

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*

1	INDICATIONS AND USAGE	8.4	Pediatric Use
2	DOSAGE AND ADMINISTRATION	8.5	Geriatric Use
2.1	Basic Dosing Information	8.6	CYP2C19 Poor Metabolizers
2.2	Geriatric Patients	8.7	Renal Impairment
2.3	CYP2C19 Poor Metabolizers	8.8	Hepatic Impairment
2.4	Patients with Renal Impairment	9	DRUG ABUSE AND DEPENDENCE
2.5	Patients with Hepatic Impairment	9.1	Controlled Substance
2.6	Gradual Withdrawal	9.2	Abuse
3	DOSAGE FORMS AND STRENGTHS	9.3	Dependence
4	CONTRAINDICATIONS	10	OVERDOSAGE
5	WARNINGS AND PRECAUTIONS	10.1	Signs and Symptoms of Overdosage
5.1	Somnolence or Sedation	10.2	Management of Overdosage
5.2	Concomitant Use with Central Nervous System Depressants	11	DESCRIPTION
5.3	Withdrawal	12	CLINICAL PHARMACOLOGY
5.4	Physical and Psychological Dependence	12.1	Mechanism of Action
5.5	Suicidal Behavior and Ideation	12.2	Pharmacodynamics
6	ADVERSE REACTIONS	12.3	Pharmacokinetics
6.1	Clinical Trials Experience	12.5	Pharmacogenomics
6.2	Postmarketing Experience	13	NONCLINICAL TOXICOLOGY
7	DRUG INTERACTIONS	13.1	Carcinogenesis, Mutagenesis, Impairment of Fertility
8	USE IN SPECIFIC POPULATIONS	14	CLINICAL STUDIES
8.1	Pregnancy	16	HOW SUPPLIED/STORAGE AND HANDLING
8.3	Nursing Mothers	17	PATIENT COUNSELING INFORMATION

* 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 Basic Dosing Information**

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

18
19 **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

20
21 ONFI tablets can be administered whole, or crushed and mixed in applesauce.
22 ONFI can be taken without regard to timing of meals.

23
24 **2.2 Geriatric Patients**

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

32
33 **2.3 CYP2C19 Poor Metabolizers**

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

39 additional titration to the maximum dose (20 mg/day or 40 mg/day, depending on
40 the weight group) may be started on day 21 [see *Use in Specific Populations*
41 (8.6), *Clinical Pharmacology* (12.5)].
42

43 **2.4 Patients with Renal Impairment**

44 No dose adjustment is required for patients with mild and moderate renal
45 impairment. There is no experience with ONFI in patients with severe renal
46 impairment or end stage renal disease (ESRD). It is not known if clobazam or its
47 active metabolite, N-desmethyloclobazam, is dialyzable [see *Use in Specific*
48 *Populations* (8.7), *Clinical Pharmacology* (12.3)].
49

50 **2.5 Patients with Hepatic Impairment**

51 ONFI is hepatically metabolized; however, there are limited data to characterize
52 the effect of hepatic impairment on the pharmacokinetics of ONFI. For this
53 reason, dosing titration should proceed slowly. For patients with mild to moderate
54 hepatic impairment (Child-Pugh score 5-9), the starting dose should be 5 mg/day
55 in both weight groups. Patients should then be titrated according to weight, but to
56 half the dose presented in Table 1, as tolerated. If necessary and based upon
57 clinical response, an additional titration to the maximum dose (20 mg/day or 40
58 mg/day, depending on the weight group) may be started on day 21. There is
59 inadequate information about metabolism of ONFI in patients with severe hepatic
60 impairment. Therefore no dosing recommendation in those patients can be given
61 [see *Use in Specific Populations* (8.8), *Clinical Pharmacology* (12.3)].
62

63 **2.6 Gradual Withdrawal**

64 As with all antiepileptic drugs and benzodiazepines, ONFI should be withdrawn
65 gradually. Taper by decreasing the total daily dose by 5-10 mg/day on a weekly
66 basis until discontinued [see *Warnings and Precautions* (5.3)].
67

68 **3. DOSAGE FORMS AND STRENGTHS**

69 5 mg, 10 mg, and 20 mg tablets for oral administration.

70 Each ONFI tablet is white, round, and debossed with "LU" on one side and "5,"
71 "10," or "20" on the other side.
72

73 **4. CONTRAINDICATIONS**

74 None.
75

76 **5. WARNINGS AND PRECAUTIONS**

77 **5.1 Somnolence or Sedation**

78 ONFI causes somnolence and sedation. In clinical trials, somnolence or sedation
79 were reported at all effective doses and were dose-related.
80

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

87

88 **5.2 Concomitant Use with Central Nervous System Depressants**

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

93

94 **5.3 Withdrawal**

95 Abrupt discontinuation of ONFI should be avoided. ONFI should be tapered by
96 decreasing the dose every week by 5-10 mg/day until discontinuation [see
97 *Dosage and Administration (2.6)*].

98

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

101

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

104

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

113

114 **5.4 Physical and Psychological Dependence**

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

119

120 **5.5 Suicidal Behavior and Ideation**

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

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

126
 127 Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive
 128 therapy) of 11 different AEDs showed that patients randomized to one of the
 129 AEDs had approximately twice the risk (adjusted relative risk 1.8, 95%
 130 confidence interval [CI]:1.2, 2.7) of suicidal thinking or behavior compared to
 131 patients randomized to placebo. In these trials, which had a median treatment
 132 duration of 12 weeks, the estimated incidence rate of suicidal behavior or
 133 ideation among 27,863 AED treated patients was 0.43%, compared to 0.24%
 134 among 16,029 placebo treated patients, representing an increase of
 135 approximately one case of suicidal thinking or behavior for every 530 patients
 136 treated. There were four suicides in drug treated patients in the trials and none
 137 in placebo treated patients, but the number is too small to allow any conclusion
 138 about drug effect on suicide.

139
 140 The increased risk of suicidal thoughts or behavior with AEDs was observed as
 141 early as one week after starting drug treatment with AEDs and persisted for the
 142 duration of treatment assessed. Because most trials included in the analysis did
 143 not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24
 144 weeks could not be assessed.

145
 146 The risk of suicidal thoughts or behavior was generally consistent among drugs
 147 in the data analyzed. The finding of increased risk with AEDs of varying
 148 mechanisms of action and across a range of indications suggests that the risk
 149 applies to all AEDs used for any indication. The risk did not vary substantially by
 150 age (5-100 years) in the clinical trials analyzed. Table 2 shows absolute and
 151 relative risk by indication for all evaluated AEDs.

152

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

153

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

157

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

165

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

172

173 **6. ADVERSE REACTIONS**

174

175 **6.1 Clinical Trials Experience**

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

180

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

189

190 Adverse Reactions Leading to Discontinuation in an LGS Placebo Controlled 191 Clinical Trial (Study 1)

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

195

196 Most Common Adverse Reactions in an LGS Placebo Controlled Clinical Trial 197 (Study 1).

198 Table 3 lists the adverse reactions that occurred in $\geq 5\%$ of ONFI treated patients
199 (at any dose), and at a rate greater than placebo treated patients, in the
200 randomized, double-blind, placebo-controlled, parallel group clinical study of
201 adjunctive AED therapy for 15 weeks (Study 1).
202

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

203 ^a Maximum daily dose of 5 mg for ≤30 kg body weight; 10 mg for >30 kg body weight
 204 ^b Maximum daily dose of 10 mg for ≤30 kg body weight; 20 mg for >30 kg body weight
 205 ^c Maximum daily dose of 20 mg for ≤30 kg body weight; 40 mg for >30 kg body weight
 206

207 **6.2 Post Marketing Experience**

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

216

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

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

219 **Gastrointestinal Disorders:** Abdominal distention

220 **Investigations:** Hepatic enzyme increased

221 **Musculoskeletal:** Muscle spasms

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

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

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

227

228 **7. DRUG INTERACTIONS**

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

231

232 Effect of ONFI on other drugs

233 ONFI is a weak CYP3A4 inducer. As some hormonal contraceptives are
234 metabolized by CYP3A4, their effectiveness may be diminished when given with
235 ONFI. Additional non-hormonal forms of contraception are recommended when
236 using ONFI [see *Clinical Pharmacology (12.3)*, *Patient Counseling Information*
237 *(17)*].

238

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

241

242 Effect of other drugs on ONFI

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

248
249 Alcohol increases the maximum plasma exposure of clobazam by approximately
250 50% [see *Clinical Pharmacology (12.3)*].

251

252 **8. USE IN SPECIFIC POPULATIONS**

253 **8.1 Pregnancy**

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

260

261 **Pregnancy Category C.**

262

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

265

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

270

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

277

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

280

281 **8.3 Nursing Mothers**

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

284

285 **8.4 Pediatric Use**

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

288

289 In a study in which clobazam (4, 36, or 120 mg/kg/day) was orally administered
290 to rats during the juvenile period of development (postnatal days 14 to 48),
291 adverse effects on growth (decreased bone density and bone length) and
292 behavior (altered motor activity and auditory startle response; learning deficit)
293 were observed at the high dose. The effect on bone density, but not on behavior,
294 was reversible when drug was discontinued. The no-effect level for juvenile
295 toxicity (36 mg/kg/day) was associated with plasma exposures (AUC) to
296 clobazam and its major active metabolite, N-desmethyloclobazam, less than those
297 expected at therapeutic doses in pediatric patients.
298

299 **8.5 Geriatric Use**

300 Clinical studies of ONFI did not include sufficient numbers of subjects aged 65
301 and over to determine whether they respond differently from younger subjects.
302 However, elderly subjects appear to eliminate clobazam more slowly than
303 younger subjects based on population pharmacokinetic analysis. For these
304 reasons, the initial dose in elderly patients should be 5 mg/day. Patients should
305 be titrated initially to 10-20 mg/day. Patients may be titrated further to a
306 maximum daily dose of 40 mg if tolerated [see *Dosage and Administration (2.2)*,
307 *Clinical Pharmacology (12.3)*].
308

309 **8.6 CYP2C19 Poor Metabolizers**

310 Concentrations of clobazam's active metabolite, N-desmethyloclobazam, are
311 higher in CYP2C19 poor metabolizers than in extensive metabolizers. For this
312 reason, the initial dose in patients known to be CYP2C19 poor metabolizers
313 should be 5 mg/day. These patients should be titrated initially to 10-20 mg/day,
314 and may be titrated further to a maximum daily dose of 40 mg if tolerated [see
315 *Dosage and Administration (2.3)*, *Clinical Pharmacology (12.5)*].
316

317 **8.7 Renal Impairment**

318 The pharmacokinetics of ONFI were evaluated in patients with mild and
319 moderate renal impairment. There were no significant differences in systemic
320 exposure (AUC and C_{max}) between patients with mild or moderate renal
321 impairment and healthy subjects. No dose adjustment is required for patients
322 with mild and moderate renal impairment. There is essentially no experience
323 with ONFI in patients with severe renal impairment or ESRD. It is not known if
324 clobazam or its active metabolite, N-desmethyloclobazam, is dialyzable [see
325 *Dosage and Administration (2.4)*, *Clinical Pharmacology (12.3)*].
326

327 **8.8 Hepatic Impairment**

328 ONFI is hepatically metabolized; however, there are limited data to characterize
329 the effect of hepatic impairment on the pharmacokinetics of ONFI. For this
330 reason, the initial dose in patients with mild to moderate hepatic impairment
331 (Child-Pugh score 5-9) should be 5 mg/day. These patients should be titrated
332 initially to 10 to 20 mg/day, and may be titrated further to a maximum daily dose

333 of 40 mg if tolerated. There is inadequate information about metabolism of ONFI
334 in patients with severe hepatic impairment. Therefore no dosing
335 recommendation in those patients can be given [see *Dosage and Administration*
336 (2.5), *Clinical Pharmacology* (12.3)].
337

338 **9. DRUG ABUSE AND DEPENDENCE**

339 **9.1 Controlled Substance**

340 ONFI is listed in Schedule IV of the Controlled Substances Act (CSA).
341

342 **9.2 Abuse**

343
344 The pharmacological profile of ONFI is similar to that of other benzodiazepines
345 listed in Schedule IV of the CSA, particularly in its potentiation of GABAergic
346 transmission through its action on GABA_A receptors, which leads to sedation,
347 somnolence, and anxiolysis. Therefore, ONFI may be abused in a similar
348 manner as other benzodiazepines, such as diazepam.
349

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

352 353 **9.3 Dependence**

354 *Dependence*

355 Physical dependence is a state of adaptation that is manifested by a specific
356 withdrawal syndrome that can be produced by abrupt cessation, rapid dose
357 reduction, decreasing blood levels of the drug, and/or administration of an
358 antagonist. In clinical trials, cases of dependency were reported following abrupt
359 discontinuation of ONFI.
360

361 The risk of dependence is present even with use of ONFI at the recommended
362 dose range over periods of only a few weeks. The risk of dependence
363 increases with increasing dose and duration of treatment. The risk of
364 dependence is increased in patients with a history of alcohol or drug abuse.
365

366 *Withdrawal*

367 Abrupt discontinuation of ONFI causes withdrawal symptoms. As with other
368 benzodiazepines, ONFI should be withdrawn gradually [see *Dosage and*
369 *Administration* (2.5), *Warnings and Precautions* (5.3)].
370

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

375

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

381

382 10. OVERDOSAGE

383 10.1 Signs and Symptoms of Overdosage

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

389

390 10.2 Management of Overdosage

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

397

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

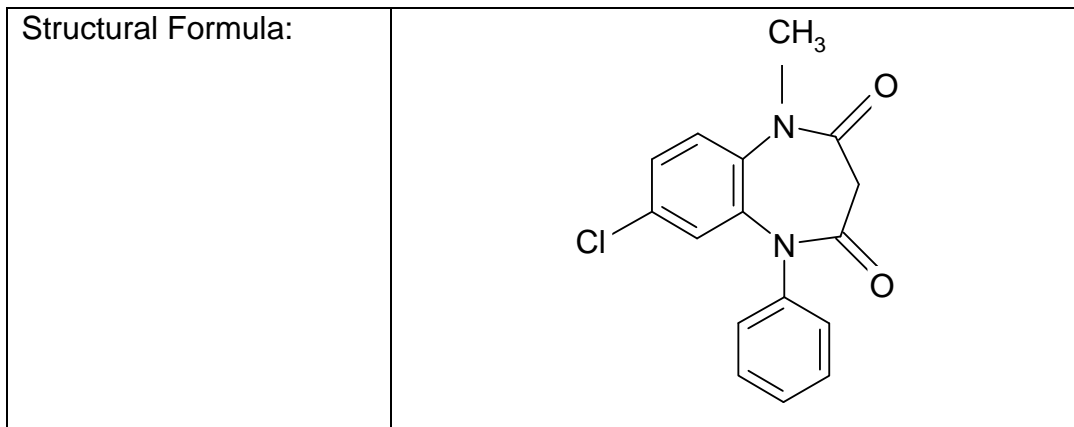
403

404 11. DESCRIPTION

405

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



406

407 Each ONFI tablet contains 5 mg, 10 mg, or 20 mg of clobazam. Tablets also
408 contain as inactive ingredients: corn starch, lactose monohydrate, magnesium
409 stearate, silicon dioxide, and talc. The molecular formula is C₁₆H₁₃O₂N₂Cl and
410 the molecular weight is 300.7.

411

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

415

416 12. CLINICAL PHARMACOLOGY

417 12.1 Mechanism of Action

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

422

423 12.2 Pharmacodynamics

424 Effects on Electrocardiogram

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

433

434 12.3 Pharmacokinetics

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

437 multiple-dose administration of ONFI. Based on a population pharmacokinetic
438 analysis, the pharmacokinetics of clobazam are linear from 5-160 mg/day.
439 Clobazam is converted to N-desmethylclobazam which has about 1/5 the activity
440 of clobazam. The estimated mean elimination half-lives ($t_{1/2}$) of clobazam and N-
441 desmethylclobazam were 36-42 hours and 71-82 hours, respectively.

442

443 Absorption

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

449

450 Distribution

451 Clobazam is lipophilic and distributes rapidly throughout the body. The apparent
452 volume of distribution at steady state was approximately 100 L. The *in vitro*
453 plasma protein binding of clobazam and N-desmethylclobazam is approximately
454 80-90% and 70%, respectively.

455

456 Metabolism and Excretion

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

470

471 The polymorphic CYP2C19 is the major contributor to the metabolism of the
472 pharmacologically active N-desmethylclobazam [see *Clinical Pharmacology*
473 (12.5)]. In CYP2C19 poor metabolizers, levels of N-desmethylclobazam were 5-
474 fold higher in plasma and 2- to 3-fold higher in the urine than in CYP2C19
475 extensive metabolizers.

476

477 Pharmacokinetics in Specific Populations

478 Age

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

482

483 Sex

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

486

487 Race

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

491

492 Renal Impairment

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

501

502 Hepatic Impairment

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

511

512 Drug Interactions

513

514 In vitro studies:

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

519

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

526

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

529

530 *In vivo studies:*

531

532 *Potential for ONFI to Affect Other Drugs*

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

538

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

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

551

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

555

556 *Potential for Other Drugs to Affect ONFI*

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

561

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

568

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

576

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

581

582 **12.5 Pharmacogenomics**

583 The polymorphic CYP2C19 is the main enzyme that metabolizes the
584 pharmacologically active N-desmethylclobazam. Compared to CYP2C19
585 extensive metabolizers, N-desmethylclobazam AUC and C_{max} are approximately
586 3-5 times higher in poor metabolizers (e.g., subjects with *2/*2 genotype) and 2
587 times higher in intermediate metabolizers (e.g., subjects with *1/*2 genotype).
588 The prevalence of CYP2C19 poor metabolism differs depending on racial/ethnic
589 background. Dosage in patients who are known CYP2C19 poor metabolizers
590 may need to be adjusted [see *Dosage and Administration (2.3)*].

591

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

594

595 **13. NONCLINICAL TOXICOLOGY**

596 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

597 **Carcinogenesis**

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

599

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

603

604 **Mutagenesis**

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

608

609 **Impairment of Fertility**

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

611

612 **14. CLINICAL STUDIES**

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

619

620 Study 1

621 Study 1 (N=238) was a randomized, double-blind, placebo-controlled study
622 consisting of a 4-week baseline period followed by a 3-week titration period and
623 12-week maintenance period. Patients age 2-54 years with a current or prior
624 diagnosis of LGS were stratified into 2 weight groups (12.5 kg to ≤30 kg or >30
625 kg) and then randomized to placebo or one of three target maintenance doses of
626 ONFI according to Table 5.

627

628 **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

629

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

631

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

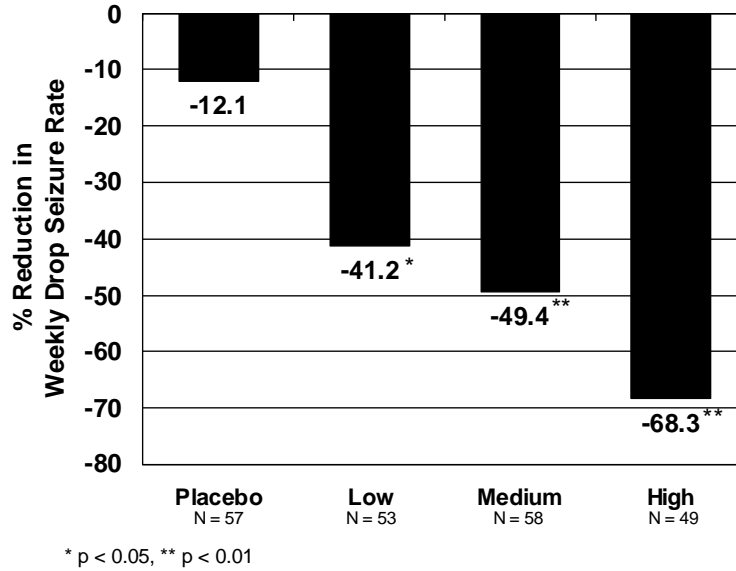
635

636 The pre-dosing baseline mean weekly drop seizure frequency was 98, 100, 61,
637 and 105 for the placebo, low-, medium-, and high-dose groups, respectively.

638 Figure 1 presents the mean percent reduction in weekly drop seizures from this
639 baseline. All dose groups of ONFI were statistically superior ($p \leq 0.05$) to the
640 placebo group. This effect appeared to be dose dependent.

641
642
643
644
645

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

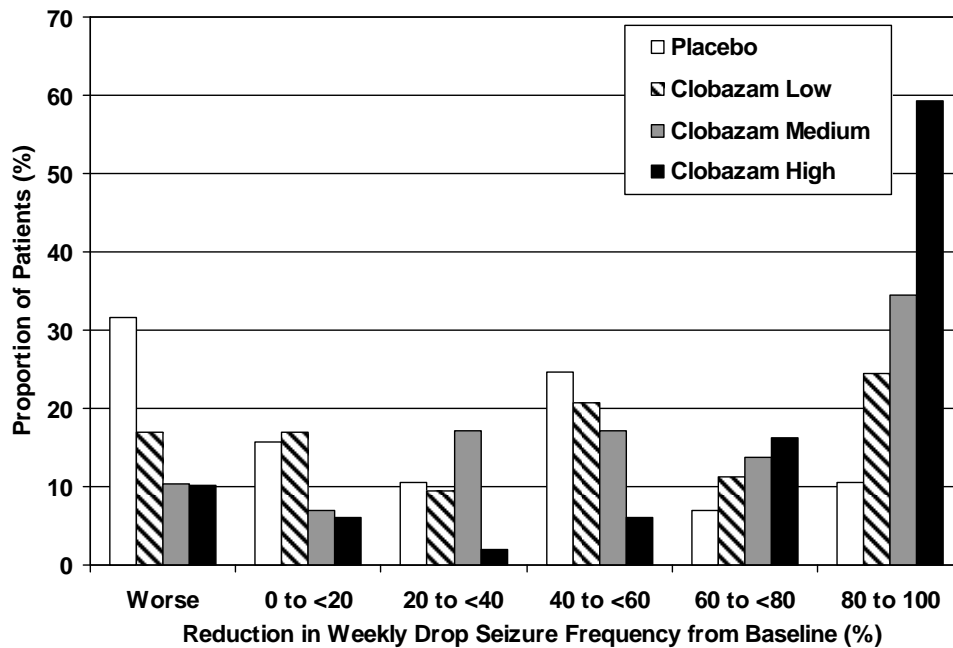


646
647

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.

652
653
654

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



655
656
657
658

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

661
662 Study 2

663 Study 2 (N=68) was a randomized, double-blind comparison study of high- and
664 low-dose ONFI, consisting of a 4-week baseline period followed by a 3-week
665 titration period and 4-week maintenance period. Patients age 2-25 years with a
666 current or prior diagnosis of LGS were stratified into 2 weight groups (12.5 kg to
667 ≤30 kg or >30 kg) then randomized to either a low target dose of ONFI (daily
668 dose of 5 mg for ≤30 kg body weight; 10 mg for >30 kg body weight) or high
669 target dose of ONFI (daily dose of 20 mg ≤30 kg body weight; 40 mg for >30 kg
670 body) and entered a 3-week titration period.

671

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

675

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

679

680 16. HOW SUPPLIED/STORAGE AND HANDLING

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

684

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

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

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

688

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

690

691 **17. PATIENT COUNSELING INFORMATION**

692 See FDA-approved patient labeling (Medication Guide).

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

698

699 Somnolence or Sedation

700

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

705

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

709

710 Increasing or Decreasing the ONFI Dose

711 Inform patients or caregivers to consult their healthcare provider before
712 increasing the ONFI dose or abruptly discontinuing ONFI. Advise patients or
713 caregivers that abrupt withdrawal of AEDs may increase their risk of seizure [see
714 *Dosage and Administration (2.6)*, *Warnings and Precautions (5.3)*].

715

716 Interactions with Hormonal Contraceptives

717 Counsel women to also use non-hormonal methods of contraception when ONFI
718 is used with hormonal contraceptives and to continue these alternative methods
719 for 28 days after discontinuing ONFI to ensure contraceptive reliability [see *Drug*
720 *Interactions (7)*, *Clinical Pharmacology (12.3)*].

721

722 Suicidal Thinking and Behavior

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

729

730 *Use in Pregnancy*

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

733

734 Encourage patients to enroll in the NAAED Pregnancy Registry if they become
735 pregnant. This registry is collecting information about the safety of antiepileptic
736 drugs during pregnancy. To enroll, patients can call the toll free number 1-888-
737 233-2334. Information on the registry can also be found at the website
738 <http://www.aedpregnancyregistry.org> [*see Use in Specific Populations (8.1)*].

739

740 *Use in Nursing*

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

743

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

746

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

749

750 **MEDICATION GUIDE**

751

752 **ONFI™ (ON-fee)**
753 **(clobazam)**
754 **Tablets**

755

756

757

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

762

763

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

765

766 **Do not stop taking ONFI without first talking to your healthcare**
767 **provider.** Stopping ONFI suddenly can cause serious problems.

768

769

ONFI can cause serious side effects, including:

770

771

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

772

773

774

- 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.

775

776

777

778

779

780

781

2. ONFI can cause withdrawal symptoms.

782

783

- 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.

784

785

786

787

788

789

- Talk to your healthcare provider about slowly stopping ONFI to avoid withdrawal symptoms.

790

791

792

793

3. ONFI can be abused and cause dependence.

794

795

- 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.

796

797

798

799

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.

800

801

802

803

804

805

806

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

807

808

809

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

810

811

- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression

812

813

814

- 815 • new or worse anxiety
- 816 • feeling agitated or restless
- 817 • panic attacks
- 818 • trouble sleeping (insomnia)
- 819 • new or worse irritability
- 820 • acting aggressive, being angry, or violent
- 821 • acting on dangerous impulses
- 822 • an extreme increase in activity and talking (mania)
- 823 • other unusual changes in behavior or mood

824

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

827

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

831

832 Call your healthcare provider between visits as needed, especially if you are
833 worried about symptoms.

834

835 Suicidal thoughts or actions can be caused by things other than medicines.
836 If you have suicidal thoughts or actions, your healthcare provider may check
837 for other causes.

838

839 **What is ONFI?**

840

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

844

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

846

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

848

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

850

- 851 • have liver or kidney problems
- 852 • have lung problems (respiratory disease)
- 853 • have or have had depression, mood problems, or suicidal thoughts or
854 behavior
- 855 • have any other medical conditions
- 856 • use birth control medicine. ONFI may cause your birth control
857 medicine to be less effective. Talk to your healthcare provider about
858 the best birth control method to use.
- 859 • are pregnant or plan to become pregnant. **ONFI may harm your**
860 **unborn baby.**

861

- 862
- 863
- 864
- 865
- 866
- 867
- 868
- 869
- 870
- 871
- 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.
- 872
- 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.
- 873
- 874
- 875
- 876
- 877
- 878
- 879
- 880
- 881

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

887

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

890

891 **How should I take ONFI?**

- 892
- 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.
- 893
- 894
- 895
- 896
- 897

898 Your healthcare provider may change your dose if needed. Do not change
899 your dose of ONFI without talking to your healthcare provider.

- 900
- Do not stop taking ONFI without first talking to your healthcare provider.
 - Stopping ONFI suddenly can cause serious problems.
- 901
- 902
- 903
- 904

905 If you take too much ONFI, call your healthcare provider or go to the nearest
906 hospital emergency room right away.

907

908 **What should I avoid while taking ONFI?**

- 909
- Do not drive, operate heavy machinery, or do other dangerous activities until you know how ONFI affects you.
- 910
- 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.
- 911
- 912
- 913
- 914
- 915

916 **What are the possible side effects of ONFI?**

917

918 **ONFI may cause serious side effects, including:**

919

920

921 **See “What is the most important information I should know about ONFI?”**

922

923

924 The most common side effects of ONFI include:

925

- sleepiness
 - drooling
 - constipation
 - cough
 - pain with urination
 - fever
 - acting aggressive, being angry, or violent
 - difficulty sleeping
 - slurred speech
 - tiredness
 - problems with breathing
- 926
- 927
- 928
- 929
- 930
- 931
- 932
- 933
- 934
- 935
- 936
- 937

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

939

940

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

942

943

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

945

946

947 **How should I store ONFI?**

948

- Store ONFI between 68°F to 77°F (20°C to 25°C).
- 949
- 950

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

952

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

954

955

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

956 prescribed. Do not give ONFI to other people, even if they have the same
957 symptoms that you have. It may harm them.

958

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

963

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

966

967 **What are the ingredients in ONFI?**

968

969 **Active ingredient:** clobazam

970

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

973

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

976

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

979

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

982



983

984

985

986 TM Trademark of Lundbeck Inc.

987

988 **October 2011**

989