drugs during pregnancy.
- ONFI can pass into breast milk. Talk to your healthcare provider about the best way to feed your baby if you take ONFI. You and your healthcare provider should decide if you will take ONFI or breastfeed. You should not do both.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Taking ONFI with certain other medicines can cause side effects or affect how well ONFI or the other medicines work. Do not start or stop other medicines without talking to your healthcare provider.

How should I take ONFI?

- Take ONFI exactly as your healthcare provider tells you to take it.
- Your healthcare provider will tell you how much ONFI to take and when to take it.
- ONFI tablets can be taken whole, broken in half along the score, or crushed and mixed in applesauce.
- ONFI tablets and oral suspension can be taken with or without food.
- **Shake the bottle of ONFI oral suspension right before you take each dose.**
- Measure your dose of ONFI oral suspension using the bottle adapter and dosing syringes that come with your ONFI oral suspension.
- Read the **Instructions for Use** at the end of this Medication Guide for information on the right way to use ONFI oral suspension.
- Your healthcare provider may change your dose if needed. Do not change your dose of ONFI without talking to your healthcare provider.
- Do not stop taking ONFI without first talking to your healthcare provider.
- Stopping ONFI suddenly can cause serious problems.
- If you take too much ONFI, call your healthcare provider or go to the nearest hospital emergency room right away.

What should I avoid while taking ONFI?

- Do not drive, operate heavy machinery, or do other dangerous activities until you know how ONFI affects you.
- Do not drink alcohol or take other medicines that may make you sleepy or dizzy while taking ONFI until you talk to your healthcare provider. When taken with alcohol or medicines that cause sleepiness or dizziness, ONFI may make your sleepiness or dizziness much worse.

What are the possible side effects of ONFI?

ONFI may cause serious side effects, including: See "What is the most important information I should know about ONFI?"

The most common side effects of ONFI include:

- sleepiness
- cough
- acting aggressive, being angry, or violent
- tiredness
- drooling
- pain with urination
- difficulty sleeping
- problems with breathing
- constipation
- fever
- slurred speech

These are not all the possible side effects of ONFI. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ONFI?

- Store ONFI tablets and oral suspension between 68°F to 77°F (20°C to 25°C).

Tablets
- Keep ONFI tablets in a dry place.

Oral Suspension
- Replace the cap securely after opening.
- Store and dispense the oral suspension in its original bottle in an upright position. Use ONFI oral suspension within 90 days of first opening the bottle.
- After 90 days safely throw away any ONFI oral suspension that has not been used.
- **Keep ONFI and all medicines out of the reach of children.**

General information about the safe and effective use of ONFI.
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use ONFI for a condition for which it was not prescribed. Do not give ONFI to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about ONFI that is written for health professionals.

What are the ingredients in ONFI?

Tablets
Active ingredient: clobazam
Inactive ingredients: modified corn starch, lactose monohydrate, magnesium stearate, silicon dioxide, and talc.

Oral Suspension
Active ingredient: clobazam
Inactive ingredients: magnesium aluminum silicate, xanthan gum, citric acid monohydrate, disodium hydrogen phosphate dihydrate, simethicone emulsion, polysorbate 80, methylparaben, propylparaben, propylene glycol, sucralose, maltitol solution, berry flavor, purified water.

Marketed by: Lundbeck, Deerfield, IL 60015, U.S.A.
ONFI is a registered trademark of Lundbeck
For more information about ONFI, go to **www.ONFI.com or call Lundbeck at 1-866-402-8520**.

This Medication Guide has been approved by the U.S. Food and Drug Administration Revised: 12/2016

Instructions for Use
ONFI® *(ON-fee)* (clobazam)
Oral Suspension, CIV

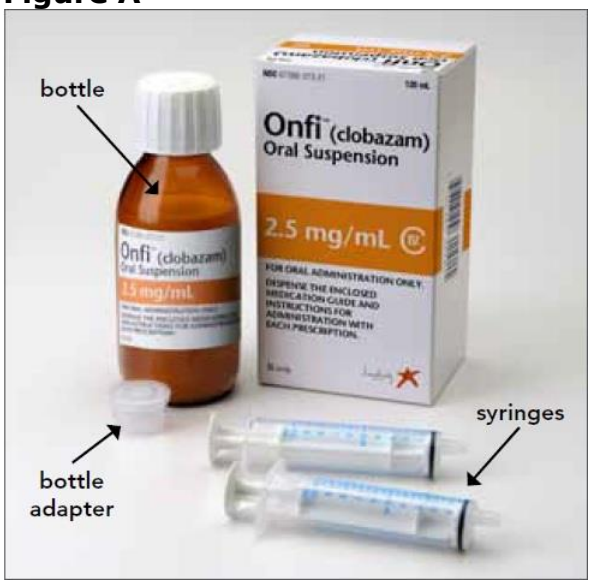
Read this Instructions for Use before using ONFI oral suspension and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your healthcare provider about your medical condition or treatment.

Prepare ONFI Oral Suspension Dose

You will need the following supplies: **See Figure A**

- ONFI oral suspension bottle
- Bottle adapter
- Oral dosing syringe (2 dosing syringes are included in the ONFI oral suspension box).
- Use only 1 syringe to take your dose of ONFI oral suspension. If you lose or damage the syringe, or cannot read the markings, use the other syringe.

Figure A



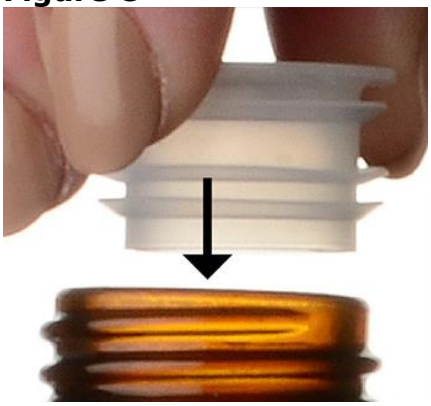
Step 1. Remove the ONFI oral suspension bottle, bottle adapter, and 1 syringe from the box.

Step 2. Shake the bottle well before each use. **See Figure B**

Figure B

Step 3. Uncap the bottle and firmly insert the bottle adapter into the bottle until the adapter top is even with the bottle top. **See Figure C**

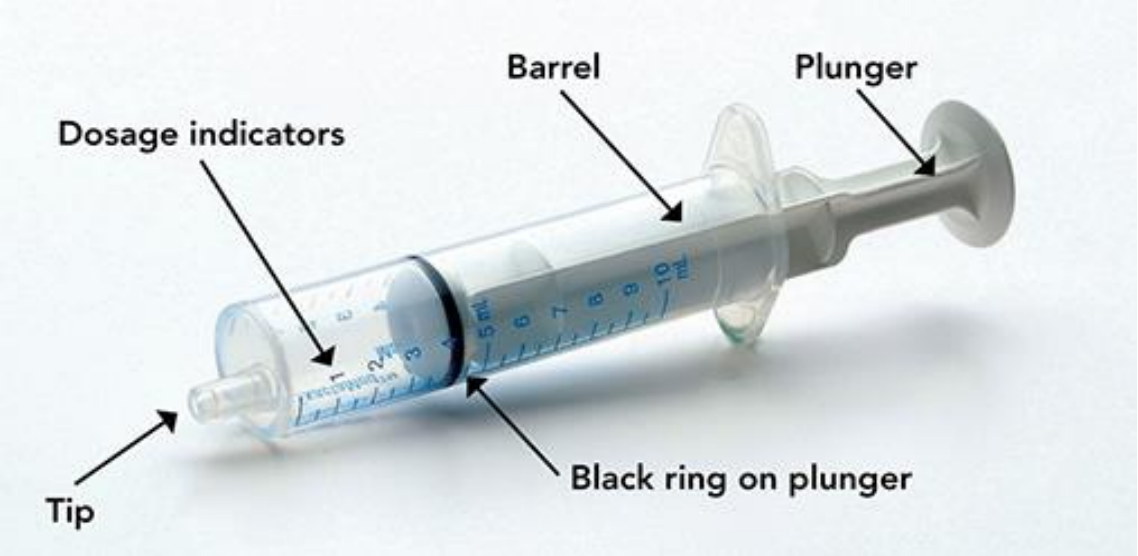
Figure C



Once the bottle adapter is in place, it should not be removed.

Step 4. Check your dose in milliliters (mL) as prescribed by your healthcare provider. Find this number on the syringe. Do not take more than the prescribed total dose in 1 day. **See Figure D**

Figure D

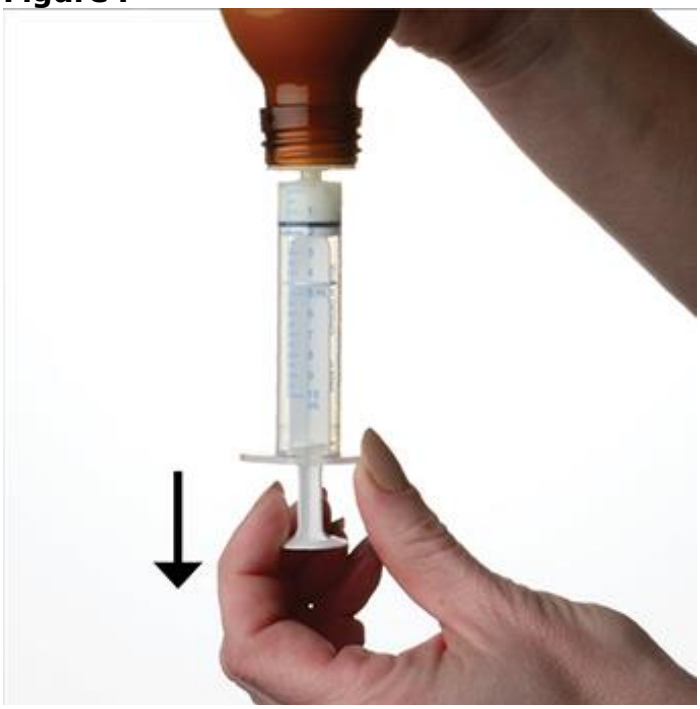


Step 5. Push the plunger all the way down and then insert the syringe into the upright bottle through the opening in the bottle adapter. **See Figure E**

Figure E

Step 6. With the syringe in place, turn the bottle upside down. Pull the plunger to the number of mLs needed (the amount of liquid medicine in Step 4). **See Figure F**

Figure F



Measure the mLs of medicine using the black ring on the white plunger. **See Figure G**

Figure G

Step 7. Remove the syringe from the bottle adapter. Slowly squirt ONFI oral suspension directly into the corner of your mouth or your child's mouth until all of the liquid medicine in the syringe is given. **See Figure H**

Figure H

Step 8. Cap the bottle tightly with the adapter in place. If the cap does not fit securely, check to see if the adapter is fully inserted. **See Figure I**

- Store and dispense ONFI oral suspension in its original bottle in an upright position at 68°F to 77°F (20°C to 25°C).
- Use ONFI oral suspension within 90 days of first opening bottle.
- After 90 days safely throw away any ONFI oral suspension that has not been used.

Figure I

Step 9. Wash the oral syringe after each use.

- To clean the oral syringe, take apart by removing the plunger completely. Pull plunger straight out of the barrel.
- The barrel and plunger can be washed with soap and water, rinsed, and allowed to dry.
- Do not wash the oral syringe in the dishwasher.

This Instruction for Use has been approved by the U.S. Food and Drug Administration.

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12/2016