

## 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

ONFI® (clobazam) oral suspension, CIV

Initial U.S. Approval: 2011

### RECENT MAJOR CHANGES

Dosage and Administration:

Important Administration Instructions (2.3) 12/2012

### 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 at 5 mg daily and titrate as tolerated up to 20 mg daily (2.1)
- Patients > 30 kg body weight: Initiate at 10 mg daily and titrate as tolerated up to 40 mg daily (2.1)
- For doses above 5 mg/day administer in two divided doses (2.1)
  - Dosage adjustment needed in following groups: Geriatric patients (2.4, 8.5)
  - Known CYP2C19 poor metabolizers (2.5)
  - Mild or moderate hepatic impairment; no information for severe hepatic impairment (2.7, 8.8)
- Reduce dose, or discontinue drug gradually (2.2)
- Tablets: Administer whole, broken in half along the score, or crush and mix in applesauce. (2.3)
- Measure prescribed amount of oral suspension using provided adapter and dosing syringe (2.3)
- Tablets and Oral suspension: Can be taken with or without food. (2.3)

### DOSAGE FORMS AND STRENGTHS

- Tablet: 10 mg and 20 mg with a functional score (3)

- Oral Suspension: 2.5 mg/mL in 120 mL bottles (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:* Monitor patients with a history of substance abuse 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 at least 10% more frequently than placebo in any ONFI dose included constipation, somnolence or sedation, pyrexia, lethargy, and drooling (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Lundbeck at 1-800-455-1141 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

- *Drugs metabolized by CYP2D6:* Lower doses of these drugs may be required when used concomitantly with ONFI (7.1)
- *Strong or Moderate CYP2C19 Inhibitors:* Dosage adjustment of ONFI may be necessary (7.2)
- *Alcohol:* Increases blood levels of clobazam by about 50% (7.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2012

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

1 **FULL PRESCRIBING INFORMATION**

2  
3 **1 INDICATIONS AND USAGE**

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

7  
8 **2 DOSAGE AND ADMINISTRATION**

9 **2.1 Dosing Information**

10  
11 A daily dose of ONFI greater than 5 mg should be administered in divided doses  
12 twice daily; a 5 mg daily dose can be administered as a single dose. Dose  
13 patients according to body weight. Individualize dosing within each body weight  
14 group, based on clinical efficacy and tolerability. Each dose in Table 1 (e.g. 5 to  
15 20 mg in ≤ 30 kg weight group) has been shown to be effective, although  
16 effectiveness increases with increasing dose [see *Clinical Studies (14)*]. Do not  
17 proceed with dose escalation more rapidly than weekly, because serum  
18 concentrations of clobazam and its active metabolite require 5 and 9 days,  
19 respectively, to reach steady-state.

20  
21 **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

22  
23  
24 **2.2 Gradual Withdrawal**

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

28  
29 **2.3 Important Administration Instructions**

30 Instruct patients to read the “Instructions for Use” carefully for complete  
31 directions on how to properly dose and administer ONFI oral suspension.

32  
33 **ONFI Tablet Oral Administration**

34 ONFI tablets can be taken with or without food.

35 ONFI tablets can be administered whole, broken in half along the score, or  
36 crushed and mixed in applesauce.

37  
38 **ONFI Oral Suspension Oral Administration**

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ONFI oral suspension can be taken with or without food [see *Clinical Pharmacology* (12.3)].

Shake ONFI Oral Suspension well before every administration. When administering the oral suspension, use only the oral dosing syringe provided with the product. Each carton includes two syringes, but only one syringe should be used for dosing. The second oral syringe is reserved as a replacement in case the first syringe is damaged or lost. Insert the provided adapter firmly into the neck of the bottle before first use and keep the adapter in place for the duration of the usage of the bottle. To withdraw the dose, insert the dosing syringe into the adapter and invert the bottle then slowly pull back the plunger to prescribed dose. After removing the syringe from the bottle adapter, slowly squirt ONFI Oral Suspension into the corner of the patient’s mouth. Replace the cap after each use. The cap fits over the adapter when the adapter is properly placed. See ONFI Oral Suspension “[Instructions for Use](#)” for complete instruction on how to properly dose and administer the ONFI Oral Suspension.

#### **2.4 Dosage Adjustments in Geriatric Patients**

Plasma concentrations at any given dose are generally higher in the elderly: proceed slowly with dose escalation. The starting dose should be 5 mg/day for all elderly patients. Then titrate elderly patients 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)].

#### **2.5 Dosage Adjustments in 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)].

#### **2.6 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)].

#### **2.7 Dosage Adjustments in Patients with Hepatic Impairment**

84 ONFI is hepatically metabolized; however, there are limited data to characterize  
85 the effect of hepatic impairment on the pharmacokinetics of ONFI. For this  
86 reason, proceed slowly with dosing escalations. For patients with mild to  
87 moderate hepatic impairment (Child-Pugh score 5-9), the starting dose should be  
88 5 mg/day in both weight groups. Then titrate patients according to weight, but to  
89 half the dose presented in Table 1, as tolerated. If necessary and based upon  
90 clinical response, start an additional titration on day 21 to the maximum dose (20  
91 mg/day or 40 mg/day, depending on the weight group). There is inadequate  
92 information about metabolism of ONFI in patients with severe hepatic  
93 impairment. Therefore no dosing recommendation in those patients can be given  
94 [see *Use in Specific Populations (8.8)*, *Clinical Pharmacology (12.3)*].

### 96 **3 DOSAGE FORMS AND STRENGTHS**

97 Tablets: 10 mg and 20 mg with a functional score for oral administration.

98 Each ONFI tablet is a white to off-white, oval tablet with a functional score on one  
99 side and either a “1” and “0” or a “2” and “0” debossed on the other side.

100  
101 Oral Suspension: 2.5 mg/mL for oral administration. Each bottle contains 120 mL  
102 of an off-white suspension.

### 104 **4 CONTRAINDICATIONS**

105 None.

### 107 **5 WARNINGS AND PRECAUTIONS**

#### 108 **5.1 Somnolence or Sedation**

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

111  
112 In general, somnolence and sedation begin within the first month of treatment  
113 and may diminish with continued treatment. Prescribers should monitor patients  
114 for somnolence and sedation, particularly with concomitant use of other central  
115 nervous system depressants. Prescribers should caution patients against  
116 engaging in hazardous activities requiring mental alertness, such as operating  
117 dangerous machinery or motor vehicles, until the effect of ONFI is known.

#### 119 **5.2 Potentiation of Sedation from Concomitant Use with Central Nervous 120 System Depressants**

121 Since ONFI has a central nervous system (CNS) depressant effect, patients or  
122 their caregivers should be cautioned against simultaneous use with other CNS  
123 depressant drugs or alcohol, and cautioned that the effects of other CNS  
124 depressant drugs or alcohol may be potentiated.

#### 126 **5.3 Withdrawal Symptoms**

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

130

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

133

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

136

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

145

#### 146 **5.4 Physical and Psychological Dependence**

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

151

#### 152 **5.5 Suicidal Behavior and Ideation**

153 Antiepileptic drugs (AEDs), including ONFI, increase the risk of suicidal thoughts  
154 or behavior in patients taking these drugs for any indication. Patients treated  
155 with any AED for any indication should be monitored for the emergence or  
156 worsening of depression, suicidal thoughts or behavior, and/or any unusual  
157 changes in mood or behavior.

158

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

171

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

177

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

184

**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

185

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

189

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

197

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

204

205 **6 ADVERSE REACTIONS**

206 Clinically significant adverse reactions that appear in other sections of the  
207 labeling include the following:

208

- 209 • Somnolence or Sedation [see *Warnings and Precautions (5.1)*]
- 210 • Potentiation of Sedation from Concomitant Use with Central Nervous  
211 System Depressants [see *Warnings and Precautions (5.2)*]
- 212 • Withdrawal Symptoms [see *Warnings and Precautions (5.3)*]
- 213 • Physical and Psychological Dependence [see *Warnings and Precautions*  
214 *(5.4)*]
- 215 • Suicidal Behavior and Ideation [see *Warnings and Precautions (5.5)*]

216

217 **6.1 Clinical Trials Experience**

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

222

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

231

232 Adverse Reactions Leading to Discontinuation in an LGS Placebo Controlled  
233 Clinical Trial (Study 1)

234 The adverse reactions associated with ONFI treatment discontinuation in  $\geq 1\%$   
235 patients in decreasing order of frequency included lethargy, somnolence, ataxia,  
236 aggression, fatigue, and insomnia.

237

238 Most Common Adverse Reactions in an LGS Placebo Controlled Clinical Trial  
239 (Study 1)

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

244



**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 <sup>a</sup> N=58 %	Medium <sup>b</sup> N=62 %	High <sup>c</sup> N=59 %	
<b>Gastrointestinal Disorders</b>					
Vomiting	5	9	5	7	7
Constipation	0	2	2	10	5
Dysphagia	0	0	0	5	2
<b>General Disorders and Administration Site Conditions</b>					
Pyrexia	3	17	10	12	13
Irritability	5	3	11	5	7
Fatigue	2	5	5	3	5
<b>Infections and Infestations</b>					
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
<b>Metabolism and Nutrition Disorders</b>					
Decreased appetite	3	3	0	7	3
Increased appetite	0	2	3	5	3
<b>Nervous System Disorders</b>					
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
<b>Psychiatric Disorders</b>					
Aggression	5	3	8	14	8
Insomnia	2	2	5	7	5
<b>Respiratory Disorders</b>					
Cough	0	3	5	7	5

245

<sup>a</sup> Maximum daily dose of 5 mg for ≤30 kg body weight; 10 mg for >30 kg body weight

246

<sup>b</sup> Maximum daily dose of 10 mg for ≤30 kg body weight; 20 mg for >30 kg body weight

247

<sup>c</sup> Maximum daily dose of 20 mg for ≤30 kg body weight; 40 mg for >30 kg body weight

248



249 **6.2 Post Marketing Experience** These reactions are reported voluntarily from  
250 a population of uncertain size; therefore, it is not possible to estimate their  
251 frequency or establish a causal relationship to drug exposure. Adverse reactions  
252 are categorized by system organ class.

253

254 **Blood Disorders:** Anemia, eosinophilia, leukopenia, thrombocytopenia

255 **Eye Disorders:** Diplopia, vision blurred

256 **Gastrointestinal Disorders:** Abdominal distention

257 **Investigations:** Hepatic enzyme increased

258 **Musculoskeletal:** Muscle spasms

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

261 **Respiratory Disorders:** Aspiration, respiratory depression

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

264

## 265 **7 DRUG INTERACTIONS**

266

### 267 **7.1 Effect of ONFI on Other Drugs**

#### 268 Hormonal Contraceptives

269 ONFI is a weak CYP3A4 inducer. As some hormonal contraceptives are  
270 metabolized by CYP3A4, their effectiveness may be diminished when given with  
271 ONFI. Additional non-hormonal forms of contraception are recommended when  
272 using ONFI [see *Clinical Pharmacology (12.3)*, *Patient Counseling Information*  
273 *(17)*].

274

#### 275 Drugs Metabolized by CYP2D6

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

278

### 279 **7.2 Effect of Other Drugs on ONFI**

#### 280 Strong and moderate inhibitors of CYP2C19

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

287

### 288 **7.3 CNS Depressants and Alcohol**

289 Concomitant use of ONFI with other CNS depressants may increase the risk of  
290 sedation and somnolence [see *Warnings and Precautions (5.2)*].

291

292 Alcohol, as a CNS depressant, will interact with ONFI in a similar way and also  
293 increases clobazam's maximum plasma exposure by approximately 50%.

294 Therefore, caution patients or their caregivers against simultaneous use with  
295 other CNS depressant drugs or alcohol, and cautioned that the effects of other  
296 CNS depressant drugs or alcohol may be potentiated [see *Warnings and*  
297 *Precautions (5.2)*].

298

## 299 **8 USE IN SPECIFIC POPULATIONS**

### 300 **8.1 Pregnancy**

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

307

### 308 **Pregnancy Category C.**

309

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

312

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

317

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

324

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

327

### 328 **8.3 Nursing Mothers**

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

331

### 332 **8.4 Pediatric Use**

333 The safety and effectiveness in patients less than 2 years of age have not been  
334 established.

335

336 In a study in which clobazam (4, 36, or 120 mg/kg/day) was orally administered  
337 to rats during the juvenile period of development (postnatal days 14 to 48),  
338 adverse effects on growth (decreased bone density and bone length) and  
339 behavior (altered motor activity and auditory startle response; learning deficit)  
340 were observed at the high dose. The effect on bone density, but not on behavior,  
341 was reversible when drug was discontinued. The no-effect level for juvenile  
342 toxicity (36 mg/kg/day) was associated with plasma exposures (AUC) to  
343 clobazam and its major active metabolite, N-desmethyloclobazam, less than those  
344 expected at therapeutic doses in pediatric patients.

345

### 346 **8.5 Geriatric Use**

347 Clinical studies of ONFI did not include sufficient numbers of subjects aged 65  
348 and over to determine whether they respond differently from younger subjects.  
349 However, elderly subjects appear to eliminate clobazam more slowly than  
350 younger subjects based on population pharmacokinetic analysis. For these  
351 reasons, the initial dose in elderly patients should be 5 mg/day. Patients should  
352 be titrated initially to 10-20 mg/day. Patients may be titrated further to a  
353 maximum daily dose of 40 mg if tolerated [see *Dosage and Administration (2.4)*,  
354 *Clinical Pharmacology (12.3)*].

355

### 356 **8.6 CYP2C19 Poor Metabolizers**

357 Concentrations of clobazam's active metabolite, N-desmethyloclobazam, are  
358 higher in CYP2C19 poor metabolizers than in extensive metabolizers. For this  
359 reason, dosage modification is recommended [see *Dosage and Administration*  
360 *(2.5)*, *Clinical Pharmacology (12.3)*].

361

### 362 **8.7 Renal Impairment**

363 The pharmacokinetics of ONFI were evaluated in patients with mild and  
364 moderate renal impairment. There were no significant differences in systemic  
365 exposure (AUC and  $C_{max}$ ) between patients with mild or moderate renal  
366 impairment and healthy subjects. No dose adjustment is required for patients  
367 with mild and moderate renal impairment. There is essentially no experience  
368 with ONFI in patients with severe renal impairment or ESRD. It is not known if  
369 clobazam or its active metabolite, N-desmethyloclobazam, is dialyzable [see  
370 *Dosage and Administration (2.6)*, *Clinical Pharmacology (12.3)*].

371

### 372 **8.8 Hepatic Impairment**

373 ONFI is hepatically metabolized; however, there are limited data to characterize  
374 the effect of hepatic impairment on the pharmacokinetics of ONFI. For this  
375 reason, dosage adjustment is recommended in patients with mild to moderate  
376 hepatic impairment (Child-Pugh score 5-9). There is inadequate information

377 about metabolism of ONFI in patients with severe hepatic impairment [see  
378 *Dosage and Administration (2.7), Clinical Pharmacology (12.3)*].  
379

## 380 **9 DRUG ABUSE AND DEPENDENCE**

### 381 **9.1 Controlled Substance**

382 ONFI contains clobazam which is a Schedule IV controlled substance.  
383

### 384 **9.2 Abuse**

385  
386 ONFI can be abused in a similar manner as other benzodiazepines, such as  
387 diazepam.  
388

389 The pharmacological profile of ONFI is similar to that of other benzodiazepines  
390 listed in Schedule IV of the Controlled Substance Act, particularly in its  
391 potentiation of GABAergic transmission through its action on GABA<sub>A</sub> receptors,  
392 which leads to sedation and somnolence.  
393

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

396 Drug abuse is the intentional non-therapeutic use of a drug, repeatedly or even  
397 sporadically, for its rewarding psychological or physiological effects.  
398

### 399 **9.3 Dependence**

#### 400 *Dependence*

401 Physical dependence is a state of adaptation that is manifested by a specific  
402 withdrawal syndrome that can be produced by abrupt cessation, rapid dose  
403 reduction, decreasing blood levels of the drug, and/or administration of an  
404 antagonist. In clinical trials, cases of dependency were reported following abrupt  
405 discontinuation of ONFI.  
406

407 The risk of dependence is present even with use of ONFI at the recommended  
408 dose range over periods of only a few weeks. The risk of dependence  
409 increases with increasing dose and duration of treatment. The risk of  
410 dependence is increased in patients with a history of alcohol or drug abuse.  
411

#### 412 *Withdrawal*

413 Abrupt discontinuation of ONFI causes withdrawal symptoms. As with other  
414 benzodiazepines, ONFI should be withdrawn gradually [see *Dosage and*  
415 *Administration (2.2), Warnings and Precautions (5.3)*].  
416

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

421

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

427

## 428 **10 OVERDOSAGE**

### 429 **10.1 Signs and Symptoms of Overdosage**

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

435

### 436 **10.2 Management of Overdosage**

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

443

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

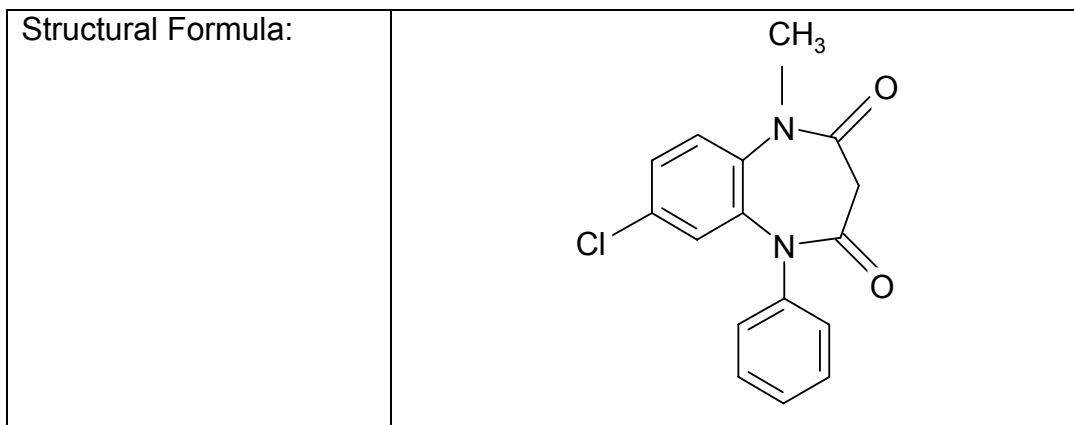
449

## 450 **11 DESCRIPTION**

451

**Table 4. Description**

Proprietary Name:	ONFI®
Established Name:	Clobazam
Dosage Forms:	Tablet and Oral Suspension
Route of Administration:	Oral
Established Pharmacologic Class of Drug:	Benzodiazepine
Chemical Name:	7-Chloro-1-methyl-5-phenyl-1H-1,5 benzodiazepine-2,4(3H,5H)-dione



452

453 Clobazam is a white or almost white, crystalline powder with a slightly bitter taste;  
 454 is slightly soluble in water, sparingly soluble in ethanol, and freely soluble in  
 455 methylene chloride. The melting range of clobazam is from 182-185°C. The  
 456 molecular formula is C<sub>16</sub>H<sub>13</sub>O<sub>2</sub>N<sub>2</sub>Cl and the molecular weight is 300.7.

457

458 Each ONFI tablet contains 10 mg or 20 mg of clobazam. Tablets also contain as  
 459 inactive ingredients: corn starch, lactose monohydrate, magnesium stearate,  
 460 silicon dioxide, and talc.

461

462 ONFI is also available for oral administration as an off-white suspension  
 463 containing clobazam at a concentration of 2.5 mg/mL. Inactive ingredients  
 464 include magnesium aluminum silicate, xanthan gum, citric acid monohydrate,  
 465 disodium hydrogen phosphate dihydrate, simethicone emulsion, polysorbate 80,  
 466 methylparaben, propylparaben, propylene glycol, sucralose, maltitol solution,  
 467 berry flavor, purified water.

468

## 469 **12 CLINICAL PHARMACOLOGY**

### 470 **12.1 Mechanism of Action**

471 The exact mechanism of action for clobazam, a 1,5-benzodiazepine, is not fully  
 472 understood but is thought to involve potentiation of GABAergic  
 473 neurotransmission resulting from binding at the benzodiazepine site of the  
 474 GABA<sub>A</sub> receptor.

475

### 476 **12.2 Pharmacodynamics**

#### 477 Effects on Electrocardiogram

478 The effect of ONFI 20 mg and 80 mg administered twice daily on QTc interval  
 479 was evaluated in a randomized, evaluator blinded, placebo-, and active-  
 480 controlled (moxifloxacin 400 mg) parallel thorough QT study in 280 healthy  
 481 subjects. In a study with demonstrated ability to detect small effects, the upper  
 482 bound of the one-sided 95% confidence interval for the largest placebo adjusted,  
 483 baseline-corrected QTc based on Fridericia correction method was below 10 ms,  
 484 the threshold for regulatory concern. Thus, at a dose two times the maximum

485 recommended dose, ONFI did not prolong the QTc interval to any clinically  
486 relevant extent.

487

### 488 **12.3 Pharmacokinetics**

489 The peak plasma levels ( $C_{max}$ ) and the area under the curve (AUC) of clobazam  
490 are dose-proportional over the dose range of 10-80 mg following single- or  
491 multiple-dose administration of ONFI. Based on a population pharmacokinetic  
492 analysis, the pharmacokinetics of clobazam are linear from 5-160 mg/day.

493 Clobazam is converted to N-desmethyclobazam which has about 1/5 the activity  
494 of clobazam. The estimated mean elimination half-lives ( $t_{1/2}$ ) of clobazam and N-  
495 desmethyclobazam were 36-42 hours and 71-82 hours, respectively.

496

#### 497 Absorption

498 Clobazam is rapidly and extensively absorbed following oral administration. The  
499 time to peak concentrations ( $T_{max}$ ) of clobazam tablets under fasted conditions  
500 ranged from 0.5 to 4 hours after single- or multiple-dose administrations. The  
501 relative bioavailability of clobazam tablets compared to an oral solution is  
502 approximately 100%. After single dose administration of the oral suspension  
503 under fasted conditions, the  $T_{max}$  ranged from 0.5 to 2 hours. Based on exposure  
504 ( $C_{max}$  and AUC) of clobazam, ONFI tablets and suspension were shown to have  
505 similar bioavailability under fasted condition. The administration of ONFI tablets  
506 with food or when crushed in applesauce does not affect absorption. Although  
507 not studied, the oral bioavailability of the oral suspension is unlikely to be  
508 affected under fed conditions.

509

#### 510 Distribution

511 Clobazam is lipophilic and distributes rapidly throughout the body. The apparent  
512 volume of distribution at steady state was approximately 100 L. The *in vitro*  
513 plasma protein binding of clobazam and N-desmethyclobazam is approximately  
514 80-90% and 70%, respectively.

515

#### 516 Metabolism and Excretion

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



528 oral dose of radiolabeled drug, approximately 11% of the dose was excreted in  
529 the feces and approximately 82% was excreted in the urine.

530

531 The polymorphic CYP2C19 is the major contributor to the metabolism of the  
532 pharmacologically active N-desmethylclobazam [see *Clinical Pharmacology*  
533 (12.5)]. In CYP2C19 poor metabolizers, levels of N-desmethylclobazam were 5-  
534 fold higher in plasma and 2- to 3-fold higher in the urine than in CYP2C19  
535 extensive metabolizers.

536

### 537 Pharmacokinetics in Specific Populations

#### 538 *Age*

539 Population pharmacokinetic analyses showed that the clearance of clobazam is  
540 lower in elderly subjects compared to other age groups (ages 2 to 64). Dosing  
541 should be adjusted in the elderly [see *Dosage and Administration* (2.4)].

542

#### 543 *Sex*

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

546

#### 547 *Race*

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

551

#### 552 *Renal Impairment*

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

561

#### 562 *Hepatic Impairment*

563 There are limited data to characterize the effect of hepatic impairment on the  
564 pharmacokinetics of clobazam. In a small study, the pharmacokinetics of a 20 mg  
565 single oral dose of ONFI in 9 patients with liver impairment were compared to  
566 healthy controls (N=6). The  $C_{max}$  and the mean plasma clearance of clobazam,  
567 as well as the  $C_{max}$  of N-desmethylclobazam, showed no significant change  
568 compared to the healthy controls. The AUC values of N-desmethylclobazam in  
569 these patients were not available. Adjust dosage in patients with hepatic  
570 impairment [see *Dosage and Administration* (2.7)].

571

572 Drug Interaction Studies

573

574 *In vitro studies:*

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

579

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

586

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

589

590 *In vivo studies:*

591

592 *Potential for ONFI to Affect Other Drugs*

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

598

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

602

603 Clobazam decreased the AUC and  $C_{max}$  of midazolam by 27% and 24%,  
604 respectively, and increased the AUC and  $C_{max}$  of the metabolite 1-  
605 hydroxymidazolam by 4-fold and 2-fold, respectively. This level of induction does  
606 not call for dosage adjustment of drugs that are primarily metabolized by  
607 CYP3A4 when used concomitantly with ONFI. Some hormonal contraceptives  
608 are metabolized by CYP3A4 and their effectiveness may be diminished when  
609 given with ONFI [see *Drug Interactions (7.1)*]. Repeated ONFI doses had no  
610 effect on caffeine and tolbutamide.

611

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

615

#### 616 *Potential for Other Drugs to Affect ONFI*

617 Co-administration of ketoconazole (a strong CYP3A4 inhibitor) 400 mg once-  
618 daily for 5 days increased clobazam AUC by 54%, with an insignificant effect on  
619 clobazam C<sub>max</sub>. There was no significant change in AUC and C<sub>max</sub> of N-  
620 desmethylclobazam (N=18).

621

622 Strong (e.g., fluconazole, fluvoxamine, ticlopidine) and moderate (e.g.,  
623 omeprazole) inhibitors of CYP2C19 may result in up to a 5-fold increase in  
624 exposure to N-desmethylclobazam, the active metabolite of clobazam, based on  
625 extrapolation from pharmacogenomic data [see *Clinical Pharmacology (12.5)*].  
626 Dosage adjustment of ONFI may be necessary when co-administered with strong  
627 or moderate CYP2C19 inhibitors [see *Drug Interactions (7.2)*].

628

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

636

637 Alcohol has been reported to increase the maximum plasma exposure of  
638 clobazam by approximately 50%. Alcohol may have additive CNS depressant  
639 effects when taken with ONFI [see *Warnings and Precautions (5.2)*, *Drug*  
640 *Interactions (7.3)*].

641

### 642 **12.5 Pharmacogenomics**

643 The polymorphic CYP2C19 is the main enzyme that metabolizes the  
644 pharmacologically active N-desmethylclobazam. Compared to CYP2C19  
645 extensive metabolizers, N-desmethylclobazam AUC and C<sub>max</sub> are approximately  
646 3-5 times higher in poor metabolizers (e.g., subjects with \*2/\*2 genotype) and 2  
647 times higher in intermediate metabolizers (e.g., subjects with \*1/\*2 genotype).  
648 The prevalence of CYP2C19 poor metabolism differs depending on racial/ethnic  
649 background. Dosage in patients who are known CYP2C19 poor metabolizers  
650 may need to be adjusted [see *Dosage and Administration (2.5)*].

651

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

654

655 **13 NONCLINICAL TOXICOLOGY**

656 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

657 **Carcinogenesis**

658 The carcinogenic potential of clobazam has not been adequately assessed.

659

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

663

664 **Mutagenesis**

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

668

669 **Impairment of Fertility**

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

671

672 **14 CLINICAL STUDIES**

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

679

680 Study 1

681 Study 1 (N=238) was a randomized, double-blind, placebo-controlled study  
682 consisting of a 4-week baseline period followed by a 3-week titration period and  
683 12-week maintenance period. Patients age 2-54 years with a current or prior  
684 diagnosis of LGS were stratified into 2 weight groups (12.5 kg to ≤30 kg or >30  
685 kg) and then randomized to placebo or one of three target maintenance doses of  
686 ONFI according to Table 5.

687

688 **Table 5. Study 1 Total Daily Dose**

	<b>≤30 kg Body Weight</b>	<b>&gt;30 kg Body Weight</b>
Low Dose	5 mg daily	10 mg daily
Medium Dose	10 mg daily	20 mg daily
High Dose	20 mg daily	40 mg daily

689

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

691

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

695

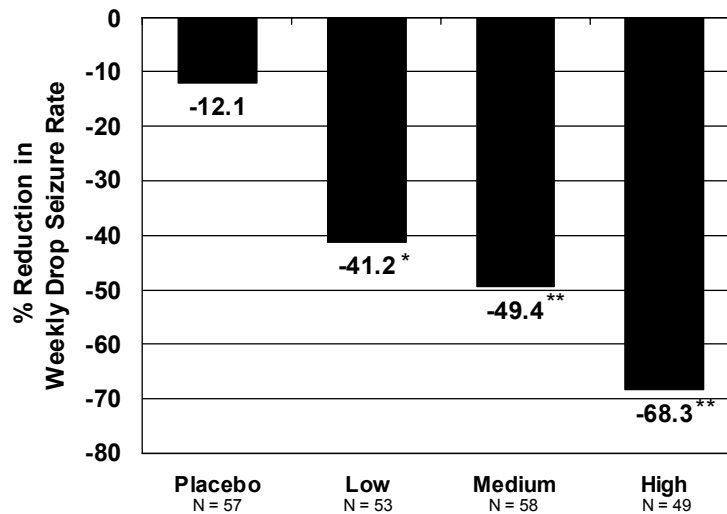
696 The pre-dosing baseline mean weekly drop seizure frequency was 98, 100, 61,  
697 and 105 for the placebo, low-, medium-, and high-dose groups, respectively.  
698 Figure 1 presents the mean percent reduction in weekly drop seizures from this  
699 baseline. All dose groups of ONFI were statistically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

701

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

704

705



\*  $p < 0.05$ , \*\*  $p < 0.01$

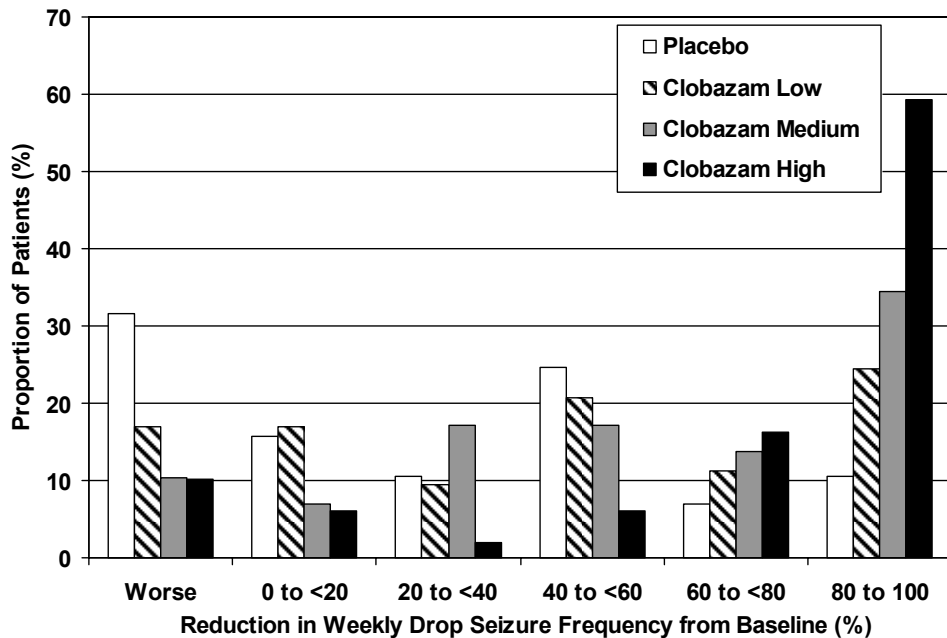
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707

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

712

713 **Figure 2. Drop Seizure Response by Category for ONFI and Placebo (Study**  
714 **1)**



715  
716  
717  
718

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

721

### 722 Study 2

723 Study 2 (N=68) was a randomized, double-blind comparison study of high- and  
724 low-dose ONFI, consisting of a 4-week baseline period followed by a 3-week  
725 titration period and 4-week maintenance period. Patients age 2-25 years with a  
726 current or prior diagnosis of LGS were stratified by weight, then randomized to  
727 either a low or high dose of ONFI, and then entered a 3-week titration period.

728

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

732

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

736

### 737 **16 HOW SUPPLIED/STORAGE AND HANDLING**

738 Each ONFI tablet contains 10 mg or 20 mg of clobazam and is a white to off-  
739 white, oval tablet with a functional score on one side and either a "1" and "0" or a  
740 "2" and "0" debossed on the other side.

741

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

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

744

745 ONFI oral suspension is a berry flavored off-white liquid supplied in a bottle with  
746 child-resistant closure. The oral suspension is packaged with a dispenser set  
747 which contains two calibrated oral dosing syringes and bottle adapter. Store the  
748 oral suspension in an upright position. Use within 90 days of first opening the  
749 bottle, then discard any remainder.

750

751 NDC 67386-313-21: Bottle containing 120 mL of suspension

752

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

755

## 756 **17 PATIENT COUNSELING INFORMATION**

757 See FDA-approved patient labeling ([Medication Guide](#) and [Instructions for Use](#)).

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

763

### 764 *Somnolence or Sedation*

765

766 Advise patients or caregivers to check with their healthcare provider before ONFI  
767 is taken with other CNS depressants such as other benzodiazepines, opioids,  
768 tricyclic antidepressants, sedating antihistamines, or alcohol [*see Warnings and*  
769 *Precautions (5.1)*].

770

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

774

### 775 *Increasing or Decreasing the ONFI Dose*

776 Inform patients or caregivers to consult their healthcare provider before  
777 increasing the ONFI dose or abruptly discontinuing ONFI. Advise patients or  
778 caregivers that abrupt withdrawal of AEDs may increase their risk of seizure [*see*  
779 *Dosage and Administration (2.2)*, *Warnings and Precautions (5.3)*].

780

### 781 *Interactions with Hormonal Contraceptives*

782 Counsel women to also use non-hormonal methods of contraception when ONFI  
783 is used with hormonal contraceptives and to continue these alternative methods  
784 for 28 days after discontinuing ONFI to ensure contraceptive reliability [*see Drug*  
785 *Interactions (7.1)*, *Clinical Pharmacology (12.3)*].



786

787 *Suicidal Thinking and Behavior*

788 Counsel patients, their caregivers, and their families that AEDs, including ONFI,  
789 may increase the risk of suicidal thoughts and behavior and advise them of the  
790 need to be alert for the emergence or worsening of symptoms of depression, any  
791 unusual changes in mood or behavior, or the emergence of suicidal thoughts,  
792 behavior, or thoughts of self-harm. Patients should report behaviors of concern  
793 immediately to healthcare providers [see *Warnings and Precautions (5.5)*].

794

795 *Use in Pregnancy*

796 Instruct patients to notify their healthcare provider if they become pregnant or  
797 intend to become pregnant during therapy.

798

799 Encourage patients to enroll in the NAAED Pregnancy Registry if they become  
800 pregnant. This registry is collecting information about the safety of antiepileptic  
801 drugs during pregnancy. To enroll, patients can call the toll free number 1-888-  
802 233-2334. Information on the registry can also be found at the website  
803 <http://www.aedpregnancyregistry.org> [see *Use in Specific Populations (8.1)*].

804

805 *Use in Nursing*

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

808

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

811

812 Oral suspension manufactured by: Rosemont Pharmaceuticals, Ltd.  
813 Leeds, West Yorkshire LS118 EX, U.K.

814

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



817

818

819 ONFI is a registered trademark of Lundbeck

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## MEDICATION GUIDE

ONFI<sup>®</sup> (ON-fee)

(clobazam)

### Tablets and Oral Suspension

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.

867 **ONFI is a federally controlled substance (C-IV) because it can be**  
868 **abused or lead to dependence. Keep ONFI in a safe place to prevent**  
869 **misuse and abuse. Selling or giving away ONFI may harm others,**  
870 **and is against the law. Tell your healthcare provider if you have ever**  
871 **abused or been dependent on alcohol, prescription medicines or**  
872 **street drugs.**

873  
874 **4. Like other antiepileptic drugs, ONFI may cause suicidal thoughts**  
875 **or actions in a very small number of people, about 1 in 500.**

876  
877 **Call your healthcare provider right away if you have any of these**  
878 **symptoms, especially if they are new, worse, or worry you:**

- 879
- 880 • thoughts about suicide or dying
  - 881 • attempts to commit suicide
  - 882 • new or worse depression
  - 883 • new or worse anxiety
  - 884 • feeling agitated or restless
  - 885 • panic attacks
  - 886 • trouble sleeping (insomnia)
  - 887 • new or worse irritability
  - 888 • acting aggressive, being angry, or violent
  - 889 • acting on dangerous impulses
  - 890 • an extreme increase in activity and talking (mania)
  - 891 • other unusual changes in behavior or mood

892  
893 **How can I watch for early symptoms of suicidal thoughts and**  
894 **actions?**

- 895
- 896 • Pay attention to any changes, especially sudden changes, in mood,  
897 behaviors, thoughts, or feelings.
  - 898 • Keep all follow-up visits with your healthcare provider as scheduled.

899  
900 Call your healthcare provider between visits as needed, especially if you are  
901 worried about symptoms.

902  
903 Suicidal thoughts or actions can be caused by things other than medicines.  
904 If you have suicidal thoughts or actions, your healthcare provider may check  
905 for other causes.

906  
907 **What is ONFI?**

908  
909 ONFI is a prescription medicine used along with other medicines to treat  
910 seizures associated with Lennox-Gastaut syndrome in people 2 years of age  
911 or older.

912  
913 It is not known if ONFI is safe and effective in children less than 2 years old.  
914

915 **What should I tell my healthcare provider before taking ONFI?**

916

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

918

919

- have liver or kidney problems
- have lung problems (respiratory disease)
- have or have had depression, mood problems, or suicidal thoughts or behavior

922

923

- 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.

924

925

- are pregnant or plan to become pregnant. **ONFI may harm your**

926

**unborn baby.**

929

930

- 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.

931

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- 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.

935

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- 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 breast feed. You should not do both.

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

957

958

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

959

960

961

961 **How should I take ONFI?**

962

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

982

#### 983 **What should I avoid while taking ONFI?**

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

990

#### 991 **What are the possible side effects of ONFI?**

992

#### 993 **ONFI may cause serious side effects, including:**

994

#### 995 **See “What is the most important information I should know about**

996 **ONFI?”**

997

998 The most common side effects of ONFI include:

999

- 1000 • sleepiness
- 1001 • drooling
- 1002 • constipation
- 1003 • cough
- 1004 • pain with urination
- 1005 • fever
- 1006 • acting aggressive, being angry, or violent
- 1007 • difficulty sleeping
- 1008 • slurred speech
- 1009 • tiredness
- 1010 • problems with breathing

1011

1012 These are not all the possible side effects of ONFI. For more information, ask  
1013 your healthcare provider or pharmacist.

1014

1015 Tell your healthcare provider if you have any side effect that bothers you or  
1016 that does not go away.

1017

1018 Call your doctor for medical advice about side effects. You may report side  
1019 effects to FDA at 1-800-FDA-1088.

1020

### 1021 **How should I store ONFI?**

1022

- 1023 • Store ONFI tablets and oral suspension between 68°F to 77°F (20°C to  
1024 25°C).

1025

#### 1026 Tablets

- 1027 • Keep ONFI tablets in a dry place

1028

#### 1029 Oral Suspension

- 1030 • Replace the cap securely after opening.
- 1031 • Keep ONFI oral suspension in an upright position.
- 1032 • Use ONFI oral suspension within 90 days of first opening the bottle.
- 1033 • After 90 days safely throw away any ONFI oral suspension that has not  
1034 been used.

1035

1036 **Keep ONFI and all medicines out of the reach of children.**

1037

### 1038 **General Information about the safe and effective use of ONFI.**

1039 Medicines are sometimes prescribed for purposes other than those listed in a  
1040 Medication Guide. Do not use ONFI for a condition for which it was not  
1041 prescribed. Do not give ONFI to other people, even if they have the same  
1042 symptoms that you have. It may harm them.

1043

1044 This Medication Guide summarizes the most important information about  
1045 ONFI. If you would like more information, talk with your healthcare provider.  
1046 You can ask your pharmacist or healthcare provider for information about  
1047 ONFI that is written for health professionals.

1048

1049 For more information about ONFI, go to [www.lundbeckus.com](http://www.lundbeckus.com) or call  
1050 Lundbeck at 1-888-514-5204.

1051

### 1052 **What are the ingredients in ONFI?**

1053

#### 1054 Tablets

1055 Active ingredient: clobazam

1056 Inactive ingredients: corn starch, lactose monohydrate, magnesium stearate,  
1057 silicon dioxide, and talc.

1058

1059 Oral Suspension  
1060 Active ingredient: clobazam  
1061 Inactive ingredients: magnesium aluminum silicate, xanthan gum, citric acid  
1062 monohydrate, disodium hydrogen phosphate dihydrate, simethicone emulsion,  
1063 polysorbate 80, methylparaben, propylparaben, propylene glycol, sucralose,  
1064 maltitol solution, berry flavor, purified water.  
1065  
1066 This Medication Guide has been approved by the U.S. Food and Drug  
1067 Administration.  
1068  
1069 Marketed by: Lundbeck, Deerfield, IL 60015, U.S.A.  
1070



1071  
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1073 ONFI is a registered trademark of Lundbeck  
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1075 **MONTH 2013**  
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**Instructions for Use**  
**ONFI<sup>®</sup> (ON-fee)**  
**(clobazam)**  
**Oral Suspension**

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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**



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**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**

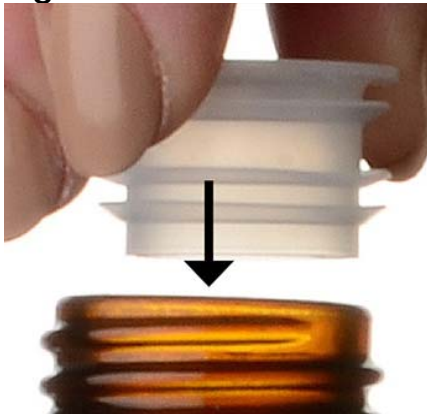
**Figure B**



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**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**

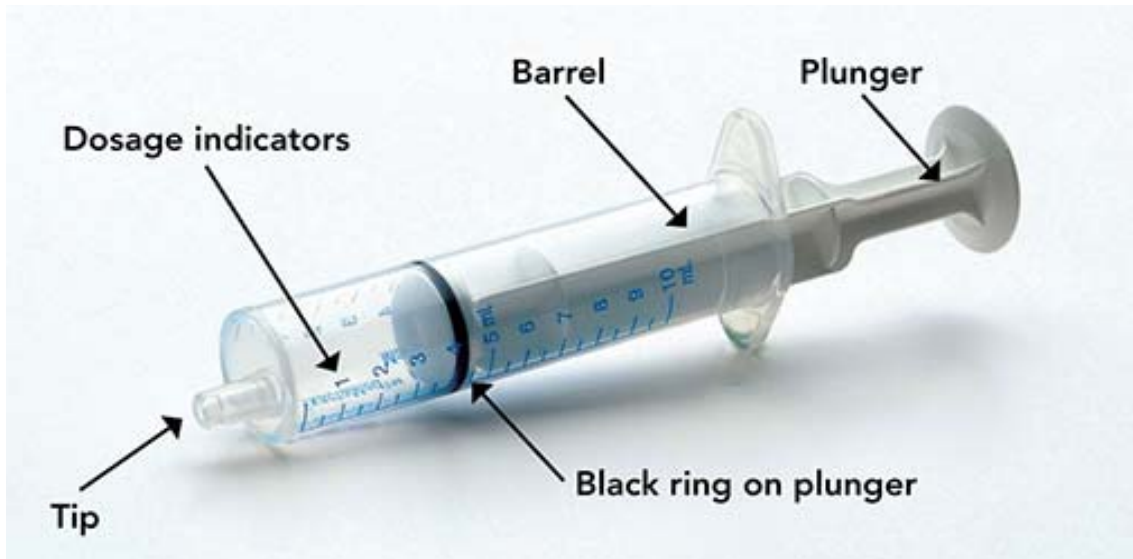


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Once the bottle adapter is in place, it should not be removed.

**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**



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**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**



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**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**

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1140

**Figure F**



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

**Figure G**



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**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**



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

Store the bottle upright 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.

1167 **Figure I**



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1169

1170 **Step 9.** Wash the oral syringe after each use.

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