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

ONFI™ (clobazam) tablets, for oral use, CIV
Initial U.S. Approval: 2011

----------INDICATIONS AND USAGE----------
ONFI is a benzodiazepine indicated for adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients 2 years of age or older (1)

----------DOSAGE AND ADMINISTRATION----------
- Patients ≤30 kg body weight: initiate therapy at 5 mg daily and titrate as tolerated up to 20 mg daily. (2.1)
- Patients >30 kg body weight: initiate therapy at 10 mg daily and titrate as tolerated up to 40 mg daily. (2.1)
- Doses above 5 mg/day should be administered in two divided doses. (2.1)
- ONFI tablets can be administered whole, or crushed and mixed in applesauce. (2.1)
- Reduce dose, or discontinue drug, gradually. (2.1)
- Dosage adjustment needed in the following groups:
  - Geriatric patients (2.2, 8.5)
  - Known CYP2C19 poor metabolizers (2.3)
  - Mild or moderate hepatic impairment; no information for severe hepatic impairment (2.5, 8.8)

----------DOSAGE FORMS AND STRENGTHS----------
Tablet: 5 mg, 10 mg, or 20 mg (3)

----------CONTRAINDICATIONS----------
None. (4)

----------WARNINGS AND PRECAUTIONS----------
- Somnolence or Sedation: Monitor for central nervous system (CNS) depression. Risk may be increased with concomitant use of other CNS depressants. (5.1, 5.2)
- Withdrawal: Symptoms may occur with rapid dose reduction or discontinuation. Discontinue ONFI gradually. (5.3)
- Physical and psychological dependence: Patients with a history of substance abuse should be monitored for signs of habituation and dependence.(5.4, 9)
- Suicidal behavior and ideation: Monitor for suicidal thoughts or behaviors. (5.5)

----------ADVERSE REACTIONS----------
Adverse reactions that occurred in at least 5% of ONFI-treated patients and more frequently than placebo included somnolence or sedation, drooling, constipation, cough, urinary tract infection, aggression, insomnia, dysarthria, and fatigue. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Lundbeck Inc. at 1-800-455-1141 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Lower doses of some drugs metabolized by CYP2D6 may be required when used concomitantly with ONFI. (7)
- Dosage adjustment of ONFI may be necessary when coadministered with strong or moderate CYP2C19 inhibitors. (7)
- Alcohol increases the blood levels of clobazam by approximately 50%. (7)

----------USE IN SPECIFIC POPULATIONS----------
- Pediatric use: Safety and effectiveness in patients <2 years of age have not been established. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

ONFI™ (clobazam) is indicated for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients 2 years of age or older.

2. DOSAGE AND ADMINISTRATION

2.1 Basic Dosing Information

ONFI should be administered in divided doses twice daily (the 5 mg dose can be administered as a single daily dose). Patients should be dosed according to body weight. Within each body weight group, dosing should be individualized based on clinical efficacy and tolerability. Each dose in Table 1 has been shown to be effective, although effectiveness increases with increasing dose *[see Clinical Studies (14)].* Dose escalation should not proceed more rapidly than weekly, because serum concentrations of clobazam and its active metabolite require 5 and 9 days, respectively, to reach steady-state.

Table 1. Recommended Total Daily Dosing by Weight Group

	≤30 kg Body Weight	>30 kg Body Weight
Starting Dose	5 mg	10 mg
Starting Day 7	10 mg	20 mg
Starting Day 14	20 mg	40 mg

ONFI tablets can be administered whole, or crushed and mixed in applesauce. ONFI can be taken without regard to timing of meals.

2.2 Geriatric Patients

Plasma concentrations at any given dose are generally higher in the elderly, and dose escalation should proceed slowly. The starting dose should be 5 mg/day for all elderly patients. Patients should then be titrated according to weight, but to half the dose presented in Table 1, as tolerated. If necessary and based upon clinical response, an additional titration to the maximum dose (20 mg/day or 40 mg/day, depending on weight) may be started on day 21 *[see Use in Specific Populations (8.5)]*.

2.3 CYP2C19 Poor Metabolizers

In CYP2C19 poor metabolizers, levels of N-desmethylclobazam, clobazam's active metabolite, will be increased. Therefore, in patients known to be CYP2C19 poor metabolizers, the starting dose should be 5 mg/day and dose titration should proceed slowly according to weight, but to half the dose presented in Table 1, as tolerated. If necessary and based upon clinical response, an

additional titration to the maximum dose (20 mg/day or 40 mg/day, depending on the weight group) may be started on day 21 *[see Use in Specific Populations (8.6), Clinical Pharmacology (12.5)]*.

2.4 Patients with Renal Impairment

No dose adjustment is required for patients with mild and moderate renal impairment. There is no experience with ONFI in patients with severe renal impairment or end stage renal disease (ESRD). It is not known if clobazam or its active metabolite, N-desmethylclobazam, is dialyzable *[see Use in Specific Populations (8.7), Clinical Pharmacology (12.3)]*.

2.5 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, dosing titration should proceed slowly. 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. Patients should then be titrated according to weight, but to half the dose presented in Table 1, as tolerated. If necessary and based upon clinical response, an additional titration to the maximum dose (20 mg/day or 40 mg/day, depending on the weight group) may be started on day 21. 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)]*.

2.6 Gradual Withdrawal

As with all antiepileptic drugs and benzodiazepines, ONFI should be withdrawn gradually. Taper by decreasing the total daily dose by 5-10 mg/day on a weekly basis until discontinued *[see Warnings and Precautions (5.3)]*.

3. DOSAGE FORMS AND STRENGTHS

5 mg, 10 mg, and 20 mg tablets for oral administration.

Each ONFI tablet is white, round, and debossed with “LU” on one side and “5,” “10,” or “20” on the other side.

4. CONTRAINDICATIONS

None.

5. WARNINGS AND PRECAUTIONS

5.1 Somnolence or Sedation

ONFI causes somnolence and sedation. In clinical trials, somnolence or sedation were reported at all effective doses and were 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.

5.2 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.

5.3 Withdrawal

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 (2.6)]*.

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.

5.4 Physical and Psychological Dependence

Patients with a history of substance abuse should be under careful surveillance when receiving ONFI or other psychotropic agents because of the predisposition of such patients to habituation and dependence *[see Drug Abuse and Dependence (9)]*.

5.5 Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs), including ONFI, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated

with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted relative risk 1.8, 95% confidence interval [CI]:1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27,863 AED treated patients was 0.43%, compared to 0.24% among 16,029 placebo treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug treated patients in the trials and none in placebo treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5-100 years) in the clinical trials analyzed. Table 2 shows absolute and relative risk by indication for all evaluated AEDs.

Table 2. Risk by Indication for Antiepileptic Drugs in the Pooled Analysis

Indication	Placebo Patients with Events per 1000 Patients	Drug Patients with Events per 1000 Patients	Relative Risk: Incidence of Drug Events in Drug Patients/Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events per 1000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing ONFI or any other AED must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

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.

During its development for the adjunctive treatment of seizures associated with LGS, ONFI was administered to 333 healthy volunteers and 300 patients with a current or prior diagnosis of LGS, including 197 patients treated for 12 months or more. The conditions and duration of exposure varied greatly and included single- and multiple-dose clinical pharmacology studies in healthy volunteers and two double-blind studies in patients with LGS (Study 1 and 2) *[see Clinical Studies (14)]*. Only Study 1 included a placebo group, allowing comparison of adverse reaction rates on ONFI at several doses to placebo.

<u>Adverse Reactions Leading to Discontinuation in an LGS Placebo Controlled Clinical Trial (Study 1)</u>

The adverse reactions associated with ONFI treatment discontinuation in ≥1% patients in decreasing order of frequency included lethargy, somnolence, ataxia, aggression, fatigue, and insomnia.

<u>Most Common Adverse Reactions in an LGS Placebo Controlled Clinical Trial (Study 1).</u>

Table 3 lists the adverse reactions that occurred in ≥5% of ONFI treated patients (at any dose), and at a rate greater than placebo treated patients, in the randomized, double-blind, placebo-controlled, parallel group clinical study of adjunctive AED therapy for 15 weeks (Study 1).

Table 3. Adverse Reactions Reported for ≥5% of Patients and More Frequently than Placebo in Any Treatment Group

	Placebo N=59 %	ONFI Dose Level			All ONFI N=179 %
		Low[a] N=58 %	Medium[b] N=62 %	High[c] N=59 %	
Gastrointestinal Disorders					
Vomiting	5	9	5	7	7
Constipation	0	2	2	10	5
Dysphagia	0	0	0	5	2
General Disorders and Administration Site Conditions					
Pyrexia	3	17	10	12	13
Irritability	5	3	11	5	7
Fatigue	2	5	5	3	5
Infections and Infestations					
Upper respiratory tract infection	10	10	13	14	12
Pneumonia	2	3	3	7	4
Urinary tract infection	0	2	5	5	4
Bronchitis	0	2	0	5	2
Metabolism and Nutrition Disorders					
Decreased appetite	3	3	0	7	3
Increased appetite	0	2	3	5	3
Nervous System Disorders					
Somnolence or Sedation	15	17	27	32	26
Somnolence	12	16	24	25	22
Sedation	3	2	3	9	5
Lethargy	5	10	5	15	10
Drooling	3	0	13	14	9
Ataxia	3	3	2	10	5
Psychomotor hyperactivity	3	3	3	5	4
Dysarthria	0	2	2	5	3
Psychiatric Disorders					
Aggression	5	3	8	14	8
Insomnia	2	2	5	7	5
Respiratory Disorders					
Cough	0	3	5	7	5

[a] Maximum daily dose of 5 mg for ≤30 kg body weight; 10 mg for >30 kg body weight

[b] Maximum daily dose of 10 mg for ≤30 kg body weight; 20 mg for >30 kg body weight

[c] Maximum daily dose of 20 mg for ≤30 kg body weight; 40 mg for >30 kg body weight

6.2 Post Marketing Experience

The following serious adverse reactions have been reported from sources outside the United States, prior to approval in the United States. All serious adverse reactions that are not listed above as adverse reactions reported in clinical trials, that are not relatively common in the population and are not too vague to be useful are listed in this section. These reactions are reported voluntarily from a population of uncertain size; therefore, it is not possible to estimate their frequency or establish a causal relationship to drug exposure. Adverse reactions are categorized by system organ class.

Blood Disorders: Anemia, eosinophilia, leukopenia, thrombocytopenia

Eye Disorders: Diplopia, vision blurred

Gastrointestinal Disorders: Abdominal distention

Investigations: Hepatic enzyme increased

Musculoskeletal: Muscle spasms

Psychiatric Disorders: Agitation, anxiety, apathy, confusional state, depression, delirium, delusion, hallucination

Respiratory Disorders: Aspiration, respiratory depression

Skin and Subcutaneous Tissue Disorders: Rash, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), urticaria

7. DRUG INTERACTIONS

ONFI may have significant interactions with other drugs *[see Clinical Pharmacology (12.3)].*

Effect of ONFI on other drugs

ONFI is a weak CYP3A4 inducer. As some hormonal contraceptives are metabolized by CYP3A4, their effectiveness may be diminished when given with ONFI. Additional non-hormonal forms of contraception are recommended when using ONFI *[see Clinical Pharmacology (12.3), Patient Counseling Information (17)]*.

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

Effect of other drugs on ONFI

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

Alcohol increases the maximum plasma exposure of clobazam by approximately 50% *[see Clinical Pharmacology (12.3)]*.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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/.

Pregnancy Category C.

There are no adequate and well-controlled studies of ONFI in pregnant women and no adequate developmental toxicity studies of clobazam in animals.

Although limited, the available animal data suggest developmental toxicity, including an increased incidence of fetal abnormalities following oral administration of clobazam to pregnant animals at doses similar to those used clinically.

Data for other benzodiazepines suggest the possibility of adverse effects in animals and humans. Long-term effects on neurobehavioral and immunological function have been reported in rodents following prenatal exposure to benzodiazepines. Neonatal flaccidity, respiratory and feeding difficulties, hypothermia, and withdrawal symptoms have been reported in infants born to mothers who received benzodiazepines, including clobazam, late in pregnancy.

Therefore, ONFI should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers

ONFI is excreted in human milk. The effects of this exposure on infants are unknown.

8.4 Pediatric Use

The 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 effect on bone density, but not on behavior, was reversible when drug was discontinued. The no-effect level for juvenile toxicity (36 mg/kg/day) was associated with plasma exposures (AUC) to clobazam and its major active metabolite, N-desmethylclobazam, less than those expected at therapeutic doses in pediatric patients.

8.5 Geriatric Use

Clinical studies of ONFI did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. However, elderly subjects appear to eliminate clobazam more slowly than younger subjects based on population pharmacokinetic analysis. For these reasons, the initial dose in elderly patients should be 5 mg/day. Patients should be titrated initially to 10-20 mg/day. Patients may be titrated further to a maximum daily dose of 40 mg if tolerated *[see Dosage and Administration (2.2), Clinical Pharmacology (12.3)]*.

8.6 CYP2C19 Poor Metabolizers

Concentrations of clobazam's active metabolite, N-desmethylclobazam, are higher in CYP2C19 poor metabolizers than in extensive metabolizers. For this reason, the initial dose in patients known to be CYP2C19 poor metabolizers should be 5 mg/day. These patients should be titrated initially to 10-20 mg/day, and may be titrated further to a maximum daily dose of 40 mg if tolerated *[see Dosage and Administration (2.3), Clinical Pharmacology (12.5)]*.

8.7 Renal Impairment

The pharmacokinetics of ONFI were evaluated in patients with mild and moderate renal impairment. There were no significant differences in systemic exposure (AUC and C_{max}) between patients with mild or moderate renal impairment and healthy subjects. No dose adjustment is required for patients with mild and moderate renal impairment. There is essentially no experience with ONFI in patients with severe renal impairment or ESRD. It is not known if clobazam or its active metabolite, N-desmethylclobazam, is dialyzable *[see Dosage and Administration (2.4), Clinical Pharmacology (12.3)]*.

8.8 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, the initial dose in patients with mild to moderate hepatic impairment (Child-Pugh score 5-9) should be 5 mg/day. These patients should be titrated initially to 10 to 20 mg/day, and may be titrated further to a maximum daily dose

of 40 mg if tolerated. 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 Dosage and Administration (2.5), Clinical Pharmacology (12.3)]*.

9. DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

ONFI is listed in Schedule IV of the Controlled Substances Act (CSA).

9.2 Abuse

The pharmacological profile of ONFI is similar to that of other benzodiazepines listed in Schedule IV of the CSA, particularly in its potentiation of GABAergic transmission through its action on $GABA_A$ receptors, which leads to sedation, somnolence, and anxiolysis. Therefore, ONFI may be abused in a similar manner as other benzodiazepines, such as diazepam.

The World Health Organization epidemiology database contains reports of drug abuse, misuse, and overdoses associated with clobazam.

9.3 Dependence

Dependence

Physical dependence is a state of adaptation that is manifested by a specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood levels of the drug, and/or administration of an antagonist. In clinical trials, cases of dependency were reported following abrupt discontinuation of ONFI.

The risk of dependence is present even with use of ONFI at the recommended dose range over periods of only a few weeks. The risk of dependence increases with increasing dose and duration of treatment. The risk of dependence is increased in patients with a history of alcohol or drug abuse.

Withdrawal

Abrupt discontinuation of ONFI causes withdrawal symptoms. As with other benzodiazepines, ONFI should be withdrawn gradually *[see Dosage and Administration (2.5), Warnings and Precautions (5.3)].*

In ONFI clinical pharmacology trials in healthy volunteers, the most common withdrawal symptoms after abrupt discontinuation were headache, tremor, insomnia, anxiety, irritability, drug withdrawal syndrome, palpitations, and diarrhea *[see Warnings and Precautions (5.3)].*

Other withdrawal reactions to clobazam reported in the literature include restlessness, panic attacks, profuse sweating, difficulty in concentrating, nausea and dry retching, weight loss, blurred vision, photophobia, and muscle pain and stiffness. In general, benzodiazepine withdrawal may cause seizures, psychosis, and hallucinations *[see Warnings and Precautions (5.3)]*.

10. OVERDOSAGE

10.1 Signs and Symptoms of Overdosage

Overdose and intoxication with benzodiazepines, including ONFI, may lead to CNS depression, associated with drowsiness, confusion and lethargy, possibly progressing to ataxia, respiratory depression, hypotension, and, rarely, coma or death. The risk of a fatal outcome is increased in cases of combined poisoning with other CNS depressants, including alcohol.

10.2 Management of Overdosage

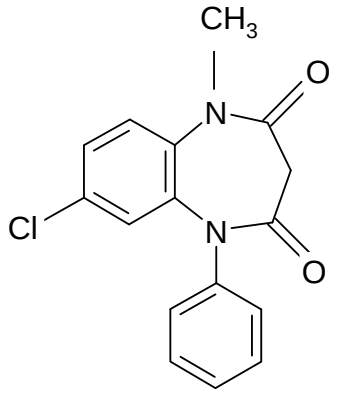
The management of ONFI overdose may include gastric lavage and/or administration of activated charcoal, intravenous fluid replenishment, early control of airway and general supportive measures, in addition to monitoring level of consciousness and vital signs. Hypotension can be treated by replenishment with plasma substitutes and, if necessary, with sympathomimetic agents.

The efficacy of supplementary administration of physostigmine (a cholinergic agent) or of flumazenil (a benzodiazepine antagonist) in ONFI overdose has not been assessed. The administration of flumazenil in cases of benzodiazepine overdose can lead to withdrawal and adverse reactions. Its use in patients with epilepsy is typically not recommended.

11. DESCRIPTION

Table 4. Description

Proprietary Name:	ONFI™
Established Name:	Clobazam
Dosage Form:	Tablet
Route of Administration:	Oral
Pharmacologic Class of Drug:	Antiepileptic drug of the benzodiazepine class
Chemical Name:	7-Chloro-1-methyl-5-phenyl-1H-1,5 benzodiazepine-2,4(*3H,5H*)-dione

Structural Formula:	

Each ONFI tablet contains 5 mg, 10 mg, or 20 mg of clobazam. Tablets also contain as inactive ingredients: corn starch, lactose monohydrate, magnesium stearate, silicon dioxide, and talc. The molecular formula is $C_{16}H_{13}O_2N_2Cl$ and the molecular weight is 300.7.

Clobazam is a white or almost white, crystalline powder which is freely soluble in methylene chloride, slightly soluble in water, and sparingly soluble in ethanol. The melting range of clobazam is from 182-185ºC.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The exact mechanism of action for clobazam, a 1,5-benzodiazepine, is not fully understood but is thought to involve potentiation of GABAergic neurotransmission resulting from binding at the benzodiazepine site of the $GABA_A$ receptor.

12.2 Pharmacodynamics

Effects on Electrocardiogram

The effect of ONFI 20 mg and 80 mg administered twice daily on QTc interval was evaluated in a randomized, evaluator blinded, placebo-, and active-controlled (moxifloxacin 400 mg) parallel thorough QT study in 280 healthy subjects. In a study with demonstrated ability to detect small effects, the upper bound of the one-sided 95% confidence interval for the largest placebo adjusted, baseline-corrected QTc based on Fridericia correction method was below 10 ms, the threshold for regulatory concern. The dose of 80 mg twice daily is adequate to represent the high exposure clinical scenario.

12.3 Pharmacokinetics

The peak plasma levels (C_{max}) and the area under the curve (AUC) of clobazam are dose-proportional over the dose range of 10-80 mg following single- or

multiple-dose administration of ONFI. Based on a population pharmacokinetic analysis, the pharmacokinetics of clobazam are linear from 5-160 mg/day. Clobazam is converted to N-desmethylclobazam which has about 1/5 the activity of clobazam. The estimated mean elimination half-lives ($t_{½}$) of clobazam and N-desmethylclobazam were 36-42 hours and 71-82 hours, respectively.

Absorption

Clobazam is rapidly and extensively absorbed following oral administration. The time to peak concentrations (T_{max}) range from 0.5 to 4 hours after single- or multiple-dose administrations. The relative bioavailability of clobazam tablets compared to an oral solution is approximately 100%. The administration of ONFI with food or when crushed in applesauce does not affect absorption.

Distribution

Clobazam is lipophilic and distributes rapidly throughout the body. The apparent volume of distribution at steady state was approximately 100 L. The *in vitro* plasma protein binding of clobazam and N-desmethylclobazam is approximately 80-90% and 70%, respectively.

Metabolism and Excretion

Clobazam is extensively metabolized in the liver, with approximately 2% of the dose recovered in urine and 1% in feces as unchanged drug. The major metabolic pathway of clobazam involves N-demethylation, primarily by CYP3A4 and to a lesser extent by CYP2C19 and CYP2B6. N-desmethylclobazam, an active metabolite, is the major circulating metabolite in humans, and at therapeutic doses, plasma concentrations are 3-5 times higher than those of the parent compound. Based on animal and *in vitro* receptor binding data, estimates of the relative potency of N-desmethylclobazam compared to parent compound range from 1/5 to equal potency. N-desmethylclobazam is extensively metabolized, mainly by CYP2C19. N-desmethylclobazam and its metabolites comprise ~94% of the total drug-related components in urine. Following a single oral dose of radiolabeled drug, approximately 11% of the dose was excreted in the feces and approximately 82% was excreted in the urine.

The polymorphic CYP2C19 is the major contributor to the metabolism of the pharmacologically active N-desmethylclobazam *[see Clinical Pharmacology (12.5)]*. In CYP2C19 poor metabolizers, levels of N-desmethylclobazam were 5-fold higher in plasma and 2- to 3-fold higher in the urine than in CYP2C19 extensive metabolizers.

Pharmacokinetics in Specific Populations

Age

Population pharmacokinetic analyses showed that the clearance of clobazam is lower in elderly subjects compared to other age groups (ages 2 to 64). Dosing should be adjusted in the elderly *[see Dosage and Administration (2.2)]*.

Sex

Population pharmacokinetic analyses showed no difference in the clearance of clobazam between women and men.

Race

Population pharmacokinetic analyses including Caucasian (75%), African American (15%), and Asian (9%) subjects showed that there is no evidence of clinically significant effect of race on the clearance of clobazam.

Renal Impairment

The effect of renal impairment on the pharmacokinetics of clobazam was evaluated in patients with mild (creatinine clearance [CL_{CR}] > 50 to 80 mL/min; N=6) and moderate (CL_{CR}=30 to 50 mL/min; N=6) renal dysfunction, with matching healthy controls (N=6), following administration of multiple doses of ONFI 20 mg/day. There were insignificant changes in C_{max} (3-24%) and AUC (≤13%) for clobazam or N-desmethylclobazam in patients with mild or moderate renal impairment compared to patients with normal renal function. Patients with severe renal impairment or ESRD were not included in this study.

Hepatic Impairment

There are limited data to characterize the effect of hepatic impairment on the pharmacokinetics of clobazam. In a small study, the pharmacokinetics of a 20 mg single oral dose of ONFI in 9 patients with liver impairment were compared to healthy controls (N=6). The C_{max} and the mean plasma clearance of clobazam, as well as the C_{max} of N-desmethylclobazam, showed no significant change compared to the healthy controls. The AUC values of N-desmethylclobazam in these patients were not available. Adjust dosage in patients with hepatic impairment *[see Dosage and Administration (2.5)]*.

Drug Interactions

In vitro studies:

Clobazam did not inhibit CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, UGT1A1, UGT1A4, UGT1A6, or UGT2B4 *in vitro*. N-desmethylclobazam showed weak inhibition of CYP2C9, UGT1A4, UGT1A6 and UGT2B4.

Clobazam and N-desmethylclobazam did not significantly increase CYP1A2 or CYP2C19 activities, but did induce CYP3A4 activity in a concentration-dependent manner. Clobazam and N-desmethylclobazam also increased UGT1A1 mRNA but at concentrations much higher than therapeutic levels. The potential for clobazam or N-desmethylclobazam to induce CYP2B6 and CYP2C8 has not been evaluated.

Clobazam and N-desmethylclobazam do not inhibit P-glycoprotein (P-gp), but are P-gp substrates.

In vivo studies:

Potential for ONFI to Affect Other Drugs

The effect of repeated 40 mg once-daily doses of ONFI on the pharmacokinetic profiles of single-dose dextromethorphan (CYP2D6 substrate), midazolam (CYP3A4 substrate), caffeine (CYP1A2 substrate), and tolbutamide (CYP2C9 substrate), was studied when these probe substrates were given as a drug cocktail (N=18).

Clobazam increased AUC and C_{max} of dextromethorphan by 90% and 59%, respectively, reflecting its inhibition of CYP2D6 *in vivo*. Drugs metabolized by CYP2D6 may require dose adjustment when used with ONFI.

Clobazam decreased the AUC and C_{max} of midazolam by 27% and 24%, respectively, and increased the AUC and C_{max} of the metabolite 1-hydroxymidazolam by 4-fold and 2-fold, respectively. This level of induction does not call for dosage adjustment of drugs that are primarily metabolized by CYP3A4 when used concomitantly with ONFI. Some hormonal contraceptives are metabolized by CYP3A4, and their effectiveness may be diminished when given with ONFI. Additional non-hormonal forms of contraception are recommended when using ONFI *[see Drug Interactions (7)]*. Repeated ONFI doses had no effect on caffeine and tolbutamide.

A population pharmacokinetic analysis indicated clobazam did not affect the exposure of valproic acid (a CYP2C9/2C19 substrate) or lamotrigine (a UGT substrate).

Potential for Other Drugs to Affect ONFI

Co-administration of ketoconazole (a strong CYP3A4 inhibitor) 400 mg once-daily for 5 days increased clobazam AUC by 54%, with an insignificant effect on clobazam C_{max}. There was no significant change in AUC and C_{max} of N-desmethylclobazam (N=18).

Strong (e.g., fluconazole, fluvoxamine, ticlopidine) and moderate (e.g., omeprazole) inhibitors of CYP2C19 may result in up to a 5-fold increase in exposure to N-desmethylclobazam, the active metabolite of clobazam, based on extrapolation from pharmacogenomic data *[see Clinical Pharmacology (12.5)]*. Dosage adjustment of ONFI may be necessary when coadministered with strong or moderate CYP2C19 inhibitors *[see Drug Interactions (7)]*.

The effects of concomitant antiepileptic drugs that are CYP3A4 inducers (phenobarbital, phenytoin, and carbamazepine), CYP2C9 inducers (valproic acid, phenobarbital, phenytoin, and carbamazepine), and CYP2C9 inhibitors (felbamate and oxcarbazepine) were evaluated using data from clinical trials. Results of population pharmacokinetic analysis show that these concomitant antiepileptic drugs did not significantly alter the pharmacokinetics of clobazam or N-desmethylclobazam at steady-state.

Alcohol has been reported to increase the maximum plasma exposure of clobazam by approximately 50%. Alcohol may have additive CNS depressant effects when taken with *ONFI [see Warnings and Precautions (5.2), Drug Interactions (7)]*.

12.5 Pharmacogenomics

The polymorphic CYP2C19 is the main enzyme that metabolizes the pharmacologically active N-desmethylclobazam. Compared to CYP2C19 extensive metabolizers, N-desmethylclobazam AUC and C_{max} are approximately 3-5 times higher in poor metabolizers (e.g., subjects with *2/*2 genotype) and 2 times higher in intermediate metabolizers (e.g., subjects with *1/*2 genotype). The prevalence of CYP2C19 poor metabolism differs depending on racial/ethnic background. Dosage in patients who are known CYP2C19 poor metabolizers may need to be adjusted *[see Dosage and Administration (2.3)]*.

The systemic exposure of clobazam is similar for both CYP2C19 poor and extensive metabolizers.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

The carcinogenic potential of clobazam has not been adequately assessed.

In a limited study in rats, oral administration of clobazam (4, 20, and 100 mg/kg/day) for 2 years resulted in an increased incidence of thyroid follicular cell adenomas in males at the high dose.

Mutagenesis

Clobazam and the major active metabolite, N-desmethylclobazam, were negative for genotoxicity, based on data from a battery of *in vitro* (bacteria reverse mutation, mammalian clastogenicity) and *in vivo* (mouse micronucleus) assays.

Impairment of Fertility

There are no adequate studies of the effects of clobazam on fertility.

14. CLINICAL STUDIES

The effectiveness of ONFI for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome was established in two multicenter controlled studies (Study 1 and Study 2). Both studies were similar in terms of disease characteristics and concomitant AED treatments. The most common concomitant AED treatments at baseline included: valproate, lamotrigine, levetiracetam, and topiramate.

Study 1

Study 1 (N=238) was a randomized, double-blind, placebo-controlled study consisting of a 4-week baseline period followed by a 3-week titration period and 12-week maintenance period. Patients age 2-54 years with a current or prior diagnosis of LGS were stratified into 2 weight groups (12.5 kg to ≤30 kg or >30 kg) and then randomized to placebo or one of three target maintenance doses of ONFI according to Table 5.

Table 5. Study 1 Total Daily Dose

	≤30 kg Body Weight	>30 kg Body Weight
Low Dose	5 mg daily	10 mg daily
Medium Dose	10 mg daily	20 mg daily
High Dose	20 mg daily	40 mg daily

Doses above 5 mg/day were administered in two divided doses.

The primary efficacy measure was the percent reduction in the weekly frequency of drop seizures (atonic, tonic, or myoclonic), also known as drop attacks, from the 4-week baseline period to 12-week maintenance period.

The pre-dosing baseline mean weekly drop seizure frequency was 98, 100, 61, and 105 for the placebo, low-, medium-, and high-dose groups, respectively. Figure 1 presents the mean percent reduction in weekly drop seizures from this baseline. All dose groups of ONFI were statistically superior ($p \leq 0.05$) to the placebo group. This effect appeared to be dose dependent.

Figure 1. Mean Percent Reduction from Baseline in Weekly Drop Seizure Frequency (Study 1)

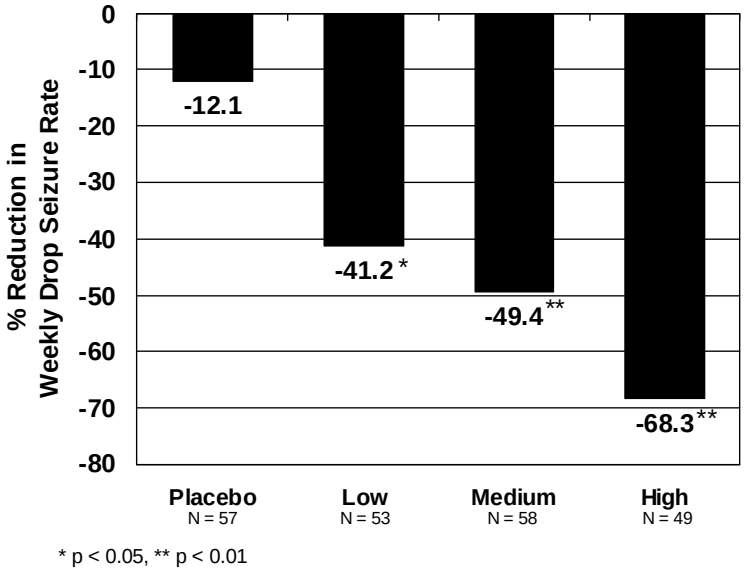
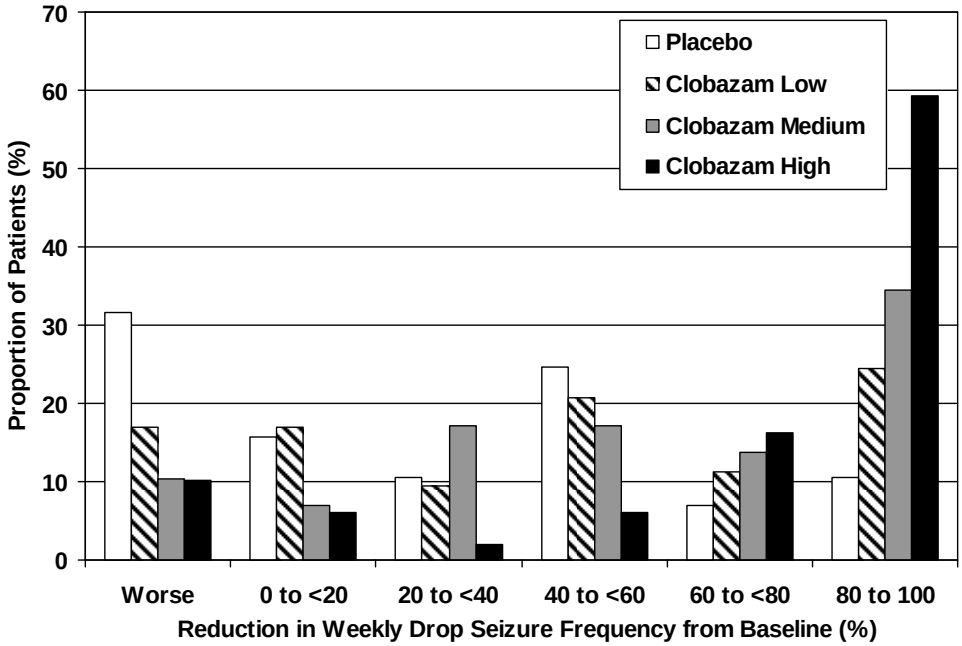


Figure 2 shows changes from baseline in weekly drop seizure frequency by category for patients treated with ONFI and placebo in Study 1. Patients in whom the seizure frequency increased are shown at left as "worse." Patients in whom the seizure frequency decreased are shown in five categories.

Figure 2. Drop Seizure Response by Category for ONFI and Placebo (Study 1)



There was no evidence that tolerance to the therapeutic effect of ONFI developed during the 3-month maintenance period.

Study 2

Study 2 (N=68) was a randomized, double-blind comparison study of high- and low-dose ONFI, consisting of a 4-week baseline period followed by a 3-week titration period and 4-week maintenance period. Patients age 2-25 years with a current or prior diagnosis of LGS were stratified into 2 weight groups (12.5 kg to ≤30 kg or >30 kg) then randomized to either a low target dose of ONFI (daily dose of 5 mg for ≤30 kg body weight; 10 mg for >30 kg body weight) or high target dose of ONFI (daily dose of 20 mg ≤30 kg body weight; 40 mg for >30 kg body) and entered a 3-week titration period.

The primary efficacy measure was the percent reduction in the weekly frequency of drop seizures (atonic, tonic, or myoclonic), also known as drop attacks, from the 4-week baseline period to the 4-week maintenance period.

A statistically significantly greater reduction in seizure frequency was observed in the high-dose group compared to the low-dose group (median percent reduction of 93% vs 29%; $p<0.05$).

16. HOW SUPPLIED/STORAGE AND HANDLING

Each ONFI tablet contains 5 mg, 10 mg, or 20 mg of clobazam and is white, round, and debossed with “LU” on one side and “5,” “10,” and “20” on the other side, respectively.

NDC 67386-310-01: 5 mg tablet, Bottles of 100

NDC 67386-311-01:10 mg tablet, Bottles of 100

NDC 67386-312-01: 20 mg tablet, Bottles of 100

Store at 20-25°C (68-77°F). See USP controlled room temperature.

17. PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

Inform patients or caregivers of the availability of a Medication Guide and instruct them to read the Medication Guide prior to initiating treatment with ONFI and with each prescription refill. Review the ONFI Medication Guide with every patient or caregiver prior to initiation of treatment. Instruct patients or caregivers that ONFI should be taken only as prescribed.

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 (5.1)].*

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 (2.6), Warnings and Precautions (5.3)].*

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), Clinical Pharmacology (12.3)].*

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 (5.5)].*

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)]*.

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

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

MEDICATION GUIDE

ONFI™ (ON-fee)
(clobazam)
Tablets

Read this Medication Guide before you start taking ONFI and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment.

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 problems.

ONFI can cause serious side effects, including:

1. ONFI can make you sleepy or dizzy, slow your thinking, and make you clumsy which may get better over time.

- 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 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.

2. 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.

3. 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 federally controlled substance (C-IV) 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.

4. 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
- attempts to commit suicide
- new or worse depression

- new or worse anxiety
- feeling agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- 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.

What should I tell my healthcare provider before taking ONFI?

Before you take ONFI, tell your healthcare provider if you:

- have liver or kidney problems
- have lung problems (respiratory disease)
- have or have had depression, mood problems, or suicidal thoughts or behavior
- have any other medical conditions
- 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.
- Children 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. 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 breast feed. You should not do both.

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

Know the medicines you take. Keep a list of them and show it to your healthcare provider and pharmacist when you get a new medicine.

How should I take ONFI?

- ONFI can be taken whole, or crushed and mixed in applesauce.
- 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.

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

These are not all the possible side effects of ONFI. For more information, ask your healthcare provider or pharmacist.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

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 between 68°F to 77°F (20°C to 25°C).

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.

This Medication Guide summarizes the most important information about ONFI. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about ONFI that is written for health professionals.

For more information about ONFI, go to www.lundbeckinc.com or call Lundbeck Inc. at 1-888-514-5204.

What are the ingredients in ONFI?

Active ingredient: clobazam

Inactive ingredients: corn starch, lactose monohydrate, magnesium stearate, silicon dioxide, and talc.

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

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

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

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