IN THE UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF TEXAS
DALLAS DIVISION

MADELINE AND ROGELIO ESCARENO, AS PARENTS AND ON BEHALF OF THEIR MINOR CHILD, ANTONIO ESCARENO	§	
Plaintiffs,	§	
vs.	§	
LUNDBECK, LLC, LUNDBECK PHARMACEUTICALS SERVICES, LLC, and H. LUNDBECK A/S	§	**NO. 3:14-cv-257**
Defendants.	§	**JURY TRIAL DEMANDED**

PLAINTIFFS' ORIGINAL COMPLAINT

Plaintiffs Madeline Escareno and Rogelio Escareno, individually and on behalf of their minor child, Antonio Escareno (collectively "Plaintiffs"), file their Original Complaint against Defendants Lundbeck, LLC, Lundbeck Pharmaceuticals Services, LLC and H. Lundbeck A/S (collectively "Defendants") as follows:

I. Parties

1. Plaintiffs Madeline and Rogelio Escareno, and their minor son Antonio Escareno, are citizens of Texas.

2. Defendant Lundbeck, LLC ("Lundbeck") is a Delaware limited liability company with its principal place of business at 4 Parkway North, Suite 200, Deerfield, IL 60015, and may be served through its agent for service of process: Antonio D. Forrester, 4 Parkway North, Deerfield, IL 60015. Lundbeck has engaged in business activities in Texas including, but not limited to, the transactions made the basis of this suit. All or a substantial part of the events giving rise to this lawsuit resulted from Lundbeck's business activities in and

directed to Texas. Based on a diligent search of the Texas Secretary of State's records, Plaintiffs are informed and believe that Lundbeck has not registered to do business in Texas and does not maintain a designated agent for service of process in Texas. Accordingly, Lundbeck may be served with process through the Texas Secretary of State. A copy of the Citation and Petition may be forwarded to Lundbeck at the home office address set forth above.

3. Defendant Lundbeck Pharmaceuticals Services, LLC ("Lundbeck Pharmaceutical Services") is an Illinois limited liability company with its principal place of business at 4 Parkway North, Deerfield, IL, 60015, and may be served through its agent for service of process: Staffan Schuberg, 4 Parkway North, Deerfield, IL 60015. Lundbeck Pharmaceutical Services has engaged in business activities in Texas including, but not limited to, the transactions made the basis of this suit. All or a substantial part of the events giving rise to this lawsuit resulted from Lundbeck Pharmaceutical Services's business activities in and directed to Texas. Based on a diligent search of the Texas Secretary of State's records, Plaintiffs are informed and believe that Lundbeck Pharmaceutical Services has not registered to do business in Texas and does not maintain a designated agent for service of process in Texas. Accordingly, Lundbeck Pharmaceutical Services may be served with process through the Texas Secretary of State. A copy of the Citation and Petition may be forwarded to Lundbeck Pharmaceutical Services at the home office address set forth above.

4. Defendant H. Lundbeck A/S is a Dutch corporation with its principal place of business at Ottiliavej 9, 2500 Valby, Denmark. Denmark is a signatory to the Hague Convention. Thus, H. Lundbeck A/S may be served via an officer, a managing or general agent, or any other agent authorized by appointment or by law to receive service of process, at its home office address in Denmark.

II. Jurisdiction

5. This Court has subject matter jurisdiction over this lawsuit pursuant to 28 U.S.C. §1332 because there is diversity of citizenship between the parties and the amount in controversy exceeds $75,000.

6. Venue is proper pursuant to 28 U.S.C. §1391(a)(2) in that Plaintiffs' claims arose from events taking place within this judicial district and Plaintiffs reside in this district.

III. Statement of Facts

Preliminary Statement

7. This case stems from a severe adverse drug reaction suffered by eleven-year-old Antonio Escareno following his ingestion of the pharmaceutical drug ONFI (clobazam), which was manufactured and aggressively marketed by Defendants, off-label, to a broad range of child and adult patients for indications that have never received approval from the FDA. As a result of Defendants' improper off-label promotion, Antonio was prescribed ONFI and developed a severe adverse skin reaction to ONFI called Stevens-Johnson syndrome ("SJS"), which escalated to a more severe form of the reaction, toxic epidermal necrolysis ("TEN"). Antonio's SJS reaction resulted in the blistering, burning, sloughing and peeling of the skin from a large portion of his body, including the inside and outside of his mouth, throat and genital areas, and required him to remain in Cook Children's Medical Center in Fort Worth for approximately one month in March of 2013. Antonio's SJS reaction was so severe that he lost much of his skin, his hair and fingernails. He is permanently scarred and psychologically traumatized.

8. Antonio suffers from epilepsy/seizure disorder. He has never been diagnosed with Lennox-Gastaut syndrome (LGS), which is the sole indication for which ONFI was approved by the FDA in 2011. Lennox-Gastaut syndrome (LGS), or childhood epileptic

encephalopathy, is a pediatric epilepsy syndrome characterized by multiple seizure types and abnormal findings on electroencephalography (EEG). There were several safer alternative drugs that could have been used to treat Anthony's seizure disorders other than ONFI. In fact, ONFI never should have been marketed to Cook Children's Hospital or its physicians for any unapproved indication or prescribed to Antonio.

9. Even though Defendants knew for many years that their drug was causally related to SJS and TEN and warned of the risk of SJS/TEN associated with their similar products marketed in foreign countries, Defendants failed to include ***any*** warning in their ONFI label regarding SJS and TEN. Following Antonio's (and other children's) SJS/TEN reaction to ONFI, the FDA approved a label change to Defendants' drug, specifically to include a (still deficient) warning relating to SJS/TEN.

10. From inception, Defendants sought to save millions of dollars through limited and deficient clinical trials relating to ONFI, knowing the entire time that they intended to market the drug off-label for all types of seizure disorders and, thereby, reap hundreds of millions of dollars in profit through the marketing of ONFI to the entirety of the U.S. population (including children) inflicted with any type of seizure disorder. Importantly, the only ONFI clinical trials that Defendants submitted to the FDA in furtherance of their efforts to receive FDA approval for the drug were clinical trials restricted to patients with LGS. Despite this limitation and Defendants' knowledge regarding the high risk of SJS/TEN associated with their drug, Defendants promoted ONFI off-label to countless patients nationally, reaping hundreds of millions of dollars in profits for a drug that was only approved for use by the FDA in a total patient population of fewer than 200,000 individuals per year in the United States. Defendants' planned-deception initiated with their Orphan Drug Application – under which a drug company receives substantial cost savings for seeking

approval for drugs with limited patient populations such as LGS – and carried through their mass-marketing plan, resulting in substantial over-and-off-label promotion of ONFI. The end result is vast profits to Defendants, on the one hand, and severe injuries to child patients, like Antonio, on the other, by a drug that has not been subjected to the rigorous clinical trials and safety reviews for drugs in children that are typically required of drugs that are marketed to patient pools of the magnitude to which Defendants have and always intended to market their dangerous product.

Regulatory Overview of ONFI

11. Sanofi-Aventis is the primary marketing authorization holder for clobazam in the majority of worldwide markets. The Lundbeck entities (formerly Ovation Pharmaceuticals) acquired the U.S., Canadian, and Mexican marketing rights for clobazam from Sanofi-Aventis in 2004.

12. Lundbeck's U.S. predecessor (Ovation Pharmaceuticals) filed an Investigational New Drug Application (IND) on May 25, 2005 and was notified by the Division of Neurology Products on June 24, 2005 that clinical studies with clobazam under IND 70,125 could proceed to evaluate the use of clobazam to treat a very rare epileptic condition called Lennox-Gastaut syndrome (LGS). Lennox-Gastaut syndrome (LGS) is estimated to represent 1% to 2% of all childhood epilepsy cases. LGS, therefore, is a very rare epileptic disease that affects fewer than 200,000 people in the U.S.

13. Any use in the United States of a drug not previously authorized for marketing in the United States first requires submission of an IND to the FDA. At the time of the Ovation IND, there were already five AEDs (clonazepam, felbamate, lamotrigine, topiramate and rufinamide) on the market that had demonstrated clinical efficacy and were approved by the FDA for the treatment of LGS. Current regulations 21 C.F.R. §312.22 and §312.23 contain the

general principles underlying the IND submission and the general requirements for an IND's content and format. FDA regulations require that a drug be the subject of an approved marketing application before it is transported or distributed across state lines. Because a sponsor (*i.e.*, the drug company) typically ships the investigational drug to clinical investigators in many states, it must seek an exemption from that legal requirement. The IND is the means through which the sponsor typically obtains this exemption from the FDA.

14. Pursuant to 21 C.F.R. § 312.21, an IND may be submitted for one or more phases of an investigation. The clinical investigation of a previously untested drug is generally divided into three phases. These three phases of an investigation are as follows:

- Phase 1 includes the initial introduction of an investigational new drug into humans. Phase 1 studies are typically closely monitored and may be conducted in patients or normal volunteer subjects. These studies are designed to determine the metabolism and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness.

- Phase 2 includes the controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks associated with the drug. Phase 2 studies are typically well controlled, closely monitored, and conducted in a relatively small number of patients, usually involving no more than several hundred subjects.

- Phase 3 studies are expanded controlled and uncontrolled trials. They are performed after preliminary evidence suggesting effectiveness of the drug has been obtained, and are intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug and to provide an adequate basis for physician labeling. Phase 3 studies usually include from several hundred to several thousand subjects.

15. From 2005 through 2007, Lundbeck and its predecessor filed their IND for the purpose of conducting either Phase 1 or 2 studies, wherein human subjects were exposed to the investigational drug, clobazam/ONFI. Lundbeck and its predecessor also recruited and hired clinical investigators, including physicians who practice medicine at epilepsy clinics at academic

centers with hospitals, and paid them hundreds of thousands of dollars to conduct clinical trials using this unapproved drug on humans (including on children), thereby exposing them to unreasonably dangerous risks from serious cutaneous reactions that had been known to be caused by ONFI during its forty-year marketing experience outside the U.S. Indeed, before Defendants' IND filing, there were reports in the published scientific literature that reported that there were increased risks of serious skin reactions associated with clobazam and benzodiazepines, including SJS and TEN. This safety information was known by or readily available to Defendants and was withheld or omitted from the submission by Lundbeck and its predecessor in the IND submission to the FDA in furtherance of Defendants' efforts to obtain permission to conduct Phase 1-3 studies with ONFI.

16. As noted above, in order to distribute ONFI legally to clinical investigators located across the U.S., Lundbeck and its predecessors were required to obtain legal approval under the IND in order to import an unapproved drug from a foreign country (Canada) into the U.S., and then distribute ONFI across state lines to various locations within the U.S. This importing and distribution of ONFI for use in the Defendants' clinical trials was conducted without the drug's label containing adequate warnings or proper directions for use, and without disclosing safety information of the unreasonable serious risks of harm from serious skin reactions to which these children were exposed. As a result, Plaintiffs contend that the product was misbranded pursuant to 21 U.S.C. §352.

17. Defendants recruited, financed, and provided all of the clinical research and development documents that were used in the ONFI study design, protocols, and study monitoring, including the informed consent forms and the disclosure and explanation of risks versus benefits for the drug. Defendants submitted false and misleading documents regarding

the risk-benefits of ONFI in the IND, including its orphan drug application. Through its false and deficient submissions, Defendants deprived their study participants of the ability to make an informed decision regarding the risk and benefit of ONFI, especially given there were safer and less expensive alternative drugs available to treat LGS seizures.

Defendants' Misleading Orphan Drug Application

18. Prior to filing the NDA, Lundbeck's predecessor (Ovation Pharmaceuticals) submitted an Orphan Drug Application on August 24, 2007, requesting an Orphan Drug Designation for ONFI or clobazam to treat a rare epilepsy disease called LGS. Pursuant to the Federal Food, Drug, and Cosmetic Act as amended by section 2 of the Orphan Drug Act (§§ 525-528 (21 U.S.C. 360aa-360dd)), Congress granted authority to the FDA for the Orphan Drug program in order to encourage and facilitate the development of drugs for ***rare diseases or conditions***. In exchange for a drug company participating in the program, it typically receives financial incentives, identified below.

19. The FDA created standards of care for the pharmaceutical industry in order to submit the Orphan Drug Application and seek the approval of drugs that meet the FDA standards for an Orphan Drug Designation. The purpose of these standards and procedures was to determine eligibility for the benefits provided for in section 2 of the Orphan Drug Act, including written recommendations for investigations of orphan drugs, a 7-year period of exclusive marketing, and treatment use of investigational orphan drugs.

20. The benefits of Orphan Drug approval to the drug company applicant are several-fold: one, substantial cost savings to the drug company. Specifically, the drug company can qualify to receive up to a 50% tax credit from the IRS for qualified clinical trial expenses. The drug company is eligible for annual grant funding to defray the cost of clinical testing and the waiver of Prescription Drug User Fee Act (PDUFA) filing fees (which were over $1,000,000 per

application in 2009). Two, Orphan Drug exclusive approval means that, effective on the date of FDA approval, no approval will be given to a subsequent sponsor of the same drug for the same use or indication for 7 years, except as otherwise provided by law. A designated drug will receive Orphan Drug exclusive approval only if the same drug has not already been approved for the same use or indication. This provides the drug company protection from any competition and allows them to reap profits without competitive forces encroaching on profits.

21. Three, the profit potential is substantial. Specifically, the global orphan drugs market reached $84.9 billion in 2009, growing from $54.5 billion in 2005. The market is expected to grow at a compound annual growth rate (CAGR) of nearly 6% to reach $112.1 billion by 2014. Sharma et al. J Pharm Bioallied Sci. 2010 Oct-Dec; 2(4): 290–299. Through Defendants' Orphan Drug application, Defendants sought to take advantage of all of these benefits, while knowing the entire time that it intended to embark on mass off-label promotional efforts in order to reach a vast patient population and reap substantial profits, while receiving the benefits of lower investigative costs.

22. In order to qualify for the Orphan Drug designation approval, the drug company applicant must represent under the penalties of perjury to the FDA that:

> "…**Documentation, with appended authoritative references, to demonstrate that** …**that there is *no reasonable expectation* that the costs of research and development of the drug for the indication will be recovered in future sales of the drug in the United States as specified in §316.21(c).**

23. Under §316.21(c), Lundbeck and its predecessor was required to submit documentation for the estimated costs and sales data should be submitted as provided for in §316.21(c). Defendants deliberately exploited the Orphan Drug application process by misleading the FDA and others that they intended to limit the marketing of ONFI to patients with

LGS in order to avoid spending millions of dollars to conduct the typical extensive clinical trials that are required to prove that a drug is safe and effective.

Critically, the only clinical trials that Defendants submitted to the FDA in furtherance of their efforts to receive FDA approval for ONFI were clinical trials restricted to patients with LGS. Despite this limitation to such a rare subset of the general population (LGS) and restrictive data provided to the FDA in support of their applications, Defendants embarked on a wide-ranging, profit-seeking mission that broadly expanded the scope of their purported consumer base and, in turn, exploited children and adults with all types of seizure disorders.

24. Ovation/Lundbeck were also required to represent in their application that there was ***no expectation*** that they did not expect to recover their development costs, let alone a profit for ONFI. Instead, Lundbeck has made hundreds of millions of dollars off of this drug. Based on their misleading application, Defendants ultimately received FDA approval for ONFI in October of 2011 for the treatment of patients with LGS. The approval of ONFI by the FDA was without the benefit of all risk information that was not reviewed and considered by the FDA. In the two years since approval, Lundbeck has recorded record sales of ONFI to the tune of hundreds of millions of dollars, despite the fact that it represented to the FDA in its Orphan Drug Application that it would not recoup its R&D costs for ONFI based on the limited number of individuals inflicted with LGS.[1] The contrast between the massive sales of the product in the two years since it was approved and the small number of LGS patients (and the availability of

[1] In fact, Lundbeck's Annual Report for 2012 and 2013 reported total revenues of sales for ONFI in the U.S. to be $225 million for 2012, with 4th quarter sales for ONFI in 2012 showing nearly $80 million. In 2013, Lundbeck recorded blockbuster total sales that were up 122% from prior year, and resulted in total sales revenue of $111 million for the 2nd quarter of 2013 by itself. Lundbeck can be predicted to have sales revenue for 2013 of approximately nearly $500 million dollars.

other LGS drugs on the market) is utterly inconsistent and clear evidence that Defendants have engaged in substantial off-label promotion from day one.

25. Plaintiffs further contend that Defendants consciously withheld or omitted critical regulatory and safety information with its original Orphan Drug Application, and in doing so, were not in compliance with the pharmaceutical standards set out by 21 C.F.R. §316.10 subsections 7-10, because they did not submit all of the material worldwide regulatory experience, safety data and marketing information. More specifically, clobazam had been marketed outside the U.S. for 40 years. From this historical marketing experience, there were publications, clinical trial data, serious skin reaction registry data, WHO-Upsalla *Vigibase* spontaneous reporting data, and spontaneous reporting data from numerous foreign countries that were not analyzed, submitted, or disclosed with the IND, Orphan Drug Application, or subsequent submissions by Lundbeck and its predecessors.

26. The remaining subsections of 21 C.FR. §316.10 also required Lundbeck and its predecessors to submit study populations, protocols and the intended indications for which they sought marketing approval were limited to patients only diagnosed with LGS. The Defendants, however, knew that they had to market the drug in an off-label manner in order to not only recover their development costs and investments, but to actually turn profits of millions of dollars by the off-label marketing of ONFI to patients as young as two years of age who had never been diagnosed with LGS.

27. Plaintiffs contend that Defendants always intended to market ONFI beyond the approved and limited LGS patient base as a drug that was safe and effective to treat all seizure disorders. Defendants' illegal business plan started in 2005 when they began recruiting hospitals with large academic epilepsy centers that specialize in the treatment of children with epilepsy

across the U.S. In particular, Defendants recruited academic centers and physicians located at Barrow Neurological Institute, St. Joseph's Hospital and Medical Center, Phoenix, Arizona; Cook Children's Hospital in Ft. Worth, Texas; Emory University School of Medicine in Atlanta, Georgia, and others. Defendants retained these epilepsy centers and pediatric neurologists as paid consultants, speakers, or as primary or secondary clinical trial investigators to write papers before the approval of ONFI in the U.S. in order to promote ONFI for off-label indications or diseases.

28. Plaintiffs contend that Defendants failed to disclose the risks of serious skin reactions associated with ONFI to the FDA between 2005 and December of 2013, and at the same time, also failed to disclose those risks to clinical trial investigators, academic centers and hospitals, and Institutional Review Boards where the clinical trials or studies were conducted, including Barrow and Cook Children's. The IRBs, clinical trial investigators and clinical trial subjects were not informed or advised during the clinical research and development program of the risk of serious skin reactions associated with ONFI. Had Defendants warned these groups, Defendants' clinical trials would not have gone forward; the results would not have led to the approval of ONFI in the U.S.; or the FDA would have required greater study of the risks of serious skin reactions to children before Defendants' drug could be approved under more stringent warnings and more restriction population subsets.

29. Plaintiffs allege that Defendants paid their primary investigators for the Phase II-III clinical trials, including Dr. Yu-tze Ng and his epilepsy center, hundreds of thousands of dollars to support the use of ONFI for the treatment of seizures, even for patients that did not have an LGS diagnosis. Indeed, Defendants had already hired Dr. Ng as a paid consultant to make speeches and write medical articles promoting the potential efficacy of ONFI for use in children with or without LGS as early as 2007, before or right after the NDA was filed, and well

before his published paper in 2011 that reported on the Lundbeck-funded clinical trial that was relied upon to support approval for a very limited indication for ONFI in October of 2011. Ovation/Lundbeck and Dr. Ng, even before the pivotal Phase III study had begun, and prior to completing the Phase III studies, were over-promoting the efficacy of ONFI and omitting the serious risks of cutaneous reactions caused by ONFI to the medical community before a single indication was approved to treat any seizure with ONFI. *See Ng et al*. Neurotherapeutics*:* "Clobazam," Vol. 4:138–144, January 2007.[2]

30. Although the Defendant-sponsored safety studies limited the data to patients with LGS, Defendants' subsequent marketing efforts immediately expanded far beyond this limited patient base to individuals suffering from all types of seizures, all without the approval of the FDA.

Defendants Only Submitted LGS Studies to the FDA

31. Even though ONFI was not approved by the FDA for treatment of all types of seizure disorders, Ovation Pharmaceuticals (now Lundbeck), contracted with Cook Children's Hospital in Fort Worth, Texas, in part due to its large pediatric epilepsy center, to aid the Defendants in developing clinical research for the use of ONFI to treat children with a broad range of epilepsy disorders.

32. Cook Children's Hospital (where Antonio was prescribed ONFI) has a sizeable pharmacy section that is dedicated to conducting research on children for drug companies. The

[2] The article was written at a time that Ovation/Lundbeck were seeking approval for its orphan drug indication to limit its treatment to just patients diagnosed with LGS, however, Lundbeck's paid consultant, Dr. Ng's talks at length about the off-label uses of ONFI and how great those benefits were with ONFI (clobazam). Mr. Collins and Dr. Ng downplayed the risks most adverse events, and says nothing at all about the risks for serious skin reactions associated with ONFI or clobazam, even though there were children who developed serious skin reactions during the Phase 2 and 3 studies sponsored by Ovation/Lundbeck, including a child that had to be hospitalized with a serious skin reaction associated with ONFI, Lundbeck has never disclosed this in its ONFI labeling, even today.

FDA requirements set out for Cook's drug company clients, like Lundbeck, require compliance with Institutional Review Board standards, data safety monitoring board committees, and clinical research regulations set out by FDA and other hospital research standards.

33. In soliciting Cook Children's Hospital, Barrow Institute of Neurology, and other clinical investigator sites to test ONFI on child subjects that have never been diagnosed with LGS, Defendants failed to comply with FDA regulations regarding adequate disclosure of risks from serious skin reactions and failed to obtain adequate informed consent during the clinical ONFI trials.

34. Based upon a published study by Cook Children's Epilepsy Center and its physicians (including Antonio's prescribing physician), ONFI (clobazam) was imported from a foreign country (Canada) into the United States and shipped to Cooks Children's Epilepsy Center in Ft. Worth, Texas where it was used to treat children for seizure disorders other than LGS – before ONFI had received FDA approval for use in the United States. *See* Perry et al., J Child Neurol, 2013 Jan; 28(1):34-9, doi: 10.1177/0883073812461943. The published article notes:

> We included patients with both localization-related and generalized epilepsies, secondary to a variety of etiologies beyond Lennox-Gastaut syndrome, and analyzed the response of specific seizure types to clobazam therapy.

35. Plaintiffs contend Defendants failed to provide these test-patients with adequate informed consent, adequate warnings or adequate instructions or directions of use, including full disclosure regarding the risks versus benefits with the use of the unapproved drug.

36. In contrast to the Cook's study, which tested ONFI on patients with a broad range of seizure disorders, in 2009, Defendants' highly compensated consultant Dr. Ng and several other paid consultants published an article reporting on the results of the use clobazam for the treatment of LGS in children and adults. *See* Conry JA, Ng YT, Paolicchi JM, Kernitsky L,

Mitchell WG, Ritter FJ, Collins SD, Tracy K, Kormany WN, Abdulnabi R, Riley B, Stolle J. Clobazam in the treatment of Lennox-Gastaut syndrome. *Epilepsia* 2009;50:1158–1166.

37. From 2007-2009, Lundbeck fully sponsored another clinical trial restricted to LGS patients, known as OV-0012. This phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group trial was conducted at 51 sites in the United States, India, Europe, and Australia between August 2007 and December 2009. This study was called the CONTAIN study or the **C**l**O**bazam in Patie**NT**s with Lennox-G**A**staut Sy**N**drome. The CONTAIN study was only supposed to include patients aged 2–60 years who had onset of LGS before 11 years of age. In order to participate in this study, a clinical diagnosis of LGS was required. At all times material, Defendants knew that they were required to follow this study design in order to get approval for their Orphan Drug designation for treatment of LGS. Defendants also knew, however, that the intended target population was much broader.

38. The CONTAIN study was submitted to the FDA and used to gain FDA approval for the use of ONFI. Despite Lundbeck's intent to market the product the product to patients with or without LGS, Lundbeck deliberately *excluded* patients from this study who had not been diagnosed with LGS prior to age 11. This pivotal study greatly differed from what Lundbeck ultimately did after approval of ONFI – *i.e.*, marketing to treat patients with no diagnosis of LGS.

39. Despite the occurrence of two separate reports of serious skin reactions in children in Lundbeck's Phase 2-3 clinical trials for ONFI (including one hospitalization), Lundbeck did not submit a comprehensive safety assessment for serious skin reactions associated with ONFI. The comprehensive safety assessment that Lundbeck failed to submit to the FDA should have i) acknowledged the strong association and risks between benzodiazepines, including ONFI and serious skin reactions, ii) requested proposed warnings in the WARNINGS,

PRECAUTIONS, INFORMATION FOR PATIENTS, and ADVERSE REACTIONS section of Lundbeck's professional labeling (ONFI prescription insert), iii) included a discussion of the associated risks and directions for safe use in a Medication Guide for ONFI with their NDA and with their proposed ONFI launch labeling, among other risk submissions. In failing to tender the required submissions, Defendants failed to comply with the minimum standards of care for a pharmaceutical company.

40. While Lundbeck attempted to supplement its ONFI clinical trial safety database with the postmarketing experience for ONFI to make up for this shortfall,[3] Plaintiffs contend that Defendants deliberately withheld from the FDA vital safety information from their clinical trials and worldwide marketing experience regarding serious skin reactions associated with ONFI.[4]

41. Plaintiffs contend that ONFI should not have been approved for use in children to treat any type seizures, should not have been marketed off-label, should be withdrawn from the market, and/or should have its use or approved indications restricted to mitigate the risks of SJS and TEN in children, especially for use in children without a diagnosis of LGS, like Antonio Escareno. In addition to Defendants' far-reaching off-label promotion, insufficient clinical trials and withholding of information from regulators, physicians, testing centers and patients, Defendants ignored or failed to disclose readily available literature regarding the risk of serious skin reactions associated with their drug. For example, multiple published studies, including epidemiological studies, reported that this class of benzodiazepines were strongly associated with

[3] Lundbeck only conducted small Phase 1-3 trials and only directly involving a few hundred patients. The NDA and clinical trials data that were submitted to the FDA revealed patient exposure that falls substantially short of the International Conference of Harmonization (ICH) requirements of 1500 subjects total and short of the requirement of 300 subjects for 6 months, but meets the minimum requirement of 100 subjects for 1 year. In order to meet this basic requirement of sufficient human exposures, it appeared that Lundbeck used an old Legacy Epilepsy trial that was nearly 20 years old, and contributed those to the database in order to fulfill the requirement for 300 subjects for 6 months.

[4] Defendants' suspect clinical trial data included the OV-1012 study where approximately 23% of patients came from India and approximately another 7% came from outside the U.S.

SJS and TEN in children as early as 2009; and that there were cases of DRESS, SJS and TEN involving clobazam and other benzodiazepines as early as 20 years prior to the approval of ONFI. In fact, another benzodiazepine used for seizures had been withdrawn from the European market due its risks of SJS and TEN, despite having been on the European market for 30 years.

42. Plaintiffs contend that Lundbeck misinformed the FDA that there were no literature publications regarding DRESS/drug hypersensitivity syndrome implicating clobazam and failed to submit, report or properly analyze all serious skin reactions for clobazam with regard to the multiple cases of serious skin reactions involving DRESS, AGEP, SJS, TEN and EM from benzodiazepines, including clobazam, in violation of the minimum pharmaceutical standards of care set out by 21 C.F.R. 314.50, 21 C.F.R. 314.80 and 314.81.

43. Defendants did not include in their IND, orphan drug application, or even in the NDA submission(s) for ONFI, a full and comprehensive description or discussion of all available scientific literature, and spontaneous reports of serious skin reactions and ONFI, or benzodiazepines. Nor did Defendants propose any SJS/TEN warnings in their proposed or approved labeling to prescribers or patients or contact or retain a qualified medical expert to evaluate these risks of serious skin reactions during the IND or during the Phase 2-3 clinical studies despite the clinical trial data that demonstrated increased risks of serious skin reactions in children exposed to ONFI. Defendants ignored the adverse event reports in the worldwide scientific literature and the risks identified in the available spontaneous data from the U.S. FDA AERs database, and the World Health Organization's (WHO's) *Vigibase*, and from other foreign regulatory agencies adverse event reporting databases on a worldwide basis. Defendants failed to provide submissions of any foreign safety assessments along with all foreign labeling from the marketed products outside of the U.S. to the FDA, physicians, state pharmacy boards, insurance companies all who relied upon Lundbeck's misrepresentations of safety and efficacy for ONFI.

Lundbeck Warned of SJS/TEN in its Foreign Labeling But Did Not Include Those Warnings in the U.S. Label

44. Clobazam is a benzodiazepine derivative, which is marketed under the names Frisium, Urbanol, and ONFI. Frisium and ONFI are both manufactured and marketed by Defendants. Between 2006-2011, Defendants had released a Product Monograph regarding Frisium in Canada, indicating that "[r]eports have been received of Stevens-Johnson Syndrome (SJS), including toxic epidermal necrolysis (TEN)" related to Frisium's use. In the Product Monograph, Defendants cited to a medical journal reporting the onset of Stevens Johnson Syndrome triggered by a combination of clobazam (also the active ingredient in ONFI), lamotrigine, and valproic acid. This document explicitly reflects this was not an isolated occurrence, opining that Stevens Johnson syndrome and TEN are "Uncommon Side Effects"—as opposed to "Very Rare" side effects—of the drug's use. *See* Attachment 1, Lundbeck's Product Monograph for Canada-Frisium (clobazam).

45. At all times material, Defendants knew that Clobazam or ONFI causes SJS and TEN. Despite this acute knowledge (well before Antonio's injury) and SJS/TEN warnings in foreign countries, Lundbeck withheld any warnings regarding the association between ONFI and SJS and TEN from U.S. patients and prescribing physicians. Defendants misled and failed to adequately warn ONFI prescribers and users of its potential serious dangers. Defendants instead violated basic pharmaceutical standards of care set out by the applicable code of federal regulations by misleading clinical trial investigators, clinical trial IRBs, FDA, physicians, patients, pharmacy boards, hospitals, government regulatory agencies that evaluate the safety and efficacy of ONFI for use for their insured members, and did so by failing to include a warning that these life threatening conditions were known side effects from the ingestion of ONFI. Knowing that SJS and TEN were side effects of ONFI, the Defendants

failed to timely amend their product label to bring it in compliance with these standards and federal law and state laws. Antonio's prescribing physician was deprived of the ability to fully assess the risks of ONFI when making the decision to prescribe these drugs due to Defendants' lack of adequate directions of use and failure to provide any warnings, precautions, information for patients, and adequate risk-benefit information in the Medication Guide regarding SJS/TEN. *See* Attachment 2, Lundbeck's prescribing package insert and Medication Guide for Patients dated October of 2011-March of 2013.

Defendants' Off-Label Promotion to Children

46. At all times material, Defendants knowingly engaged in illegal promotion of ONFI for the use of seizures for patients who had not been diagnosed with LGS. To facilitate their scheme of off-label promotion, Defendants compensated large academic centers, like Cook Children's Hospital, and physicians to promote and prescribe ONFI to patients for unapproved indications – including children like Antonio who did not have LGS. Defendants funded epileptology research clinics – such as the one where Antonio Escareno received treatment – as a part of their illegal promotion of a drug to children for broad seizure disorders for the sole purpose of recovering millions of dollars in profits. Lundbeck funded these pediatric epilepsy centers (and the physicians that work there) to promote ONFI and developed a pediatric epilepsy research database(s), including the epilepsy database at Cook Children's, where Antonio was recruited and enrolled to participate in the Lundbeck-sponsored research database where children, like Antonio Escareno, were subjected to off-label experimental use of this epilepsy drug. Defendants consciously put and continue to put the lives of children at serious risk of death, blindness, and permanent injuries from SJS and TEN.

47. In addition to patients, Defendants have defrauded major health insurance carriers through their illegal off-label promotion, including Antonio's provider United

HealthCare.

48. Patients like Antonio were never informed by Defendants of the inferiority of the efficacy of ONFI to treat seizures, and to treat seizures in patients who have never been diagnosed with LGS, or that Defendants failed to disclose the risk of serious skin reactions that were exposes by the Phase 2 & 3 ONFI clinical trials. If such information had been disclosed, ONFI would never have been prescribed to Antonio because the epilepsy clinic would not approve its use in its patients and/or Antonio's prescribing physician would not have prescribed the drug. Even if the prescriber would have prescribed the drug (he would not) despite the risk of harm, United HealthCare would not have agreed to pay for ONFI and it would not have been dispensed ONFI by the pharmacy to Antonio's parents.

49. On or about December of 2012, Antonio's parents were provided an informed consent form at Cook Children's in order to authorize the academic epilepsy center located at Cook's to allow them to include Antonio as part of their research database to assist in research that may have been funded by Defendants. The "informed consent" provided to and executed by Antonio's parents was procured through deception by Defendants. Specifically, Defendants failed to provide adequate directions of use and warnings regarding ONFI, which rendered their ONFI products misbranded. Lundbeck used research institutions, like Cook Children's, to falsely lure patients like Antonio to seek treatment there for the purpose to allow the institution and the clinics to illegally promote ONFI for off-label conditions. Indeed, Antonio has never been diagnosed with LGS and his seizure type did not emanate from LGS seizure disorders.

After Antonio's Reaction, Defendants Change Their Labeling

50. Following Defendants' FDA-ONFI approval in October of 2011, Defendants knew that there were at least 5-6 reports of SJS and TEN stemming from this drug – including

another Hispanic child in Texas who was blinded and nearly killed by the drug. These patients, and many more ONFI users were subjected to serious injuries from ONFI-induced SJS and TEN, yet Defendants did nothing to fully investigate, report and disclose the risk information regarding SJS and TEN for nearly 2 years after approval in the U.S. It was not until May of 2013 – and after they had generated hundreds of millions of dollars in sales for ONFI and after counsel for Plaintiffs in this case had notified Lundbeck and reported the incident of SJS and TEN sustained by Antonio Escareno – did Defendants submit their Changes Being Effected (CBE) submission to the FDA requesting changes to the product's label to add warnings about SJS and TEN in the U.S., and to add warnings specific to the Medication Guide that is provided to patients when they pick up their prescription. *See* Attachment 3, FDA Press Release and Risk Communication regarding ONFI and serious skin reactions. The FDA approved Lundbeck's new warnings regarding SJS and TEN to the prescription package insert and the patient Medication Guide in late 2013. *See* Attachment 4, current revised ONFI label.

51. Defendants' warnings were added to their websites as early as May of 2013 for ONFI, months before FDA approval of the label change in December of 2013. Despite Defendants' knowledge that their label was and is deficient, Defendants never issued any risk communication, such as Dear Doctor/Healthcare provider letters, patient information leaflets, press releases, or presentations at medical or scientific meetings and conferences to inform prescribers of the risk of SJS/TEN, and did not provide warnings in the Medication Guides for patients or their parents.

52. Defendants did not submit or request warnings for the package inserts for ONFI in order to warn physicians about the risks, frequencies, mortality/morbidity, early symptoms of SJS and TEN prior to their submissions of their IND, orphan drug application, or NDA, and

failed to do so until after Antonio Escareno's SJS and TEN reaction from ONFI. Defendants also failed to seek a Patient Medication Guide that had warnings for serious skin reactions associated with ONFI under Sections 21 C.F.R. §208 as they should have done when filing their applications for approval by FDA, and failed to update the Medication Guide for ONFI, *after* many cases of ONFI-induced SJS and TEN occurred, including death and blindness.

53. Had Defendants requested a Medication Guide identifying the serious skin reactions prior to or just after approval in October of 2011 and added warnings regarding SJS and TEN, Antonio's parents and prescriber would have received those warnings of SJS and TEN and Antonio's parents would not have allowed their son to take ONFI.

54. The current labeling that added the new SJS and TEN warnings after Antonio Escareno developed SJS and TEN, still today remain inadequate in that it does not provide all material postmarketing experience of serious skin reactions associated with ONFI, does not disclose any frequency or relative risks or reporting ratios for serious skin reactions associated with ONFI, does not warn of the increased risk of SJS/TEN to subpopulations, and does not warn about early discontinuation and to watch for certain early symptoms such as blistering and skin reddening. These new warnings also do not disclose that Defendants have known that certain populations cannot safely metabolize ONFI because these patients possess a genetic allele that impairs the ability of patients to safely take the drug. This genetic phenotyping is mentioned in the labeling. Defendants know that this genetic phenotyping is associated with increased risks of adverse events associated with ONFI therapy, including skin reactions, yet does not recommend this test prior to being prescribed ONFI. *In stark contrast to its failure to recommend this testing to the general population, Defendants performed genetic phenotyping all clinical trial subjects who were in the premarketing trials for ONFI.*

55. As a result of the false and misleading claims made by Defendants regarding

the safety and effectiveness of their ONFI product, Antonio suffered and will continue to suffer from severe painful and permanent injuries due to SJS/TEN.

56. These conditions and resulting injuries were caused by Antonio's ingestion of Defendants' product ONFI. Had Plaintiffs known of the off label nature of the drug, and the risks and dangers associated with Defendants' product ONFI, or had Defendants disclosed such information to Plaintiffs, Antonio would not have taken ONFI and would not have suffered the aforementioned adverse reaction and subsequent complications.

57. Defendants failed to perform adequate premarketing and postmarketing testing on ONFI, that would have shown that the medication possessed serious side effects to which Defendants should have taken appropriate measures to ensure that its defectively designed product would not be placed into the stream of commerce and/or should have provided full and proper warnings accurately, or would have been restricted in its use, and fully reflecting the scope and severity of symptoms of those side effects, and provide adequate directions of use to avoid these serious reactions.

58. Prior to the manufacturing, sale and distribution of Defendants' product ONFI, Defendants, through their officers, directors and managing agents, had notice and knowledge that ONFI presented substantial and unreasonable risks of harm to consumers, especially to patients who the drug had not been tested prior to approval, i.e. patients with no diagnosis of LGS. As a result, consumers, including Plaintiffs, were unreasonably subjected to risk of injury or death from the consumption of the medication.

59. Despite such knowledge, Defendants, through their officers, directors, and managing agents, for the purpose of increasing sales and enhancing profits, knowingly and deliberately failed to remedy the known defects of ONFI and failed to adequately warn the public, including Plaintiffs, of the serious risk of injury occasioned by the defects inherent in

the medication. Defendants and their officers, agents and managers intentionally proceeded with the manufacturing, sale and marketing of ONFI, and did so promoting the drug for off-label uses, knowing that persons would be exposed to serious potential danger, in order to advance their own pecuniary interests. Defendants' conduct was wanton and willful, and displayed a conscious disregard for the safety of the public and particularly of Plaintiffs, entitling Plaintiffs to exemplary damages.

60. Defendants acted with conscious and wanton disregard of the health and safety of Plaintiffs, who request an award of additional damages for the sake of example and for the purpose of punishing such entities for their conduct, in an amount sufficiently large to be an example to others, and to deter Defendants and others from engaging in similar conduct in the future. The above-described wrongful conduct was done with knowledge, authorization, and ratification of officers, directors and managing agents of Defendants.

61. As a result of ingesting the products manufactured, supplied, and/or sold by Defendants, Plaintiffs suffered severe, painful and permanent injuries, specifically a severe adverse reaction of SJS and TEN. As a result of the dangerously defective nature of ONFI at the time of manufacture and distribution, Antonio, by using ONFI, and his parents sustained the injuries and damages alleged herein.

62. As a direct and proximate result of Defendants' wrongful conduct as described herein, Plaintiffs have sustained harm, including permanent and debilitating injuries, specifically, systematic symptoms of Stevens-Johnson Syndrome and TEN, and resultant injury, harm and economic loss as set forth within.

IV. Causes of Action

COUNT I - TEX. CIV. PRAC. & REM. CODE §82.007(b)(3)/OFF-LABEL PROMOTION

63. Plaintiffs incorporate by reference each and every paragraph of this complaint as set forth in full below.

64. TEX. CIV. PRAC. & REM. CODE §82.007 creates a presumption in favor of a drug company defendant as to adequacy of a product's labeling under certain circumstances. Rather than bar all plaintiffs (including minor children like Antonio) from bringing claims against drug companies under any circumstances, the Code sets forth certain exceptions to the presumptions contained therein. Applicable here, Plaintiffs allege that all Defendants are subject to liability pursuant to TEX. CIV. PRAC. & REM. CODE §82.007(b)(3), which states as follows:

> (b) The claimant may rebut the presumption in Subsection (a) as to each defendant by establishing that:
>
> ***
>
> (3)(A) the defendant recommended, promoted, or advertised the pharmaceutical product for an indication not approved by the United States Food and Drug Administration;
> (B) the product was used as recommended, promoted, or advertised; and
> (C) the claimant's injury was casually related to the recommended, promoted, or advertised use of the product…

65. Plaintiffs allege Defendants recommended, promoted and advertised ONFI for an indication that was not approved by the FDA; that ONFI was prescribed to Antonio as recommended by Defendants; and Plaintiffs' injuries were caused by Defendants' wrongful recommendation, promotion and advertising of ONFI.

66. As stated above, ONFI has not been approved by the FDA for treatment of general seizure disorders and, instead, approval was limited to the exceedingly rare Lennox Gastaut Syndrome (LGS), which affects a mere 200,000 patients in the U.S. At the time of his ingestion

of ONFI and today, Anthony did not have LGS and, indeed, he has never been diagnosed with LGS. In an effort to expand its sales base well beyond the approximately 200,000 LGS sufferers to the hundreds of thousands of individuals (like Anthony) who suffer seizure disorders without an etiology from LGS and to deceptively receive the cost savings associated with an FDA approval pursuant to an Orphan Drug Application, Defendants strategically promoted off-label uses of ONFI through so-called "clinical trials" and through their paid physicians and hospitals where Defendants-funded ONFI research on children based on their wrongful withholding of critical safety information. Defendants' funding to Cook Children's Hospital and provision of misleading safety materials that Defendants provided directly to Antonio's prescribing physician as well as Defendants' direct or indirect misrepresentations to Plaintiffs in their Medication guide or the Defendants' "informed consent" materials that were presented to Plaintiffs and precipitated Antonio's participation in Defendants' investigational trials on this child all led to Antonio's ingestion of ONFI, his prescribing physician's prescription of ONFI and Antonio's serious injuries.

67. Defendants failed to make Antonio's prescribing physician aware of the risk of SJS/TEN associated with ONFI. Particularly given ONFI was not approved by the FDA for any seizure disorders other than LGS and in light of the myriad available safer alternative seizure drugs that were readily available on the market, Antonio's prescribing physician would not have prescribed ONFI to Antonio if he had known of the occurrence of serious reactions in the clinical trials, and the overall risks of SJS/TEN associated with the drug. Defendants' illegal off-label promotion led to Antonio's prescribing physician prescribing ONFI to Antonio; led to Antonio's insurance carrier approving to pay for the ONFI; and ultimately led to the dispensing of the drug at the pharmacy and Antonio's crippling injuries from SJS and TEN and DRESS.

COUNT II - STRICT PRODUCTS LIABILITY/FAILURE TO WARN

68. Plaintiffs incorporate by reference each and every paragraph of this complaint as set forth in full below.

69. Defendants designed, tested, manufactured, marketed, distributed and supplied ONFI. As such, Defendants had a duty to adequately test the product in conformance with the standards of care to ensure that the risks and benefits of the drug were sufficient for the safe and effective use of the drug for its approved indications, and to warn healthcare providers, including hospitals, clinics, prescribers and patients, including Plaintiffs, of the health risks and dangers associated with using the medication, especially in off-label uses, both in the premarketing and post-approval lifecycle phases of ONFI. Defendants failed to adequately disclose the risks associated with ONFI to the clinical trial investigators, study subjects in their Phase 2 & 3 clinical studies, and also in their IND, Orphan Drug Application and in its' NDA for ONFI, and did not warn Antonio Escareno's healthcare providers at Cook Children's or his physicians of the risks of serious skin reactions referenced in the previous paragraphs of this complaint.

70. ONFI was in the exclusive control of Defendants and was sold without adequate directions of use and without adequate warnings regarding the risk of SJS, TEN and other risks associated with its use.

71. As a direct and proximate result of the defective condition of ONFI, as tested, designed, manufactured, marketed and/or supplied by Defendants, and as a direct and proximate result of negligence, gross negligence, willful and wanton misconduct, or other wrongdoing and actions of Defendants described herein, Plaintiffs suffered personal injury, damages and economic loss as alleged herein.

72. Upon information and belief, Defendants knew of the defective nature of ONFI,

but continued to design, test, manufacture, market, and sell the medication to maximize sales and profits at the expense of public health and safety, in knowing, conscious, and deliberate disregard of the foreseeable harm caused by the medication, and in violation of their duty to provide accurate, adequate, and complete directions for use and warnings concerning the use of ONFI, especially for use in off-label indications.

73. Defendants failed to warn the public, Plaintiffs, or Plaintiffs' prescribing physician of the dangerous propensities of ONFI, which were known or should have been known to Defendants, as they were scientifically readily available, especially for off-label uses when Defendants knew that it would be used in patients without being diagnosed with LGS.

74. Defendants knew and intended for ONFI to be prescribed by physicians and be used by persons with a prescription, without any inspection for defects. Defendants also knew that hospitals, clinics, physicians, insurance companies, pharmacies and users, such as Plaintiffs, would rely upon the representations made by Defendants in their dossiers, and on the product labels and Medication Guides, and in other promotion and sales materials, and upon which Plaintiffs and his prescribing physician did so rely.

75. As a direct and proximate result of Defendants' sale of ONFI without adequate directions of use or adequate warnings regarding the risk of SJS, TEN and other risks associated with its use, Plaintiffs suffered harm as alleged herein, including ascertainable economic loss, including purchase price of Defendants' product ONFI, out-of-pocket costs of medical tests and treatment, future medical care and/or services, and other costs incidental to Plaintiff's ingestion of ONFI, as well as extreme pain and suffering, loss of enjoyment of life, and other substantial damages.

76. Defendants' conduct in the testing, packaging, warning, marketing, advertising, promotion, distribution, and sale of Defendants' product ONFI was committed with knowing,

conscious and deliberate disregard for the rights and safety of consumers such as Plaintiffs, thereby entitling Plaintiffs to punitive damages in an amount to be determined at trial that is appropriate to punish Defendants and deter them from similar conduct in the future.

COUNT II - DEFECTIVE DESIGN AND MANUFACTURING DEFECT

77. Plaintiffs incorporate by reference each and every paragraph of this complaint as though set forth in full herein.

78. Defendants were the designers, testers, manufacturers, sellers, distributors, marketers, and/or suppliers of Defendants' product ONFI, which was defective and unreasonably dangerous to consumers.

79. Defendants' product ONFI was sold, distributed, supplied, manufactured, marketed, and/or promoted by Defendants, and was expected to reach and did reach consumers without substantial change in the condition in which it was manufactured and sold by Defendants.

80. The product ONFI manufactured, supplied, and/or sold by Defendants was defective in design or formulation in that when it left the hands of the manufacturers and/or sellers and was unreasonably dangerous in that its foreseeable risks exceeded the benefits associated with its design or formulation.

81. Upon information and belief, Defendants actually knew of the defective nature of Defendants' product ONFI but continued to design, manufacture, market, and sell it so as to maximize sales and profits at the expense of the public health and safety, in conscious disregard of the foreseeable harm caused by Defendants' product ONFI.

82. There were safer alternative methods and designs for the like product. Specifically, there were other benzodiazepines, and other designs that would not impact the utility of the product, and that would lower the risks of SJS and TEN, and other skin reactions

that Lundbeck could have utilized to submit for approval to treat seizures that were scientifically available and feasible, and would not render the product defective. But Lundbeck and its predecessors failed to do so.

83 At all times material, ONFI was designed, tested, inspected, manufactured, assembled, developed, labeled, sterilized, licensed, marketed, advertised, promoted, sold, packaged, supplied and/or distributed by Defendants in a defective and unreasonably dangerous condition in ways which include, but are not limited to, one or more of the following:

a. When placed in the stream of commerce, the drug contained unreasonably dangerous design defects and was not reasonably safe and fit for its intended or reasonably foreseeable purpose or as intended to be used, thereby subjecting users and/or consumers of the drug, including Antonio, to risks which exceeded the benefits of the drug;

b. The drug was insufficiently tested because there was inadequate informed consent for ONFI, both in clinical trials, and after approval of ONFI, and that before it could be shipped across state lines, Lundbeck did not adhere with minimum standards of care for the pharmaceutical industry;

c. The drug caused harmful side effects that outweighed any potential utility;

d. The drug was not accompanied by adequate labeling, directions/instructions for use and/or warnings to fully apprise the medical, pharmaceutical and/or scientific communities, and users and/or consumers of the drug, including Plaintiffs, of the potential risks and serious side effects associated with its use, thereby rendering Defendants liable to Plaintiffs; and

e. In light of the potential and actual risk of harm associated with the drug's use, a reasonable person who had actual knowledge of this potential and actual risk of

harm would have concluded that ONFI should not have been marketed in that condition.

84. At all times material, the drug ONFI was designed, tested, inspected, manufactured, assembled, developed, labeled, sterilized, licensed, marketed, advertised, promoted, sold, packaged, supplied and/or distributed, to reach, and did reach, users and/or consumers of the drug across the United Sates, including Antonio, without substantial change in the defective and unreasonably dangerous condition in which it was sold.

85. At all times, Antonio used ONFI for its intended or reasonably foreseeable purpose. As a direct, legal, proximate and producing result of the defective and unreasonably dangerous condition of ONFI, Antonio has sustained harm for which Plaintiffs are entitled to damages. These injuries have caused extensive pain and suffering, severe emotional distress to Plaintiffs, and caused Plaintiffs, to expend substantial sums of money for medical, hospital and related care.

86. As a direct, legal, proximate and producing result of the defective and unreasonably dangerous condition of ONFI, Antonio was injured in health, strength and activity and has suffered physical injuries as well as mental anguish. All of these injuries caused Plaintiffs intense anxiety, distress, fear, pain and suffering secondary to physical injury and damages, for which Plaintiffs are entitled to damages.

87. As a direct, legal, proximate and producing result of the defective and unreasonably dangerous condition, Antonio required reasonable and necessary healthcare treatment and services and incurred expenses in the past, and will do so in the foreseeable future, for which Antonio is entitled to damages.

88. As a direct and proximate result of the design and manufacturing defects of Defendants' product ONFI, Plaintiffs have suffered injury and harm as previously alleged herein,

including ascertainable economic loss, including the purchase price of Defendants' product ONFI, out-of-pocket costs of medical tests and treatment, future medical care and/or services, and other costs incidental to Antonio's ingestion of harmful and defective products, as well as extreme pain and suffering, loss of enjoyment of life, and other injuries and damages.

89. Defendants' aforementioned conduct was committed with knowing, conscious, and deliberate disregard for the rights and safety of consumers such as Antonio, including Defendants' knowingly withholding and/or misrepresenting information to the public including Antonio, which information was material and relevant to the harm in question, punitive damages in an amount to be determined at trial that are appropriate to punish Defendants and deter them from similar conduct in the future.

COUNT III – FRAUD AND FRAUDULENT INDUCEMENT

90. Plaintiffs incorporate by reference each and every paragraph of this complaint as though set forth in full herein.

91. At all material times, Defendants were engaged in the business of manufacturing, marketing, distributing, promoting, and selling Defendants' product ONFI.

92. Defendants made misrepresentations of material facts to, and omitted and/or concealed material facts from, various entities in the cycle of the product, including the clinical trial investigators, study subjects, hospitals, clinics, the epilepsy clinic and Plaintiff's prescribing physician in the promotion, advertising, marketing, distribution and sale of Defendants' product ONFI regarding its efficacy and safety, and adequate directions for use.

93. Defendants deliberately and intentionally misrepresented to, and omitted and/or concealed material facts from, consumers, including Plaintiffs, and prescribing physicians, that Defendants' product ONFI was safe when used as intended. Such misrepresentations, omissions, and concealments of facts include, but are not limited to:

a. Failing to disclose, and/or intentionally concealing, the results of tests showing the potential risks of serious skin reactions, erythema multiforme exudativum (EM), bullous fixed drug eruption (BDFE), severe cutaneous adverse reaction, acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), exfoliative dermatitis, toxic epidermal necrolysis (TEN), Stevens-Johnson Syndrome (SJS), and other injuries associated with the use of Defendants' product ONFI during the premarketing and post-approval phases of the lifecycle of the drug product ONFI;

b. Failing to include adequate warnings with Defendants' product ONFI about the potential and actual risks and the nature, scope, severity, frequency and duration of serious adverse effects of Defendants' product ONFI;

c. Concealing and/or providing false or inaccurate information regarding the known risks of serious skin reactions, exfoliative dermatitis, toxic epidermal necrolysis, Stevens-Johnson Syndrome and other risks associated with Defendants' product ONFI; and

d. Concealing the known incidents of serious skin reactions, exfoliative dermatitis, toxic epidermal necrolysis, Stevens-Johnson Syndrome and other injuries, and the mortality and morbidity rates, at risk populations, and postmarketing experience, and early symptoms of SJS and TEN, and the need for greater care and monitoring during first 8 weeks of therapy, as previously alleged herein.

94. Defendants concealed facts known to them, as alleged herein, in order to ensure increased sales of Defendants' product ONFI, without providing all of the essential scientific information for the safe and effective use of the product, through informed consent forms, applications to FDA, applications to other entities, through Dear Healthcare letters, press

releases, patient information leaflets, and/or Patient Medication Guides, or through other risk communication mediums that are used by drug makers to inform medical community and patients, and other entities regarding the risk-benefit profile of ONFI.

95. Defendants had a duty to disclose the foregoing risks and failed to do so, despite possession of information concerning those risks. Defendants' representations that Defendants' product ONFI was safe for its intended purpose were false, misleading, as Defendants' product ONFI was, and in fact, is dangerous to children and to Antonio's health. Moreover, Defendants knew that their statements were false, knew of incidents of serious injuries, such as serious skin reactions, erythema multiforme exudativum, bullous fixed drug eruption, severe cutaneous adverse reaction, acute generalized exanthematous pustulosis, drug reaction with eosinophilia and systemic symptoms, exfoliative dermatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome associated with ONFI and other benzodiazepines prior to, and after approval of ONFI in the U.S., and knew that their omissions rendered their statements false or misleading.

96. Further, Defendants failed to exercise reasonable care in ascertaining the accuracy of the information regarding the safe use of Defendants' product ONFI, and failed to disclose that Defendants' product ONFI caused serious skin reactions, erythema multiforme exudativum, bullous fixed drug eruption, severe cutaneous adverse reaction, acute generalized exanthematous pustulosis, drug reaction with eosinophilia and systemic symptoms, exfoliative dermatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, among other serious adverse effects. Defendants also failed to exercise reasonable care in communicating the information concerning Defendants' product ONFI to Plaintiffs, and/or concealed facts that were known to Defendants.

97. Plaintiffs were not aware of the falsity of the foregoing representations, nor were Plaintiffs aware that material facts concerning the safety of Defendants' product ONFI had been concealed or omitted. In reliance upon Defendants' misrepresentations (and the absence of

disclosure of the serious health risks), Antonio ingested Defendants' product ONFI. Had Plaintiffs known the true facts concerning the risks associated with Defendants' product ONFI, Antonio would not have taken it.

98. The reliance by Plaintiffs upon Defendants' misrepresentations was justified because said misrepresentations and omissions were made by individuals and entities that were in a position to know the true facts concerning Defendants' product ONFI. Plaintiffs were not in a position to know the true facts because Defendants aggressively promoted the use of Defendants' product ONFI and concealed the risks associated with their use, thereby inducing Antonio and his prescribing physician to use Defendants' product ONFI. Defendants' false and misleading representations to Cook Children's Hospital, the prescribing physician, and to the parents of Plaintiff, including the false and misleading representations made in the research program at Cook Children's involved the failure to obtain adequate informed consent from the parents of Plaintiff, and from others involved in the Lundbeck programs, including the patient-assistance program operated by Lundbeck.

99. As a direct and proximate result of Defendants' misrepresentations and/or concealment, Plaintiffs suffered conscious pain and suffering, and suffered injury and harm as previously alleged herein.

100. Defendants' conduct in concealing material facts and making the foregoing misrepresentations, as alleged herein, was committed with conscious or reckless disregard of the rights and safety of consumers such as Plaintiffs, thereby entitling Plaintiffs to punitive damages in an amount to be determined at trial that is appropriate to punish Defendants and deter them from similar conduct in the future. Plaintiffs are not alleging any cause of action for fraud on the FDA.

COUNT IV - BREACH OF WARRANTY

101. Plaintiffs incorporate by reference each and every paragraph of this complaint as though set forth in full herein.

102. Defendants manufactured, marketed, sold, and distributed Defendants' product ONFI.

103. At the time Defendants marketed, sold, and distributed Defendants' product ONFI for use by Antonio, Defendants knew of the purpose for which Defendants' product ONFI was intended and impliedly warranted Defendants' product ONFI to be of merchantable quality and safe and fit for such use.

104. Antonio's prescribing physician reasonably relied on the skill, superior knowledge, and judgment of Defendants as to whether Defendants' product ONFI was of merchantable quality and safe and fit for its intended use.

105. Antonio used Defendants' product ONFI which was provided to Antonio's hospital and through his prescribing physician by the Defendants. Due to Defendants' wrongful conduct as alleged herein, Plaintiffs could not have known about the risks and side effects associated with Defendants' product ONFI until after Antonio ingested it because there were no warnings or adequate directions for use for ONFI.

106. Contrary to such implied warranty, Defendants' product ONFI was not of merchantable quality and was not safe or fit for its intended use.

107. As a direct and proximate result of Defendants' breach of implied warranty, Antonio suffered conscious pain and suffering and suffered injury and harm as previously alleged herein.

108. Defendants' aforementioned conduct was committed with knowing, conscious, and deliberate disregard for the rights and safety of consumers such as Antonio, thereby entitling

Plaintiffs to punitive damages in an amount to be determined at trial that is appropriate to punish Defendants and deter them from similar conduct in the future.

COUNT V - BREACH OF EXPRESS WARRANTY

109. Defendants expressly warranted that ONFI was safe and well-accepted by patients and was safe for long-term use.

110. ONFI does not conform to these express representations because ONFI is not safe and has high levels of serious, life-threatening side effects.

COUNT VI – NEGLIGENCE

111. Plaintiffs repeat and incorporate herein by reference the allegations made in the above Paragraphs as if restated herein in full.

112. Plaintiffs incorporate by reference each and every paragraph as set forth in full herein.

113. Defendants owed a duty to the clinical trial centers, study subjects, prescribing physicians, and consumers of ONFI, including Plaintiffs, to use reasonable care in designing, testing, labeling, manufacturing, marketing, supplying, distributing, and selling ONFI, including a duty to ensure that ONFI did not cause users to suffer from unreasonable, unknown, and/or dangerous side effects, or to contain all of the essential scientific information for the safe and effective use of the drug, and to provide adequate directions for use along with adequate warnings for all its risks.

114. Defendants failed to exercise reasonable care in the warning, designing, testing, labeling, manufacturing, marking, selling, sale, and/or distribution of ONFI and breached its duty to Plaintiffs in that, and not by way of limitation, they failed to warn of the known risks associated with the use of ONFI and did not exercise an acceptable standard of care—what a

reasonable manufacturer would have known or warned about. Moreover, the product lacked sufficient warnings regarding the hazards and dangers to users of ONFI, and failed to provide safeguards to prevent injuries sustained by Plaintiffs. Defendants failed to properly test ONFI prior to its sale, and as a result subjected users to an unreasonable risk of injury when those products were used as directed.

115. Defendants additionally breached their duty and were negligent in their actions, misrepresentations, and omissions towards Plaintiffs in the following ways:

a. Failed to exercise due care in designing, developing, testing, marketing and manufacturing of ONFI to avoid the aforementioned risks to individuals involving those products during the ONFI lifecycle;

b. Failed to include adequate directions for use and warnings with ONFI to alert all entities, including prescribers, and Plaintiffs and other consumers of its potential risks and side effects;

c. Failed to adequately and properly test ONFI before placing it on the market by not disclosing all risks in its studies, applications, and labeling, and marketing and advertising materials and documents;

d. Failed to conduct sufficient clinical testing on ONFI, which if properly performed would have shown that ONFI had serious side effects, including, but not limited to Stevens-Johnson syndrome, TEN, and other serious side effects; and would have led to other negative regulatory actions, that would not have made the product available to prescribe, or to be used in certain populations, or to be distributed by hospitals, clinics or pharmacies, or by Plaintiffs.

e. Failed to adequately warn Plaintiffs and physicians that use of ONFI about the risks prior to, and after the clinical trials, and prior to and after the IND, orphan drug application, and the NDA, and prior to and after post-approval of ONFI that cases of serious skin reactions had occurred in humans that were reported in the literature, in spontaneous reporting databases, in ONFI clinical trials, and reported directly to the defendants, regarding the risks of Stevens Johnson Syndrome, TEN, and other serious side effects, and the risk to subpopulations, risks compared to the benefits for use outside of patients diagnosed with LGS, failed to conduct adequate pharmacovigilance to prepare a PV assessment and plan to mitigate the risks of SJS/TEN; and failed to warn through various risk communication vehicles, including patient information leaflets or patient Medication guides, Dear Healthcare letters, press releases, Internet announcements on their product websites, and other risk communication vehicles.

f. Failed to provide adequate post-marketing warning or instructions after Defendants knew or should have known of the significant risk of reactions to the use of ONFI; and sought to restrict the use of ONFI for certain populations and for certain seizures;

g. Placed an unsafe product into the stream of commerce; and

h. Was otherwise careless or negligent.

116. Defendants knew or should have known that ONFI caused unreasonably dangerous risks and serious side effects of which Plaintiffs would not be aware. Defendants nevertheless advertised, marketed, sold, and/or distributed ONFI, despite knowing of its unreasonable risks of injury.

117. Defendants knew or should have known that consumers such as Plaintiffs would suffer injury as a result of Defendants' failure to exercise reasonable care as described above.

118. Upon information and belief, Defendants knew or should have known of the defective nature of ONFI, as set forth herein, but continued to design, manufacture, market, and sell ONFI so as to maximize sales and profits at the expense of the health and safety of the public, including Plaintiffs, in conscious and/or negligent disregard of the foreseeable harm caused by the medication.

119. Defendants failed to disclose to Plaintiffs and the general public facts known or available to them in order to ensure continued and increased sales of ONFI. This failure to disclose deprived Plaintiffs of the information necessary for Plaintiffs to weigh the true risks of taking ONFI against the benefits.

120. As a direct and proximate result of Plaintiffs' use of ONFI, Plaintiffs suffered serious bodily injury including, but not limited to, Stevens-Johnson syndrome and TEN.

121. By virtue of Defendants' negligence, Defendants have directly, foreseeably and

proximately caused Plaintiffs to suffer serious bodily injury. As a result, the imposition of punitive damages against Defendant is warranted.

122. As a direct and proximate result of Defendants' negligence, Plaintiffs suffered harm as alleged herein, including severe pain and suffering, loss of enjoyment of life, ascertainable economic loss, including the purchase price of ONFI, out-of-pocket costs of medical tests and treatment, future medical care and/or services, and other costs incidental to Plaintiff's ingestion of harmful and defective products.

COUNT VII - GROSS NEGLIGENCE

123. Plaintiffs incorporate by reference each and every paragraph of this complaint as set forth in full herein.

124. Defendants had the duty to exercise reasonable care in warning about, designing, testing, manufacturing, marketing, labeling, selling, and/or distributing its ONFI product, including a duty to ensure that ONFI did not cause users to suffer from unreasonable and dangerous side effects, including death, blindness, scarring of vagina and penis, and direct injuries to all organ systems, including lungs, eyes, liver, kidney, heart, brain, skin, vascular and other systems of the human body.

125. Defendants failed to exercise reasonable care in warning about, designing, testing, manufacturing, marketing, labeling, selling, and/or distributing ONFI in that they:

a. Failed to provide adequate warnings with OFNI regarding its possible risks and adverse effects, as well as the comparative severity and duration of such adverse effects;

b. Failed to adequately and properly test ONFI before placing it on the market;

c. Failed to conduct sufficient testing on ONFI, which if properly performed would have shown that ONFI had serious side effects, including, but not limited to Stevens-Johnson syndrome, TEN, and other serious side effects;

d. Failed to adequately warn Plaintiffs and physicians that use of ONFI carried a

risk of Stevens Johnson syndrome, TEN, and other serious side effects;

e. Failed to provide adequate post-marketing warning or instructions after Defendants knew or should have known, of the significant risk of reactions to the use of ONFI;

f. Placed an unsafe product into the stream of commerce; and

g. Was otherwise grossly negligent;

126. As a direct and proximate result of the Defendants' sale of the product ONFI without adequate warnings regarding the risk of Stevens-Johnson syndrome, TEN and other risks associated with its use, Plaintiffs suffered harm as alleged herein, including ascertainable economic loss, including purchase price of Defendant's product ONFI, out-of-pocket costs of medical tests and treatment, future medical care and/or services, and other costs incidental to Plaintiff's ingestion of Defendants' harmful and defective product ONFI. All of said injuries have caused and continue to cause Plaintiffs' intense anxiety, distress, fear, pain, suffering and distress secondary to the physical injury and damages.

127. As a direct result of the gross negligence, willful and wanton misconduct, and/or other wrongdoing and actions of Defendants, which constitute a deliberate act or omission with knowledge of a high degree of probability of harm and reckless indifference to the consequences, Plaintiffs will in the future be required to obtain medical and/or hospital care, attention and services. As a result, Plaintiffs may incur expenses for such health care treatment in an amount not yet ascertained.

128. Defendants' aforementioned conduct was committed with knowing, conscious and/or deliberate disregard for the rights and safety of consumers such as Plaintiffs, thereby entitling Plaintiffs to punitive damages in an amount appropriate to punish Defendants and deter them from similar conduct in the future. Defendants continued to promote the efficacy and safety of Defendants' product ONFI, while providing little or no warnings, and

downplayed the risks, even after Defendants knew of the risks and injuries associated with their use.

DAMAGES

As a direct and proximate cause of Antonio's ingestion and use of Defendants' product ONFI, Plaintiffs sustained the following damages and seeks recovery from all Defendants for the following damages:

a. Physical and mental pain and suffering, in the past and in the foreseeable future;

b. Physical impairment and disability, in the past and in the foreseeable future;

c. Past and future mental anguish, in the past and in the foreseeable future;

d. Mental pain and suffering, in the past and in the foreseeable future;

e. Past medical expenses, in the past and in the foreseeable future;

f. Loss of enjoyment of life, in the past and in the foreseeable future; and

g. Punitive and exemplary damages to the fullest extent permitted by law.

REQUEST FOR RELIEF

Plaintiffs respectfully request the following relief against all Defendants:

a. Awarding all actual and compensatory damages to Plaintiffs in amount to be determined at trial;

b. Awarding exemplary damages to Plaintiffs;

c. Awarding pre-judgment and post-judgment interest to Plaintiffs;

d. Awarding the costs and expenses of litigation to Plaintiffs;

e. Awarding reasonable attorneys' fees to Plaintiffs; and

f. Such further relief as this Court deems necessary, proper and just.

Respectfully submitted,

By: /s/ *Connor G. Sheehan*
Connor G. Sheehan
State Bar No. 24046827
John David Blakley
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ATTORNEY FOR PLAINTIFFS

Attachment 1

PRODUCT MONOGRAPH

Frisium®
(clobazam)

Tablets, 10 MG

Anticonvulsant

for Adjunctive Therapy

Manufactured by:
Lundbeck
Four Parkway North
Deerfield, IL 60015, U.S.A.

Distributed by:
Accuristix
6090 White Hart Lane
Mississauga, ONT L5R 3Y4

Control No. 149753

Date of Revision:
July 24, 2012

NAME OF DRUG

Frisium® (clobazam) Tablets, 10 mg

THERAPEUTIC CLASSIFICATION

Anticonvulsant for adjunctive therapy.

PART I. HEALTH PROFESSIONAL INFORMATION

ACTIONS

FRISIUM (clobazam) is a 1,5-benzodiazepine with anticonvulsant properties.

In general, the mode of antiepileptic action of clobazam is probably largely analogous to that of the 1,4-benzodiazepines. The differences between clobazam (a 1,5-benzodiazepine) and the 1,4-benzodiazepines in terms of therapeutic efficacy and neurotoxicity are possibly due to the variation in degree of the agonist action at the high affinity benzodiazepine receptor or to differing relative action at the high and low affinity benzodiazepine receptors.

Regarding the mechanism of action, it is likely that modifications to the function of gamma-aminobutyric acid (GABA) as an important inhibitory neurotransmitter underlie the pharmacological effects of the benzodiazepines. Electrophysiological studies have shown that benzodiazepines potentiate GABA-ergic transmission at all levels of the neuroaxis, including the spinal cord, hypothalamus, hippocampus, substantia nigra, cerebellar cortex and cerebral cortex. The changes induced by the interaction of GABA with its receptors is enhanced by benzodiazepines, resulting in a decrease in the firing rate of critical neurons in many regions of the brain.

The oral absorption of clobazam, like that of all benzodiazepines, is fast and complete and amounts to at least 87%. Relative bioavailability of clobazam tablets or solution (in propylene glycol) is not significantly different. After a single dose of 20 mg clobazam, marked interindividual variability in maximum plasma concentrations (222 to 709 ng/ml) was observed after 0.25 to 4 hours. The administration of food with the drug has variable effects on the rate of absorption.

Clobazam is highly lipophilic and is rapidly distributed in fat and cerebral gray matter. Within 1 to 4 hours of administration it has accumulated in white matter and is then redistributed widely. The volume of distribution is large. Approximately 85% to 91% of clobazam is bound to plasma protein.

After oral administration of ^{14}C-labelled clobazam to man, approximately 90% of the radioactivity was recovered in urine. Clobazam is extensively metabolized and is not excreted in unchanged form by any species studied. Clobazam is primarily metabolized in the liver. It undergoes dealkylation and hydroxylation before conjugation. Main

metabolites found in plasma are N-desmethyl clobazam and 4-hydroxyclobazam. Lesser quantities of 4-hydroxy-N-desmethyl clobazam are also found.

N-desmethyl clobazam is an active metabolite. After a single dose of 30 mg clobazam, N-desmethyl clobazam attains maximum plasma concentrations after 24 to 72 hours. The half-life of N-desmethyl clobazam is much longer (mean 42 hours; range 36-46 hours) than for that of clobazam (mean 18 hours; range 10-30 hours).

The half-life of clobazam increases with the patient's age. In the elderly, there is a tendency to a reduction in clearance following oral administration; terminal half-life is prolonged and the distribution volume increased. This may lead to a more extensive accumulation of the drug when administered on a multiple-dose basis than in younger subjects. The effect of age on the clearance and accumulation profile of clobazam seems also to apply to the active metabolite (see WARNINGS and PRECAUTIONS section).

Hepatic disease may alter both the metabolism of the drug and its protein binding thus affecting plasma clobazam levels. In patients with severe liver disease, the distribution volume of clobazam is increased and the terminal half-life is prolonged (see CONTRAINDICATIONS and PRECAUTIONS sections).

In patients with renal impairment, plasma concentrations of clobazam are reduced, possibly due to impaired absorption of the drug; terminal half-life is largely independent of renal function (see PRECAUTIONS section).

There have been no studies that have demonstrated a clear-cut correlation between serum levels of clobazam or of N-desmethylclobazam to clobazam efficacy. Most reports indicate there is no, or only a very weak, correlation between the clobazam dose, or blood levels, and its clinical effects. Therapeutic blood levels for clobazam are in the range of 50 ng - 300 ng/mL with the corresponding range for N-desmethylclobazam being from 1000- 4000 ng/mL. The serum levels at which anticonvulsant effects can be expected are not known but it can be assumed that the therapeutic range lies in the order of the figures given above. Since N-desmethyl-clobazam blood levels are 10-20 times higher than those for clobazam, and this metabolite also has antiepileptic effects, it may be more important to the antiepileptic efficacy of clobazam than the parent compound itself.

Seven double-blind studies have been reported in which clobazam was given as adjunctive therapy versus placebo within an established antiepileptic regimen; clobazam was shown to be significantly superior to placebo.

INDICATIONS

FRISIUM (clobazam) has been found to be of value as adjunctive therapy in patients

with epilepsy who are not adequately stabilized with their current anticonvulsant therapy.

CONTRAINDICATIONS

FRISIUM (clobazam) is contraindicated in patients with the following conditions:

- hypersensitivity to clobazam or any of its excipients;
- myasthenia gravis (risk of aggravation of muscle weakness)
- narrow angle glaucoma
- any history of drug or alcohol dependence (increased risk of development of dependence)
- severe respiratory insufficiency
- sleep apnoea syndrome (risk of deterioration)
- severe impairment of liver function (risk of precipitating encephalopathy)
- during first trimester of pregnancy and breast-feeding (see WARNINGS section)

WARNINGS

Use in the elderly: FRISIUM (clobazam) should be used with caution in elderly and debilitated patients, and those with organic brain disorders, with treatment initiated at the lowest possible dose (see ACTIONS and PRECAUTIONS sections).

Potentiation of drug effects: Additive effects are to be expected if FRISIUM is combined with alcohol or drugs with central nervous system depressant effects. Moreover, concomitant consumption of alcohol can increase the serum levels of clobazam by 50%.

Patients should therefore be advised against consumption of alcohol during treatment with FRISIUM due to an increased risk of sedation and other adverse effects (see CONTRAINDICATIONS, PRECAUTIONS and ADVERSE REACTIONS sections).

Physical and psychological dependence: Physical and psychological dependence are known to occur in persons taking benzodiazepines. Caution must be exercised if it is at all necessary to administer FRISIUM to individuals with a history of drug misuse or those who may increase the dose on their own initiative. Such patients must be placed under careful surveillance (see PRECAUTIONS section).

As with other benzodiazepines, the therapeutic benefit must be balanced against the risk of habituation and dependence during prolonged use.

A rebound phenomenon or a withdrawal syndrome may follow discontinuation of use of FRISIUM; thus it should not be abruptly discontinued after prolonged use (see PRECAUTIONS section).

Use in pregnancy, lactation and perinatal period: Clobazam crosses the placental barrier. Several studies have suggested an increased risk of congenital malformations associated with the use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during the first trimester of pregnancy. FRISIUM must not be used in the first trimester of pregnancy. In the later stages of pregnancy, it must only be used if there are compelling indications. If FRISIUM is prescribed to a woman of child-bearing potential she should be warned to consult her physician regarding the discontinuation of the drug if she intends to become, or suspects she might be, pregnant.

Nursing mothers in whom therapy with FRISIUM is indicated should cease breast-feeding, since clobazam passes into breast milk.

Administration of high doses of FRISIUM immediately before or during childbirth can provoke the occurrence of hypothermia, hypotonia, respiratory depression, and difficulties in drinking in the newborn infant. Moreover, infants born to mothers who have taken benzodiazepines over longer periods during the later stages of pregnancy may have developed physical dependence and may be at risk of developing a withdrawal syndrome in the postnatal period.

Anterograde amnesia: Anterograde amnesia is known to occur even if benzodiazepines are used in the normal dose range, but especially at higher dose levels. Amnesia effects may be associated with inappropriate behaviour.

Use in patients with depression or psychosis: FRISIUM is not recommended for use in patients with depressive disorders or psychosis (see PRECAUTIONS section).

Increased risk of pneumonia: It is recognized that patients with epilepsy are at increased risk for aspiration due to recurrent seizures and that this risk is increased by the high co-morbidities seen in patients with LGS. Benzodiazepines, including clobazam, may increase the risk of pneumonia from a decreased ability to manage secretions. The risk of pneumonia increases with the dose level of clobazam (see sections Precautions, Adverse Reactions and Dosage and Administration).

PRECAUTIONS

Driving and Hazardous Activities: Clobazam possesses a mild central nervous system depressant effect. Under experimental conditions, impairment of alertness has been observed to be less pronounced after therapeutic doses of clobazam than after other benzodiazepines. Nevertheless, even when used as directed, FRISIUM may alter reactivity to such an extent as to impair driving performance or the ability to operate machinery, especially when it is taken in conjunction with alcohol. Therefore patients should be cautioned against driving, operating dangerous machinery or engaging in other hazardous activities, particularly in the dose adjustment period, or until it has been established that they do not become drowsy, dizzy or develop muscle weakness.

Use in the Elderly: Elderly and debilitated patients, or those with organic brain syndrome, have been found to be prone to the CNS depressant activity of benzodiazepines even after low doses. Manifestations of this CNS depressant activity include ataxia, oversedation and hypotension. Therefore, medication should be administered with caution to these patients, particularly if a drop in blood pressure might lead to cardiac complications. Initial doses should be low and increments should be made gradually, depending on the response of the patient, in order to avoid oversedation, neurological impairment and other possible adverse reactions. After prolonged use of benzodiazepines, impairment of consciousness, sometimes combined with respiratory disorders, has been reported in very rare cases, particularly in elderly patients; these effects sometimes persist for a considerable length of time (see ACTIONS section).

Dependence Liability: FRISIUM should not be administered to individuals prone to drug abuse. Caution should be observed in all patients who are considered to have potential for psychological dependence. The risk of dependence increases with the dose and duration of treatment. However, this risk is present even with daily intake of FRISIUM over periods of only a few weeks, and applies not only to possible abuse with particularly high doses but also to the therapeutic dose range. The risk of dependence is increased in patients with a history of alcohol or drug abuse. These patients or those who may increase the dose on their own initiative must be closely monitored (see WARNINGS section).

On withdrawal of benzodiazepines, especially if abrupt, a rebound phenomenon or a withdrawal syndrome may occur.

The rebound phenomenon is characterized by a recurrence in enhanced form of the symptoms which originally led to FRISIUM treatment (i.e. seizures). This may be accompanied by other reactions including mood changes, anxiety or sleep disturbances and restlessness.

Once physical dependence has developed, abrupt termination of FRISIUM treatment will lead to withdrawal symptoms. These may include headaches, insomnia, sleep disturbances, increased dreaming, restlessness, tension, mental impairment, confusion, extreme anxiety, excitability, irritability, nervousness, agitation, derealization, depersonalization, hallucinations and symptomatic psychoses (e.g. withdrawal delirium), numbness and tingling sensations in the extremities, muscle pain, tremors, sweating, diarrhea, abdominal cramps, vomiting, nausea, hyperacusis, hypersensitivity to light, noise and physical contact, convulsions, as well as epileptic seizures.

As with other benzodiazepines, FRISIUM should be withdrawn gradually (see WARNINGS section).

Tolerance: Loss of part or all of the anticonvulsant effectiveness of clobazam has been described in patients who have been receiving the drug for some time. There is

no absolute or universal definition for the phenomenon and reports vary widely on its development.

The reported success of clobazam in intermittent therapy in catamenial epilepsy implies that tolerance may be minimized by intermittent treatment but long-term follow-up is unreported. No studies have identified or predicted which patients are likely to develop tolerance or precisely when this might occur.

Use in Mental and Emotional Disorders: It should be recognized that suicidal tendencies may be present in patients with emotional disorders; particularly those depressed. Protective measures and appropriate treatment may be necessary and should be instituted without delay. Pre-existing depression may be unmasked during benzodiazepine use.

Since excitement and other paradoxical reactions can result from the use of benzodiazepines in psychotic patients, clobazam should not be used in patients suspected of having psychotic tendencies.

Use in Patients with Impaired Renal or Hepatic Function: Clobazam is contraindicated in patients with severe liver dysfunction. In patients with a lesser degree of liver dysfunction, and in patients with renal impairment, responsiveness to clobazam and susceptibility to adverse effects are increased. These patients require low initial doses and gradual dose increments under careful observation (see CONTRAINDICATIONS section and DOSAGE AND ADMINISTRATION section).

Use in Patients with Acute, or Chronic Respiratory Insufficiency: Clobazam can cause respiratory depression, especially if administered in high doses. Therefore, particularly in patients with pre-existing compromised respiratory function (e.g. in patients with bronchial asthma) or brain damage, respiratory insufficiency may occur or deteriorate. Reports of aspiration pneumonia and pneumonia have been reported with clobazam. FRISIUM is contraindicated in patients with severe respiratory insufficiency or sleep apnoea syndrome. In patients with a lesser degree of acute or chronic, respiratory insufficiency, respiratory function should be monitored and a dose reduction may be necessary (see WARNINGS section, CONTRAINDICATIONS section, ADVERSE REACTIONS section and DOSAGE AND ADMINISTRATION section).

Use in patients with pre-existing muscle weakness or with spinal or cerebellar ataxia: Clobazam can cause muscle weakness. FRISIUM is contraindicated in patients with myasthenia gravis. In patients with pre-existing muscle weakness or with spinal or cerebellar ataxia, special observation is required and a dose reduction may be necessary (see CONTRAINDICATIONS section, and DOSAGE AND ADMINISTRATION section).

Monitoring: If FRISIUM is administered for repeated cycles of therapy, periodic blood counts and liver, renal and thyroid function tests are advisable.

Drug Interactions: Concomitant administration of drugs that inhibit the cytochrome P-450 enzyme system may enhance and prolong the action of clobazam.

Most studies of the potential interactions of clobazam with other antiepileptic agents have failed to demonstrate significant interactions with phenytoin, phenobarbital, or carbamazepine. However, one study noted that the addition of clobazam caused a 25% increase in serum drug levels in 29% of patients taking carbamazepine, 63% of patients taking phenytoin, 13% of those taking valproate and 14% of those on phenobarbital. The contradictory findings in different studies are presumably due to variations in patient susceptibility, and although clinically significant interactions are unusual, they may occur.

Several of the established antiepileptic agents: carbamazepine, phenytoin, diphenylhydantoin, phenobarbital, valproic acid, cause the blood levels of FRISIUM to decrease slightly. Findings are less consistent with regard to N-desmethylclobazam: serum levels are lower with concurrent valproic acid, but higher with carbamazepine, phenytoin and diphenylhydantoin. Carbamazepine and phenytoin may cause an increase in the metabolic conversion of clobazam to the active metabolite N-desmethyl clobazam.

In summary, if FRISIUM is administered simultaneously with other antiepileptic drugs, the dosage must be adjusted under regular medical supervision (EEG monitoring), as there may be interactions with the patient's basic anticonvulsant medication. Blood levels monitoring of concomitant medication is advisable.

Alcohol may also significantly increase plasma clobazam levels (see WARNINGS section). Patients should also be cautioned about the possibility of additive effects when FRISIUM is combined with alcohol or other drugs with central nervous system depressant effects (see CONTRAINDICATIONS and ADVERSE REACTIONS sections).

Especially when FRISIUM is administered in higher doses, a mutually potentiating effect is to be expected if other central nervous system depressant drugs (such as antipsychotics, anxiolytics, certain antidepressant agents, anticonvulsant drugs, sedative antihistamines, anaesthetics, hypnotics or narcotic analgesics, or other sedatives) are administrated or alcohol is consumed at the same time. Special precaution is also necessary when FRISIUM is administered in cases of intoxication with such substances or with lithium (see WARNINGS section).

If FRISIUM is used concomitantly with narcotic analgesics, possible euphoria may be enhanced; this may lead to increased psychological dependence.

The effects of muscle relaxants and nitrous oxide may also be enhanced.

Toxicologic Studies: In mouse, clobazam was associated with hepatomas in high-dose males. In rat, an increased incidence of thyroid adenomas was seen in

males. There were three malignancies: two (male and female) in the thyroid and one (female) in the liver (see CARCINOGENICITY section). The relevance of these findings to man has not been established.

ADVERSE REACTIONS

From 19 published studies of FRISIUM (clobazam) use in epileptic patients, the overall incidence of side-effects was 33% of which drowsiness, dizziness and fatigue were most frequently reported. Canadian experience provides a similar overall incidence (32%) with drowsiness reported in 17.3% of patients, and 12% of patients terminating treatment because of side-effects.

The incidence of side-effects was lower in patients under 16 years of age (23.7%) than the incidence in adults (43.1%): $p<0.05$, whereas treatment discontinuation incidences were similar across age groups: 10.6% and 13.8% respectively. The following side-effects occurred at incidences of greater than 1% (ataxia [3.9%], weight gain [2.2%], dizziness [1.8%], nervousness [1.6%], behaviour disorder [1.4%], hostility and blurred vision [1.3%]) while other effects occurred at a less than 1% incidence.

Clobazam may cause sedation leading to tiredness and sleepiness, especially at the beginning of treatment with FRISIUM and when higher doses are used. Slowing of reaction time, drowsiness, numbed emotions, confusion, headaches, dryness of the mouth, constipation, loss of appetite, nausea, dizziness, muscle weakness, ataxia, disorientation, or a fine tremor of the fingers may occur.

Slowed or indistinct speech, unsteadiness of gait and other motor functions, visual disorders (nystagmus, double vision), weight gain, or loss of libido may occur. Such reactions occur particularly with high doses or following prolonged use, but are reversible.

Paradoxical reactions may occur, especially in children and in the elderly. These may include restlessness, difficulty falling asleep or sleeping through, irritability, acute agitational states, anxiety, aggressiveness, delusion, fits of rage, nightmares, hallucinations, psychotic reactions, suicidal tendencies, or frequent muscle spasms. In the event of such reactions, treatment with FRISIUM must be discontinued.

Tolerance and dependence may develop, especially during prolonged use.

Reports have been received of Stevens-Johnson Syndrome (SJS), including toxic epidermal necrolysis (TEN).

Isolated cases of skin reactions such as rashes, exanthema or urticaria have been observed in very rare cases.

Anterograde amnesia may occur even if benzodiazepines are used in the normal dose range, but especially at higher dose levels. Amnesia effects may be associated with inappropriate behavior.

Clobazam may cause respiratory depression, especially if administered in high doses. Therefore, particularly in patients with pre-existing compromised respiratory function (e.g. in patients with bronchial asthma) or brain damage, respiratory insufficiency may occur or deteriorate. Reports of aspiration pneumonia and pneumonia have been reported with the use of clobazam. In a 15 weeks Lennox-Gastaut Syndrome Placebo Controlled Trial, the frequency of pneumonia increased from 2% in placebo group, up to 7 % in clobazam - exposed patients with a maximum daily dose of 20 mg for ≤ 30 kg/body weight; 40 mg for > 30 kg/body weight.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms: Overdose and intoxication with benzodiazepines - including clobazam - may lead to central nervous depression, associated with drowsiness, confusion and lethargy, possibly progressing to ataxia, reduced reflexes, increasing sedation, respiratory depression, hypotension and, rarely, coma. The risk of fatal outcome is increased in cases of combined poisoning with other central nervous system depressants, including alcohol.

Effects on respiration, pulse and blood pressure are noticed with large overdoses. Patients exhibit some jitteriness and overstimulation usually when the effects of the drug begin to wear off.

Treatment: It is recommended that the possible involvement of multiple agents be taken into consideration. Consciousness, respiration, pulse rate and blood pressure should be monitored.

If respiratory depression and/or coma are observed, the presence of other central nervous system depressants should be suspected. General supportive measures aimed at maintaining cardiopulmonary function should be instituted and administration of intravenous fluids started. Immediate gastric lavage may be beneficial if performed soon after ingestion of FRISIUM. Secondary elimination of clobazam, by forced diuresis or hemodialysis, is ineffective. Hypotension can be treated by replenishment with plasma substitutes and, if necessary, with sympathomimetic agents.

The efficacy of supplementary administration of physostigmine (a cholinergic agent) or flumazenil (a benzodiazepine antagonist) cannot be assessed because insufficient experience is available.

DOSAGE AND ADMINISTRATION

Adults:
Small doses, 5-15 mg/day, should be used initially, gradually increasing to a maximum daily dose of 80 mg as necessary.

Children:
In infants (<2 years), the initial daily dose is 0.5-1 mg/kg/day. The initial dose in children (2-16 years) should be 5 mg/day, which may be increased at 5-day intervals to a maximum of 40 mg/day.

Patients with impaired liver or renal function: FRISIUM (clobazam) should be used at a reduced dosage in these patients.

Use in patients with acute, or chronic respiratory insufficiency: In patients with lesser degree of acute or chronic, respiratory insufficiency, respiratory function should be monitored and a dose reduction of FRISIUM (clobazam) may be necessary. (See sections: Warnings, Precautions, and Adverse Reactions)

Use in patients with pre-existing muscle weakness or with spinal or cerebellar ataxia: In patients with pre-existing muscle weakness or with spinal or cerebellar ataxia, special observation is required and a dose reduction of FRISIUM (clobazam) may be necessary.

Administration: If the daily dose is divided, the higher portion should be taken at night. Daily doses up to 30 mg may be taken as a single dose at night.

As with all benzodiazepines, abrupt withdrawal may precipitate seizures. It is therefore recommended that FRISIUM be gradually reduced in dose before treatment is discontinued.

As with other benzodiazepines, the possibility of a decrease in anticonvulsant efficacy in the course of treatment must be borne in mind.

PART II. SCIENTIFIC INFORMATION

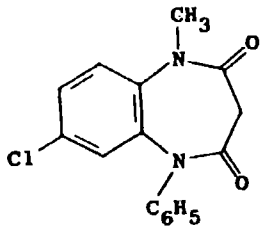
Drug Substance

Proper name: Clobazam [INN]

Chemical name:
7-chloro-1-methyl-5-phenyl-1H-1,5-benzodiazepine-2,4(3H,5H)dione

Empirical formula: $C_{16}H_{13}O_2N_2Cl$

Structural formula:



Molecular weight: 300.7

Description: White, odorless, crystalline powder. Soluble in chloroform and methanol. Very slightly soluble in water. Melting range of 182 ± 3°C.

Dosage Form

Composition: FRISIUM (clobazam) tablets, 10 mg contain clobazam as active ingredient; lactose, starch (corn), talc, colloidal silicon dioxide and magnesium stearate as non-medicinal ingredients.

Storage Conditions: FRISIUM tablets should be stored in their original containers at room temperature, between 15°C and 30°C.

Availability: FRISIUM is available as white, uncoated, biconvex, round tablets of 7 mm in diameter, scored on one side. Each tablet is debossed with **"B"** above score line and **"GL"** below score line. Other side debossed with the Hoechst "Tower and Bridge" logo.

FRISIUM 10 mg tablets are packaged in blisters of PVC film and aluminum foil and are distributed in packs of 30 tablets.

PHARMACOLOGY

Pharmacologic studies in animals have shown that clobazam can suppress seizures induced by a variety of experimental procedures. With respect to electro-shock induced seizures in the mouse, clobazam is more effective than valproic acid but less effective than clonazepam.

Although comparison with diazepam and phenobarbital produced inconsistent results in this model, the anticonvulsant effects of all three substances can probably be regarded as similar.

The anticonvulsant effect of clobazam in acoustically induced seizures in the mouse were less marked than those of clonazepam and diazepam as shown by ED_{50}. In most cases however, in particular with chemically induced seizures, clobazam was more potent than the other antiepileptic agents: phenytoin, phenobarbital, carbamazepine and valproic acid (Table 1).

Table 1: Anticonvulsant activity of antiepileptic drugs in mice (chemically induced seizures) (ED_{50} [mg/kg orally])

	Pentetrazol 125 mg/kg	Picrotoxin 15 mg/kg	Bicuculline 5 mg/kg	Isoniazid 600 mg/kg	Nicotine 1.5 mg/kg	Strychnine 1.2 mg/kg
Clobazam	1.7	4.7	16.2	10.7	2.3	10.4
Diazepam	0.41	4.1	10	2.8	0.8	4.9
Clonazepam	0.038	2.3	1	0.075	0.14	>5
Phenobarbital	6.7	12.2	20.5	18.7	7.6	46.9
Phenytoin	7.6	3.6	10.4	21.8	19.8	>100
Carbamazepine	11.2	7.3	16.2	25	18.1	>100
Valproate	158	75.4	362	494	168	>800

Although the ED_{50} is an important index, it is not a measure of the therapeutic value, since it has the disadvantage of not reflecting any undesired effects of the drug which might limit its subsequent use. The protective index (PI) is a more reliable indicator in this regard. The PI is equal to the quotient TD_{50}/ED_{50} where the TD_{50} is the dose at which 50% of the animals in the Rota rod test show signs of ataxia. Hence, if the PI>1, anticonvulsant effects occur before the undesired ataxic effects. The greater the PI, the wider is the margin between the desirable anticonvulsant effect and the undesired ataxic effect. Comparing this index, clobazam was superior to diazepam, clonazepam, phenobarbital and valproic acid. Carbamazepine and phenytoin were sometimes inferior and sometimes superior to clobazam in the respective tests (Table 2).

Table 2: Protective indices of clobazam and other antiepileptics in tests on anticonvulsant activity in mice

	Electro-convulsive Seizures	Pentetrazol (tonic)	Pentetrazol (clonic)	Picrotoxin	Bicuculline	Isoniazid	Nicotine	Strychnine
Clobazam	4.9	23.1	17.1	8.4	2.4	3.7	17.1	38
Diazepam	0.9	12.2	10	1.2	0.5	1.8	6.3	1
Clonazepam	0.6	9	7.1	0.2	0.3	4.5	2.4	<0.1
Phenobarbital	3.4	7	3	3.9	2.3	2.5	6.2	1
Phenytoin	14.6	13.3	<1	28.1	9.7	4.6	5.1	<1.0
Carbamazepine	12.6	9.1	<1	14	6.3	4.1	5.6	<1.0
Valproate	1.8	3	1.8	6.3	1.3	1	2.8	<1.0

Finally, the anxiolytic, sedative and myorelaxant effects of clobazam (a 1,5-benzodiazepine) were compared with those of 10 different 1,4-benzodiazepines. The ratios of specific effect to anticonvulsant effects showed that clobazam is a highly specific anticonvulsant.

Clobazam is extensively metabolized and is not excreted in unchanged form by any species studied. For serum concentrations between 0.05 and 10 µg/mL, the binding to serum proteins is shown in Table 3.

Table 3: Binding of ^{14}C-labelled clobazam to serum proteins

Species	% Binding	Range Measured
rat	66±2	0.05-10 µg/ml
dog	83±2	0.05-10 µg/ml
monkey	76±3	0.05-10 µg/ml
human	85±3	0.05-10 µg/ml

After oral administration, absorption of clobazam was practically complete in all three animal species. Data are given in Table 4 which shows also maximum blood levels for the total concentration in the animal species examined and the times at which they were reached. Total concentration refers to clobazam and its metabolites.

Table 4: Blood levels after oral administration of ^{14}C-labelled clobazam

Species	n	Maximum Total Concentration (µg/ml)	Time (H after application)	Dose (mg/kg)
Rat	6	0.046 ± 0.012	0.5	0.52
Dog	5	0.24 ± 0.043	22-4	0.5
Monkey	2	0.67 ± 0.82	0.5;1	2.5

Both after a single oral and intravenous dose, more than two-thirds of the drug-associated radioactivity is found in the faeces; dogs, however, excreted about 3/4 of the radioactivity with the urine, irrespective of the route of administration. In monkeys, the excretion also occurred mainly in the urine; in all three species, renal excretion was just as rapid as that from blood or plasma (Table 5). Elimination was almost completed after 48 hours in all species.

Table 5: Excretion after administration of ^{14}C-labelled clobazam to different animal species

Species	Route of Administration	Dose mg/kg	Excretion (% administered dose)		
			Urine	Faeces	Balance
Rat	Intravenously	0.1	27 ± 1	73 ± 6	100 ± 6
Rat	Orally	0.52	29 ± 6	71 ± 7	100 ± 1
Dog	Intravenously	0.1	78 ± 9	28 ± 4	106 ± 2
Dog	Orally	0.5	74 ± 5	28 ± 2	192 ± 3
Monkey	Orally	2.5	61 ± 14	N.D.	

The two most important chemical changes of clobazam during metabolism are dealkylation and hydroxylation. Dealkylation at nitrogen-1, particularly pronounced in the dog, does not differ between the 1,4- and 1,5-benzodiazepines. However, hydroxylation at the 3-position which occurs with 1,4-benzodiazepines such as diazepam, does not occur with clobazam and may be a characteristic of 1,5-benzodiazepines in general.

In several studies clobazam exhibited activity against seizures with doses usually ranging below those that cause disorders in motor activity (see ACTIONS section, Table 2). This separation is evident also with N-desmethylclobazam. The advantage of clobazam compared with 1,4-benzodiazepines lies mainly in the fact that motor activity is influenced only after very high doses, these doses being markedly above those required to induce tranquilizing and anti-aggression activities. In animal studies, clobazam had no marked effect on the cardiovascular system, respiration or excretion.

TOXICOLOGY

Acute Toxicity

In mice, the oral LD_{50} was 640-1101 mg/kg, the intraperitoneal toxicity, 289-615 mg/kg, and the subcutaneous toxicity, 2250-2500 mg/kg. In rats, the oral LD_{50} was 6000 mg/kg, the intraperitoneal LD_{50}, 740-1526 mg/kg, and the subcutaneous toxicity, >5000 mg/kg. In rabbits, the oral LD_{50} was 320 mg/kg whereas in guinea pigs it was 109 mg/kg. Signs exhibited during acute toxicity testing included somnolence, prostration, reduction in spontaneous motility, irregular breathing, ataxia, tremors, convulsions, loss of righting reflexes and reduction in body temperature. These were the most frequently observed signs in lethally poisoned animals.

Chronic Toxicity

Clobazam was administered to rats in the diet or by gavage at doses of 0, 4, 12, 20, 25, 35, 100, 200, 400, 600 and up to 1000 mg/kg of body weight /day for periods ranging from 6 to 18 months. At 100 mg/kg for 6 months a transient slight growth retardation in males and in females a transient mild anemia and leucocytosis were observed. In the dose range of 12 to 1000 mg/kg of body weight/day, there was a dose-dependent reduction in spontaneous activity and, in the highest dose group, reduction in weight increase, respiratory depression and hypothermia were noted. Piloerection, lateral position, fall in body temperature, depression and death were observed in 4 treated with 100 mg/kg, in 3 treated with 400 mg/kg and in one control animal during the treatment period. Animals treated with 100 mg/kg for 2 weeks and subsequently changed to 200 mg/kg for up to the 36th week and then 600 mg/kg for the duration of the 18-month study showed dose-dependent increases in liver and thyroid and microscopic lesions, consisting of eosinophilic inclusions in the proximal convoluted tubules of the females and yellow granules in the livers of both males and females. The eosinophilic inclusions were accompanied by proliferation of the smooth endoplasmic reticulum.

Clobazam was administered to Beagle dogs at doses of 0, 2.5, 5, 10, 20, 40 and 80 mg/kg for periods ranging from 6 to 12 months. Dose-dependent symptoms were noted and consisted of sedation, ataxia, mild tremor, somnolence, emesis, seizures and progressive rise in serum alkaline phosphatase. At the 80 mg/kg dose for 6 months a significant increase in the weight of the liver was observed in males and females. In the 12-month study using 0, 5, 10 and 40 mg/kg a dose-dependent increased accumulation of pigments in hepatocytes and Kupffer cells was observed in the 5 mg/kg group. In another 12-month study where 0, 2.5 and 5 mg/kg doses were used there were yellow granules in the epithelial cells of the proximal convoluted tubules in the 5 mg/kg group at one year. The studies have shown that convulsions were observed on the second and third day after abrupt discontinuation of the drug.

In the one year study where 0, 5, 10 and 40 mg/kg of clobazam were used and in the 6-month study where 0, 5, 20 and 80 mg/kg were used, deaths occurred (9 and 2, respectively), but the exact cause could not be ascertained. However, the animals experienced convulsive seizures with foaming at the mouth during the treatment period.

In a special study clobazam was administered orally to groups of 2 Beagle dogs (one male and one female) at doses of 0 and up to 40 mg/kg daily for 16 months. Withdrawal symptoms were assessed beyond the fourth month of treatment following the interruption of medication on several occasions for 1 to 9 days. The incidence and the severity of the withdrawal symptoms were related to the duration of treatment and the greater susceptibility of the female than the male dog.

The withdrawal symptoms consisted of tremors, accelerated respiration, violent tonic-clonic convulsions, abundant salivation, frothing at the mouth, ptosis, sedation, ataxia stereotyped movements, gasping for breath, biting of the tongue. The symptoms usually subsided following reinstitution of medication.

N-desmethylclobazam was administered orally to groups of 2 Beagle dogs (one male and one female) at doses of 0 up to 40 mg/kg daily for 12 months.

After 48 hours of drug withdrawal, symptoms occurred and consisted of short tonic-clonic convulsions and of relatively persistent tremor in the male dog whereas the female dog exhibited only a relatively persistent tremor.

Clobazam was administered to Rhesus monkeys by gavage at doses of 0, 2.5, 7.1 and 20 mg/kg for 52 weeks. Similar dose-dependent symptoms that were noted in dogs were also noted in monkeys. These consisted of sedation, somnolence, ataxia and mild tremor. There was a slight reduction in heart rate at 2.5 and 7.1 mg/kg. In addition, at 7.1 mg/kg sedation was observed. One male died in coma.

Signs of withdrawal appeared on the second day and these were aggression, piloerection, restlessness, little appetite and an unusual supine position. These withdrawal signs disappeared after readministration of clobazam.

REPRODUCTION AND TERATOLOGY

Clobazam was administered orally in the diet to rats and mice at doses up to 200 mg/kg/day for 60 days, during pairing, throughout pregnancy and for 21 days of post-natal development of the offspring. No effects on fertility in male and female animals and no effects on pregnancy or course of labour were observed in mice with 200 mg/kg/day and in rats with 85 mg/kg/day. In rats, the offspring developed normally and their behaviour during the lactation period was unremarkable. In mice, litter sizes were normal, but a dose-dependent death rate of fetuses was observed in the highest dose group (200 mg/kg). In these litters, the dams did not bite through the umbilical cords and did not clean or nurse the offspring. This abnormality in the dams could have been compound induced after parturition. Liver weights were increased at the highest dose (200 mg/kg).

Teratologic studies were performed in mice, rats and thalidomide-sensitive rabbits treated in the diet with clobazam at doses of up to 400 mg/kg of body weight/day.

In rats and mice, no teratogenic effects were noted. In the fetuses and in the neonatal animals, there were no differences between the test groups and the control group with regard to number of implantations, resorptions, number of live and dead fetuses, placental weight, crown-rump length of fetuses, and sex ratio in the live fetuses, nor were there any external, visceral or skeletal malformations or anomalies attributable to clobazam. In the reared fetuses of the dams treated with clobazam during pregnancy, no retardation in post-natal growth and no external malformations and no visceral or skeletal abnormalities were observed except for four cases of cleft palate occurring at a dose of 100 mg/kg/day.

In rabbits, the rate of fetal resorption was higher in animals treated with 100 mg/kg than in the controls. In the group treated with 4 mg/kg, one unilateral exophthalmus, one exencephalus combined with ceolosomy and syndactyly of the front legs were observed, whilst in the 20 mg/kg group, one hydrocephalus with umbilical hernia was noted; these malformations were thought not to be drug related.

CARCINOGENICITY

Carcinogenic studies were conducted in mice and in rats.

Clobazam was administered daily in the diet at doses of 0, 4, 20, and 100 mg/kg to groups of 60 male and 60 female CD-1 mice for 80 weeks.

Because of fighting in the group of males, male animals of the 100 mg/kg/day group were supplemented with a subgroup of 43 spare animals. Nine weeks after initiation of study, it was necessary to add a second subgroup of 42 spare animals.

The males of the supplemented subgroup treated with 100 mg/kg/day had more (8.3%) neoplastic changes (hepatomas) than the controls (1.7%) and the other treated male mice.

Clobazam was administered daily in the diet at doses of 0, 4, 20 and 100 mg/kg/day to groups of 60 male and 60 female CD rats for 104 weeks.

Gross lesions identified at necropsy consisted of liver pallor and thyroid gland enlargement in males dosed at 100 mg/kg/day. The non-neoplastic histopathologic changes associated with treatment included an increased incidence of endometrial hyperplasia, cystic endometrial hyperplasia, and endometrial polyps and polypoid areas in females treated with 100 mg/kg/day.

Thyroid changes included an increase in follicular cell adenomas in males (21.7% vs 5.7% in controls) treated with 100 mg/kg/day, and there was follicular carcinoma in one male (1.7%) of this group.

One male rat in the 100 mg/kg/day group (1.7%) and one female rat in the 20 mg/kg/day (1.7%) group had squamous cell carcinomas in the thyroid gland. In the liver, changes included an increase in focal hyperplasia in females treated with 20 (11.7%) or 100 (6.7%) mg/kg/day. Nodular hyperplasias were increased in females treated with 100 mg/kg/day (3.3% vs 1.7% in controls). Hepatocellular carcinoma was found in one decedent female (1.7%) treated with 20 mg/kg/day.

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PART III: CONSUMER INFORMATION

FRISIUM®
(clobazam tablets)

This leaflet is part III of a three-part "Product Monograph" published when FRISIUM was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about FRISIUM. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Add-on therapy in patients with epilepsy who are not adequately stabilized with their current anticonvulsant therapy.

What it does:
FRISIUM is an antiepileptic drug which can be used with other anticonvulsant drugs to manage epileptic seizures.

When it should not be used:
FRISIUM should not be used under the following conditions:

- If you are allergic to clobazam or any of its other ingredients
- If you have been diagnosed with myasthenia gravis
- If you have narrow angle glaucoma
- If you have any history of drug or alcohol dependence
- If you have severe difficulty breathing
- If you have sleep apnea (pauses in breathing during sleep)
- If you have severe liver or kidney disease
- During 1st trimester of pregnancy and breast-feeding.

What the medicinal ingredient is:
Clobazam is the active ingredient.

What the nonmedicinal ingredients are:

- Colloidal silicon dioxide
- Lactose
- Magnesium stearate
- Starch (corn)
- Talc

What dosage forms it comes in:
Tablet 10 mg.

WARNINGS AND PRECAUTIONS

BEFORE you use FRISIUM, talk to your doctor or pharmacist if you:

- Are elderly or debilitated
- Have been diagnosed with decreased mental function due to a medical disease
- Use alcohol or drugs with central nervous system (CNS) depressant effects
- Have a history of drug misuse or you may increase medication doses on your own. If you are dependent on drugs or alcohol, FRISIUM may increase your dependence.
- Have mental or emotional disorders such as suicidal tendencies. FRISIUM is not recommended in patients with a diagnosis of depression or psychosis (mental illness).
- Have kidney or liver disease
- Have sudden or ongoing difficulty breathing that is not severe
- Already have muscle weakness and/or spinal /cerebellar ataxia (sudden uncoordinated movements)
- Are pregnant, FRISIUM is harmful to an unborn child if used during the first trimester of pregnancy. Avoid becoming pregnant. Effective birth control methods should be used. Tell your doctor right away if you become pregnant during treatment or plan to get pregnant.
- Are breast feeding. If you have been nursing, you should stop before starting treatment with FRISIUM since clobazam passes into breast milk. Ask your baby's doctor to recommend a formula that would be best for your baby.
- Are immediately before or during childbirth because FRISIUM may have an effect on the newborn.
- Do not drive, operate dangerous machinery or engage in other dangerous activities, as FRISIUM may cause impairment of your alertness. Be sure you are not suffering from drowsiness, dizziness or muscle weakness before you resume these activities.
- Difficulty in forming new memories (anterograde amnesia) is known to occur even if anti-anxiety medications (benzodiazepines) are used in the normal dose range, but especially at higher dose levels. Amnesia effects may be associated with inappropriate behavior.

Do not drink alcohol if you are taking FRISIUM

Like other medications in this class, use of FRISIUM may lead to a need so strong that it becomes necessary to have FRISIUM to function properly (addiction).

Do not suddenly stop taking FRISIUM. Always follow your doctor's instructions. Stopping this drug quickly may lead to a rebound phenomenon (seizures) or withdrawal symptoms, such as headaches, trouble sleeping, anxiety, confusion, irritability.

Reports of aspiration pneumonia and pneumonia have been reported with clobazam.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor or pharmacist about any medication that you are taking or plan to take including any medicine obtained without a prescription, vitamin or mineral supplement, and natural health products.

When FRISIUM is given with other drugs that control epilepsy, your doctor may need to adjust the FRISIUM dosage.

If FRISIUM is given in higher doses with other CNS depressant drugs (such as antipsychotics, certain antidepressant agents, anticonvulsant drugs, antihistamines with drowsy effects, anesthetics, hypnotics or narcotic pain medication, other sedatives or alcohol), it may increase the effects of these medications including FRISIUM. Special precautions must be taken when taking FRISIUM and lithium. Your doctor may need to monitor these interactions with blood tests.

If FRISIUM is used with narcotic pain medications, increased psychological dependence (addiction) can occur.

FRISIUM can prolong the effect of muscle relaxants and nitrous oxide (products often used in surgery or during dental procedures).

PROPER USE OF THIS MEDICATION

Usual Dose:

FRISIUM is a tablet to be taken by mouth. Always follow your doctor's instructions. Do not change the prescribed dose yourself. If you think the effect of your medicine is too weak or too strong, talk to your doctor. Your doctor will advise you when to stop taking the medicine. Your doctor will slowly decrease the dosage as sudden discontinuation of treatment can cause the appearance of withdrawal symptoms or seizures.

Adults should take small doses of FRISIUM initially (5-15 mg/day) gradually increasing to no more than 80 mg/day, as needed.
Infants less than 2 years should take an initial dose of 0.5-1 mg/kg/day.
Children 2-16 years should initially take 5 mg/day, increasing to no more than 40 mg/day in 5-day intervals.

Patients with kidney or liver disease should be given a lower dose.

If the daily dose of FRISIUM is to be divided, the higher portion should be taken at night (up to 30 mg may be taken as a single dose at night). Always follow your doctor's instructions.

If your doctor prescribes repeated cycles of FRISIUM, your doctor should perform periodic tests for liver, kidney and thyroid function.

Overdose:

Contact your doctor, Regional Poison Control Centre or pharmacist immediately if you suspect you have taken an overdose or someone else accidentally takes your FRISIUM. If you are unable to contact them, go to a hospital emergency department for medical help, even though you may not feel sick. Show your doctor your bottle of tablets.

If you are given too large a dose of FRISIUM, you may become drowsy, confused, and sluggish. You may have trouble breathing, staying awake, or have low blood pressure. A coma is possible. Taking alcohol or other CNS depressant medications at the same time as FRISIUM could lead to death. When too much FRISIUM wears off, you could be excited and jittery.

Missed Dose:

If you miss a dose of FRISIUM, take it as soon as you remember. If you are close to your next dose, just take your next dose, without making up for the missed dose. Do not take 2 doses at the same time.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like most medicines, besides the beneficial effects, FRISIUM can have side effects. If you experience any of the following side effects, call your doctor right away.

The most often reported side effects in patients with epilepsy who are taking FRISIUM are drowsiness, dizziness and tiredness. Some of these patients stopped treatment because of these side effects. These side effects did not occur as often in patients under 16 years of age as they did in adult patients, however, these patients stopped treatment as often as adult patients because of the side effects.

Common side effects include:

- Loss of muscle coordination
- Dizziness
- Behavior disorders
- Nervousness
- Hostility

Blurred vision

Other side effects include:

Tiredness and sleepiness (especially at the start of your treatment with FRISIUM, and at higher doses)	Slowing reaction time Drowsiness
Numbed emotions	Confusion
Headaches	Mouth dryness

Various stomach problems (constipation, loss of appetite, nausea)
Muscle weakness

Disorientation	Slight shaking of the fingers

Sudden or ongoing difficulty breathing
Pneumonia or aspiration pneumonia cough, fever, chills

The following side effects occur after taking FRISIUM for a long time or at high doses, but they can be reversed: Slowed or slurred speech, unsteady walking and other muscle functions, vision disorders, weight gain, and loss of sexual desire.

It is possible that you may not feel the effects of FRISIUM or may come to depend on FRISIUM if you are taking it for a long time.

Withdrawal-related Side Effects

Stopping this drug quickly may lead to seizures or withdrawal symptoms, such as headaches, trouble sleeping, anxiety, confusion, irritability.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency treatment
		Only if severe	In all cases	
Common	Difficulty falling asleep or sleeping through†		√	
	Irritability†		√	
	Increased restlessness, irritation, and/or mood swings associated with mental tension (Acute agitational state†)		√	
	Anxiety†		√	
	Aggressiveness†		√	
	Unfounded ideas that can be related to suspicions or paranoid thoughts, self-		√	

	importance, illness, self-blame, or hopelessness (Delusion†)			
	Fits of Rage†		√	
	Nightmares†		√	
	See and hear things that are not there (Hallucinations†)		√	
	Severe mental disorders that cause abnormal thinking and perceptions (Psychotic reactions†)		√	
	Suicidal Tendencies†			√
	Frequent Muscle Spasms†			√
	Cough, fever, difficulty breathing		√	
Uncommon	A rare, serious disorder in which your skin and mucous membranes react severely to a medication (Stevens-Johnson syndrome [SJS])			√
	Severe skin reaction where the upper surface of your skin detaches like a patient who has suffered burns (Toxic Epidermal Necrolysis [TEN])			√
Very rare	Allergic reactions: • Swelling of lips, eyelids, face, throat, or mouth, accompanied by difficulty in breathing, speaking or swallowing (signs of anaphylactic reactions and angioedema) • Skin rash, fever, swollen glands (swelling of the lymph nodes), and pain in the			√

	muscles and joints (signs of hypersensitivity reactions) • Blistering of the skin and/or mucous membranes of the lips, eyes, mouth, nasal passages or genitals (signs of serious skin reaction) • Red blotchy rash mainly on face which may be accompanied by fatigue, fever, nausea, loss of appetite (signs of systemic lupus)			

† Opposite reactions may occur, especially in children and the elderly. In the event of such reactions, treatment with FRISIUM must be discontinued.

This is not a complete list of side effects. For any unexpected side effects while taking FRISIUM, contact your doctor or pharmacist.

HOW TO STORE IT

FRISIUM tablets should be stored in their original containers at room temperature, between 15-30°C (59-86°F).

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator: 0701D
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

Note: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full Product Monograph, prepared for health professionals, may be found by contacting the sponsor, Lundbeck, at: 1-800-586-2325.

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Attachment 2

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

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

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

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

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

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

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

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

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

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

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

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

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

2. DOSAGE AND ADMINISTRATION

2.1 Basic Dosing Information

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

Table 1. Recommended Total Daily Dosing by Weight Group

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

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

2.2 Geriatric Patients

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

2.3 CYP2C19 Poor Metabolizers

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

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

2.4 Patients with Renal Impairment

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

2.5 Patients with Hepatic Impairment

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

2.6 Gradual Withdrawal

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

3. DOSAGE FORMS AND STRENGTHS

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

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

4. CONTRAINDICATIONS

None.

5. WARNINGS AND PRECAUTIONS

5.1 Somnolence or Sedation

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

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

5.2 Concomitant Use with Central Nervous System Depressants

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

5.3 Withdrawal

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

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

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

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

5.4 Physical and Psychological Dependence

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

5.5 Suicidal Behavior and Ideation

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

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

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

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

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

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

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

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

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

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

6. ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

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

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

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

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

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

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

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

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

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

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

6.2 Post Marketing Experience

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

Blood Disorders: Anemia, eosinophilia, leukopenia, thrombocytopenia

Eye Disorders: Diplopia, vision blurred

Gastrointestinal Disorders: Abdominal distention

Investigations: Hepatic enzyme increased

Musculoskeletal: Muscle spasms

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

Respiratory Disorders: Aspiration, respiratory depression

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

7. DRUG INTERACTIONS

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

Effect of ONFI on other drugs

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

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

Effect of other drugs on ONFI

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

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

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

Pregnancy Category C.

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

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

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

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

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

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

8.5 Geriatric Use

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

8.6 CYP2C19 Poor Metabolizers

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

8.7 Renal Impairment

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

8.8 Hepatic Impairment

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

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

9. DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

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

9.2 Abuse

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

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

9.3 Dependence

Dependence

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

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

Withdrawal

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

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

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

10. OVERDOSAGE

10.1 Signs and Symptoms of Overdosage

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

10.2 Management of Overdosage

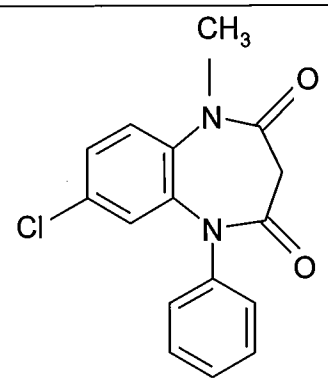
The management of ONFI overdose may include gastric lavage and/or administration of activated charcoal, intravenous fluid replenishment, early control of airway and general supportive measures, in addition to monitoring level of consciousness and vital signs. Hypotension can be treated by replenishment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

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

11. DESCRIPTION

Table 4. Description

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

Structural Formula:	

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

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

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

Effects on Electrocardiogram

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

12.3 Pharmacokinetics

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

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

Absorption

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

Distribution

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

Metabolism and Excretion

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

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

Pharmacokinetics in Specific Populations

Age

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

Sex

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

Race

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

Renal Impairment

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

Hepatic Impairment

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

Drug Interactions

In vitro studies:

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

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

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

In vivo studies:

Potential for ONFI to Affect Other Drugs

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

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

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

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

Potential for Other Drugs to Affect ONFI

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

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

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

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

12.5 Pharmacogenomics

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

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

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

The carcinogenic potential of clobazam has not been adequately assessed.

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

Mutagenesis

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

Impairment of Fertility

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

14. CLINICAL STUDIES

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

Study 1

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

Table 5. Study 1 Total Daily Dose

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

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

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

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

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

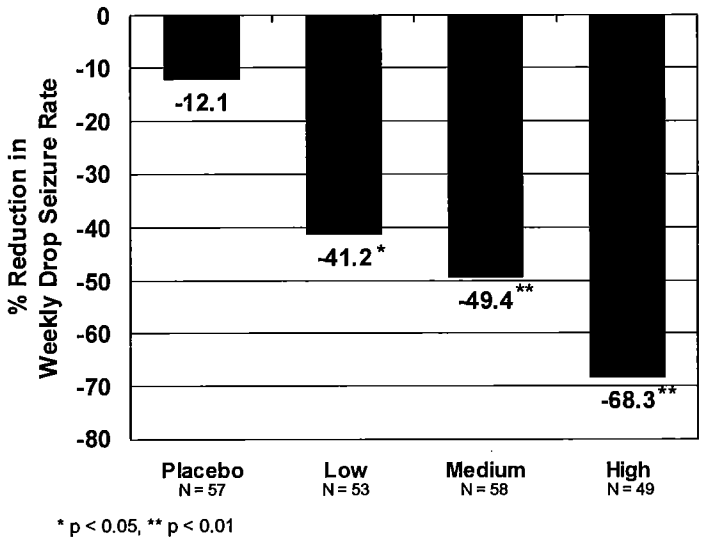
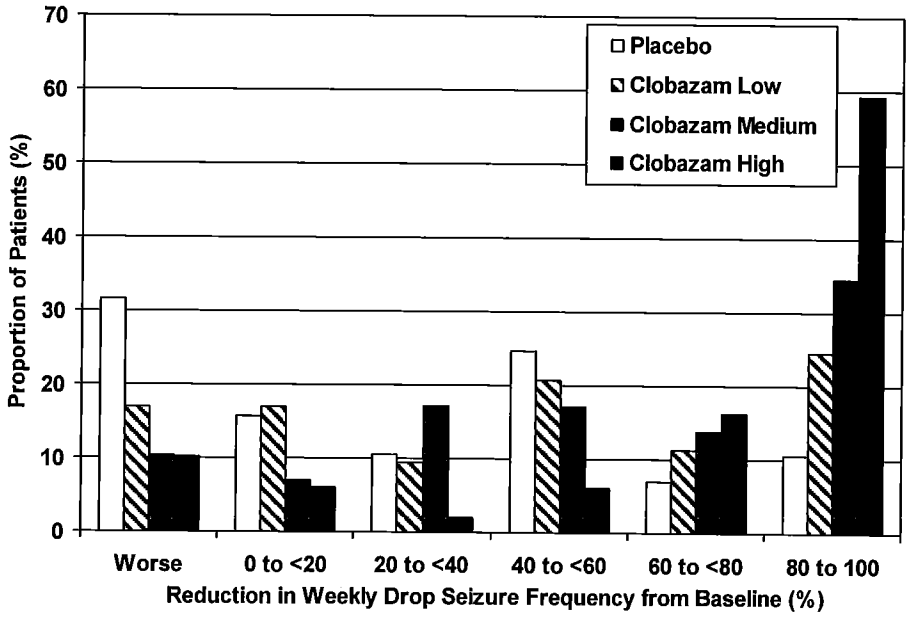


Figure 2 shows changes from baseline in weekly drop seizure frequency by category for patients treated with ONFI and placebo in Study 1. Patients in whom the seizure frequency increased are shown at left as "worse." Patients in whom the seizure frequency decreased are shown in five categories.

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



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

Study 2

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

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

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

16. HOW SUPPLIED/STORAGE AND HANDLING

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

NDC 67386-310-01: 5 mg tablet, Bottles of 100
NDC 67386-311-01:10 mg tablet, Bottles of 100
NDC 67386-312-01: 20 mg tablet, Bottles of 100

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

17. PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

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

Somnolence or Sedation

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

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

Increasing or Decreasing the ONFI Dose

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

Interactions with Hormonal Contraceptives

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

Suicidal Thinking and Behavior

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

Use in Pregnancy

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

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

Use in Nursing

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

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

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

MEDICATION GUIDE

ONFI™ (ON-fee)
(clobazam)
Tablets

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

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

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

ONFI can cause serious side effects, including:

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

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

2. ONFI can cause withdrawal symptoms.

- Do not stop taking ONFI all of a sudden without first talking to a healthcare provider. Stopping ONFI suddenly can cause seizures that will not stop (status epilepticus), hearing or seeing things that are not there (hallucinations), shaking, nervousness, and stomach and muscle cramps.

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

3. ONFI can be abused and cause dependence.

- Physical dependence is not the same as drug addiction. Your healthcare provider can tell you more about the differences between physical dependence and drug addiction.

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

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

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

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

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

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

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

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

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

What is ONFI?

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

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

What should I tell my healthcare provider before taking ONFI?

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

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

- Tell your healthcare provider right away if you become pregnant while taking ONFI. You and your healthcare provider will decide if you should take ONFI while you are pregnant.
- Children born to mothers receiving benzodiazepine medications (including ONFI) late in pregnancy may be at some risk of experiencing breathing problems, feeding problems, dangerously low body temperature, and withdrawal symptoms.

- If you become pregnant while taking ONFI, talk to your healthcare provider about registering with the North American Antiepileptic Drug Pregnancy Registry. You can register by calling 1-888-233-2334. The purpose of this registry is to collect information about the safety of antiepileptic drugs during pregnancy.
- ONFI can pass into breast milk. Talk to your healthcare provider about the best way to feed your baby if you take ONFI. You and your healthcare provider should decide if you will take ONFI or breast feed. You should not do both.

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

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

How should I take ONFI?

- ONFI can be taken whole, or crushed and mixed in applesauce.
- Take ONFI exactly as your healthcare provider tells you to take it.
- Your healthcare provider will tell you how much ONFI to take and when to take it.

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

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

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

What should I avoid while taking ONFI?

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

What are the possible side effects of ONFI?

ONFI may cause serious side effects, including:

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

The most common side effects of ONFI include:

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

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

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

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

How should I store ONFI?

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

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

General Information about the safe and effective use of ONFI.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use ONFI for a condition for which it was not

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

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

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

What are the ingredients in ONFI?

Active ingredient: clobazam

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

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

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

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

Lundbeck

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October 2011

Attachment 3

U.S. Food and Drug Administration
Protecting and Promoting You Health

Drug Safety Communications

FDA Drug Safety Communication: FDA warns of serious skin reactions with the anti-seizure drug Onfi (clobazam) and has approved label changes

Safety Announcement

[12-3-2013] The U.S. Food and Drug Administration (FDA) is warning the public that the anti-seizure drug Onfi (clobazam) can cause rare but serious skin reactions that can result in permanent harm and death. We have approved changes to the Onfi drug label and the patient Medication Guide to describe the risk of these serious skin reactions. Patients taking Onfi should seek immediate medical treatment if they develop a rash, blistering or peeling of the skin, sores in the mouth, or hives. Health care professionals should discontinue use of Onfi and consider an alternate therapy at the first sign of rash, unless it is clearly not drug-related.

These rare but serious skin reactions, called Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), can occur at any time during Onfi treatment. However, the likelihood of skin reactions is greater during the first 8 weeks of treatment or when Onfi is stopped and then re-started. All cases of SJS and TEN in the FDA case series have resulted in hospitalization, one case resulted in blindness, and one case resulted in death.

Onfi is a benzodiazepine medication used in combination with other medicines to treat seizures associated with a severe form of epilepsy called Lennox-Gastaut Syndrome. Serious skin reactions have not generally been associated with other benzodiazepines.

Patients should not stop taking Onfi without first talking to their health care professionals. Stopping Onfi suddenly can cause serious withdrawal problems, such as seizures that will not stop, hallucinations (hearing or seeing things that are not real), shaking, nervousness, and stomach or muscle cramps.

The Onfi drug label has been revised to add information about the risk for serious skin reactions to the *Warnings and Precautions* section and to the Medication Guide.

Facts about Onfi (clobazam)

- Approved as an adjunctive treatment (to be added to other anti-seizure medicines) for patients 2 years and older with Lennox-Gastaut Syndrome (LGS), a severe form of epilepsy.
- From drug approval in October 2011 through September 2013, approximately 31,000 patients received a dispensed prescription for clobazam from U.S. outpatient retail pharmacies.[1] Based on U.S. sales distribution data, the majority of all clobazam bottles (82% of clobazam sales) were distributed to U.S. outpatient retail pharmacies.[2]

- Has been marketed outside the United States for approximately 40 years under various brand names for the treatment of anxiety and seizures.

Additional Information for Patients and Caregivers

Onfi can cause serious skin reactions. These skin reactions, known as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), can result in permanent harm and death.

- Patients taking Onfi should seek immediate medical treatment if they develop rashes, blistering or peeling of the skin, sores in the mouth, or hives.
- Onfi should be stopped only under the careful guidance of a health care professional. Stopping Onfi suddenly can cause serious withdrawal problems, such as seizures that will not stop, hallucinations (hearing or seeing things that are not real), shaking, nervousness, and stomach or muscle cramps.
- Talk to your health care professional if you have any questions or concerns about Onfi or other seizure medications.
- Carefully read the patient Medication Guide that comes with the filled prescription.
- Report side effects from Onfi to the FDA MedWatch program, using the information in the Contact FDA box at the bottom of this page.

Additional Information for Health Care Professionals

- Onfi can cause serious skin reactions such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).
- Patients should be closely monitored for signs or symptoms of SJS/TEN, especially during the first 8 weeks of treatment or when re-introducing therapy.
- Patients should be informed about the signs and symptoms of serious skin reactions and told that they should seek immediate medical treatment at the first appearance of a skin rash or any other sign of hypersensitivity.
- Onfi should be discontinued at the first sign of rash, unless the rash is clearly not drug-related. If signs or symptoms suggest a serious skin reaction, use of Onfi should not be resumed and alternative therapy should be considered.
- When assessing patients with potentially drug-induced skin reactions, Onfi should be considered as a possible cause, along with other drugs already known to have such an association. Some other antiepileptic drugs can also cause serious skin reactions, and health care professionals should consider this when changing from one antiepileptic drug to another.
- Health care professionals should encourage patients to read the Medication Guide they receive with every filled prescription.
- Adverse events involving Onfi should be reported to the FDA MedWatch program, using the information in the Contact FDA box at the bottom of this page.

Data Summary

FDA reviewed the FDA Adverse Event Reporting System (FAERS) database, the medical literature, and information submitted by the manufacturer (Lundbeck) of Onfi for evidence of a causal association between Onfi (clobazam) and the serious skin reactions

known as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Because FAERS is a spontaneous and voluntary reporting system for adverse events, the exact incidence of SJS or TEN with Onfi cannot be calculated.

FDA identified 20 cases of SJS/TEN (6 U.S. cases and 14 foreign cases) in FAERS. One additional case of TEN was identified in the literature. Five of the six U.S. cases involved children. All of the cases resulted in hospitalization, with one case resulting in blindness. Two deaths occurred, one of which was deemed possibly related to Onfi. The relation to Onfi could not be assessed in the other death. Nineteen cases reported use of one or more concomitant drugs associated with SJS/TEN, including other antiepileptic drugs (n=18), beta-lactam antibiotics (n=3), or sulfasalazine (n=2). The report of TEN from the medical literature concerned a patient treated with Onfi monotherapy. Although some patients received previous or concomitant therapy with a drug thought to increase the risk of SJS and TEN, the evidence available in many of these cases indicated that Onfi was the likely cause of the serious skin reaction. Patients had been treated with the other suspect medications for prolonged durations without developing SJS/TEN, whereas there was a close temporal relationship (within two months) between initiation of Onfi and development of the serious skin reaction for 14 of the 17 cases that provided specific timing information. Moreover, many of the cases indicated that patients improved after stopping Onfi and, in some instances, after continuing or re-starting the other suspect medications.

In conclusion, FDA has approved an updated drug label for Onfi that includes a *Warnings and Precautions* statement and an addition to the Medication Guide describing the risk of serious skin reactions including SJS and TEN. Patients taking Onfi should seek immediate medical treatment and talk to their health care professional if they develop rashes, blistering or peeling of the skin, mouth sores, or hives. Serious skin reactions can happen at any time during Onfi treatment, but are more likely to happen within the first 8 weeks of treatment or when Onfi is discontinued and then re-started. Onfi should be discontinued at the first sign of rash, unless it is clearly not drug-related. If signs or symptoms suggest a serious skin reaction, use of Onfi should not be resumed and alternative therapy should be considered.

References

1. IMS Vector One: Total Patient Tracker (TPT). October 2011-September 2013. Extracted October 2013.
2. IMS Health National Sales Perspectives. October 2011-September 2013. Extracted October 2013

Attachment 4

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)	3/2013
Warnings and Precautions:	
Serious Dermatological Reactions (5.4)	11/2013

----------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----------

- For doses above 5 mg/day administer in two divided doses (2.1)
- 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)
- 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 (5.5, 9)
- *Serious Dermatological Reactions* (including Stevens-Johnson syndrome and toxic epidermal necrolysis): Discontinue ONFI at first sign of rash unless the rash is clearly not drug-related. (5.4)
- *Suicidal Behavior and Ideation:* Monitor for suicidal thoughts or behaviors (5.6)

----------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.

----------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: 11/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

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

Table 1. Recommended Total Daily Dosing by Weight Group

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

2.2 Gradual Withdrawal

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

2.3 Important Administration Instructions

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

ONFI Tablet Oral Administration

ONFI tablets can be taken with or without food.

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

ONFI Oral Suspension Oral Administration

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

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

3 DOSAGE FORMS AND STRENGTHS

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

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

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

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Somnolence or Sedation

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

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

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

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

5.3 Withdrawal Symptoms

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

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

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

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

5.4 Serious Dermatological Reactions

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

5.5 Physical and Psychological Dependence

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

5.6 Suicidal Behavior and Ideation

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

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

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

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

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

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

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

Anyone considering prescribing ONFI or any other AED must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and

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

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

6 ADVERSE REACTIONS

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

- Somnolence or Sedation *[see Warnings and Precautions (5.1)]*
- Potentiation of Sedation from Concomitant Use with Central Nervous System Depressants *[see Warnings and Precautions (5.2)]*
- Withdrawal Symptoms *[see Warnings and Precautions (5.3)]*
- Serious Dermatological Reactions *[see Warnings and Precautions (5.4)]*
- Physical and Psychological Dependence *[see Warnings and Precautions (5.5)]*
- Suicidal Behavior and Ideation *[see Warnings and Precautions (5.6)]*

6.1 Clinical Trials Experience

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

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

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

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

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

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

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

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

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

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

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

6.2 Post Marketing Experience

These reactions are reported voluntarily from a population of uncertain size; therefore, it is not possible to estimate their frequency or establish a causal relationship to drug exposure. Adverse reactions are categorized by system organ class.

Blood Disorders: Anemia, eosinophilia, leukopenia, thrombocytopenia

Eye Disorders: Diplopia, vision blurred

Gastrointestinal Disorders: Abdominal distention

Investigations: Hepatic enzyme increased

Musculoskeletal: Muscle spasms

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

Respiratory Disorders: Aspiration, respiratory depression

Skin and Subcutaneous Tissue Disorders: Rash, urticaria

7 DRUG INTERACTIONS

7.1 Effect of ONFI on Other Drugs

Hormonal Contraceptives

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

Drugs Metabolized by CYP2D6

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

7.2 Effect of Other Drugs on ONFI

Strong and moderate inhibitors of CYP2C19

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

7.3 CNS Depressants and Alcohol

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

Alcohol, as a CNS depressant, will interact with ONFI in a similar way and also increases clobazam's maximum plasma exposure by approximately 50%. Therefore, caution patients or their caregivers against simultaneous use with other CNS depressant drugs or alcohol, and caution that the effects of other CNS depressant drugs or alcohol may be potentiated *[see Warnings and Precautions (5.2)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

Pregnancy Category C.

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

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

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

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

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

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

8.5 Geriatric Use

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

8.6 CYP2C19 Poor Metabolizers

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

8.7 Renal Impairment

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

8.8 Hepatic Impairment

ONFI is hepatically metabolized; however, there are limited data to characterize the effect of hepatic impairment on the pharmacokinetics of ONFI. For this reason, dosage adjustment is recommended in patients with mild to moderate hepatic impairment (Child-Pugh score 5-9). There is inadequate information about metabolism of ONFI in patients with severe hepatic impairment *[see Dosage and Administration (2.7), Clinical Pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

ONFI contains clobazam which is a Schedule IV controlled substance.

9.2 Abuse

ONFI can be abused in a similar manner as other benzodiazepines, such as diazepam.

The pharmacological profile of ONFI is similar to that of other benzodiazepines listed in Schedule IV of the Controlled Substance Act, particularly in its potentiation of GABAergic transmission through its action on $GABA_A$ receptors, which leads to sedation and somnolence.

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

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

9.3 Dependence

Dependence

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

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

Withdrawal

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

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

Other withdrawal reactions to clobazam reported in the literature include

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

10 OVERDOSAGE

10.1 Signs and Symptoms of Overdosage

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

10.2 Management of Overdosage

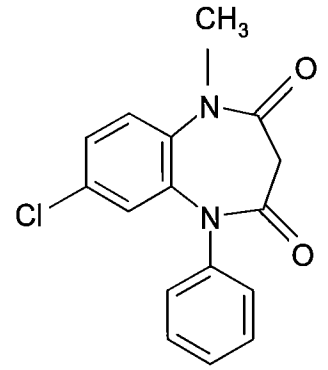
The management of ONFI overdose may include gastric lavage and/or administration of activated charcoal, intravenous fluid replenishment, early control of airway and general supportive measures, in addition to monitoring level of consciousness and vital signs. Hypotension can be treated by replenishment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

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

11 DESCRIPTION

Table 4. Description

Proprietary Name:	ONFI®
Established Name:	Clobazam
Dosage 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

Structural Formula:	

Clobazam is a white or almost white, crystalline powder with a slightly bitter taste; is slightly soluble in water, sparingly soluble in ethanol, and freely soluble in methylene chloride. The melting range of clobazam is from 182-185°C. The molecular formula is $C_{16}H_{13}O_2N_2Cl$ and the molecular weight is 300.7.

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

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

Effects on Electrocardiogram

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

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

12.3 Pharmacokinetics

The peak plasma levels (C_{max}) and the area under the curve (AUC) of clobazam are dose-proportional over the dose range of 10-80 mg following single- or multiple-dose administration of ONFI. Based on a population pharmacokinetic analysis, the pharmacokinetics of clobazam are linear from 5-160 mg/day. Clobazam is converted to N-desmethylclobazam which has about 1/5 the activity of clobazam. The estimated mean elimination half-lives ($t_{½}$) of clobazam and N-desmethylclobazam were 36-42 hours and 71-82 hours, respectively.

Absorption

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

Distribution

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

Metabolism and Excretion

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

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

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

Pharmacokinetics in Specific Populations

Age

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

Sex

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

Race

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

Renal Impairment

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

Hepatic Impairment

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

Drug Interaction Studies

In vitro studies:

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

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

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

In vivo studies:

Potential for ONFI to Affect Other Drugs

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

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

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

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

Potential for Other Drugs to Affect ONFI

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

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

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

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

12.5 Pharmacogenomics

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

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

The carcinogenic potential of clobazam has not been adequately assessed.

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

Mutagenesis

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

Impairment of Fertility

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

14 CLINICAL STUDIES

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

Study 1

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

Table 5. Study 1 Total Daily Dose

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

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

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

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

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

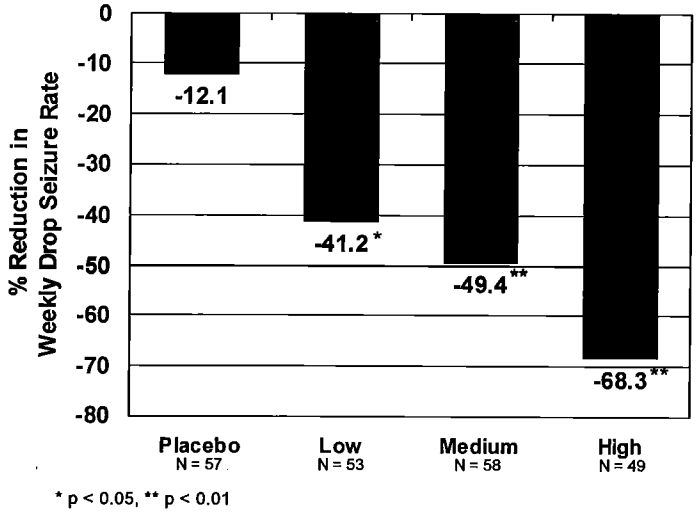
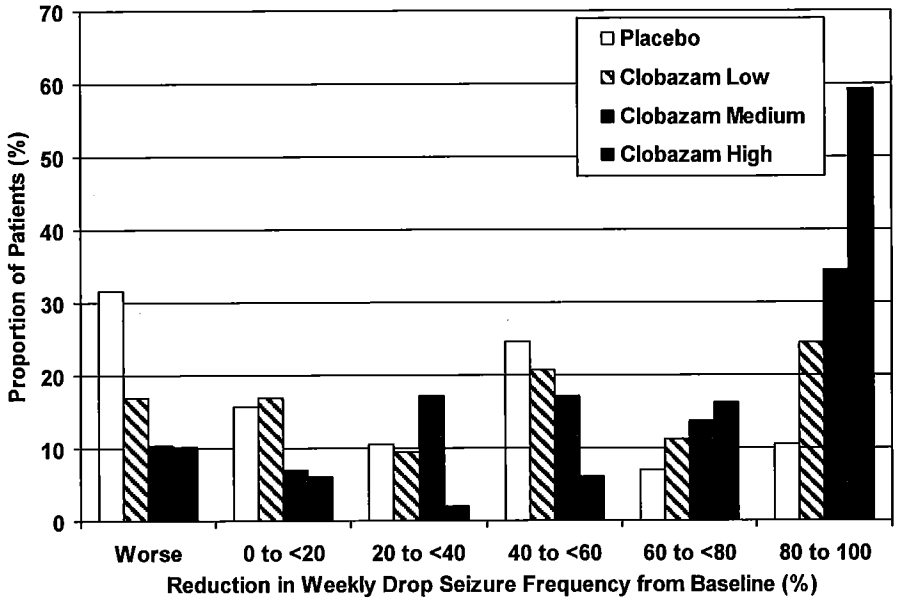


Figure 2 shows changes from baseline in weekly drop seizure frequency by category for patients treated with ONFI and placebo in Study 1. Patients in whom the seizure frequency increased are shown at left as "worse." Patients in whom the seizure frequency decreased are shown in five categories.

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



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

Study 2

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

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

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

16 HOW SUPPLIED/STORAGE AND HANDLING

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

NDC 67386-311-01: 10 mg scored tablet, Bottles of 100
NDC 67386-312-01: 20 mg scored tablet, Bottles of 100

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

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

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

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide and Instructions for Use).

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

Somnolence or Sedation

Advise patients or caregivers to check with their healthcare provider before ONFI is taken with other CNS depressants such as other benzodiazepines, opioids, tricyclic antidepressants, sedating antihistamines, or alcohol *[see Warnings and Precautions (5.1, 5.2)]*.

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

Increasing or Decreasing the ONFI Dose

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

Interactions with Hormonal Contraceptives

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

Serious Dermatological Reactions

Advise patients or caregivers that serious skin reactions have been reported in patients taking ONFI. Serious skin reactions, including SJS/TEN, may need to be treated in a hospital and may be life-threatening. If a skin reaction occurs while taking ONFI, patients or caregivers should consult with healthcare providers immediately *[see Warnings and Precautions (5.4)]*.

Suicidal Thinking and Behavior

Counsel patients, their caregivers, and their families that AEDs, including ONFI, may increase the risk of suicidal thoughts and behavior and advise them of the need to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts of self-harm. Patients should report behaviors of concern immediately to healthcare providers *[see Warnings and Precautions (5.6)]*.

Use in Pregnancy

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

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

Use in Nursing

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

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

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

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

Lundbeck

ONFI is a registered trademark of Lundbeck

MEDICATION GUIDE

ONFI® (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.

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

4. Serious skin reactions have been seen with ONFI and may require stopping its use. Do not stop taking ONFI without first talking to your healthcare provider.

- A serious skin reaction can happen at any time during your treatment with ONFI, but is more likely to happen within the first 8 weeks of treatment. These skin reactions need to be treated right away.

- Call your healthcare provider immediately if you have skin blisters, peeling rash, sores in the mouth, hives or any other allergic reaction.

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

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

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

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

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

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

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

What is ONFI?

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

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

What should I tell my healthcare provider before taking ONFI?

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

- have liver or kidney problems
- have lung problems (respiratory disease)
- have or have had depression, mood problems, or suicidal thoughts or behavior
- have any other medical conditions
- use birth control medicine. ONFI may cause your birth control medicine to be less effective. Talk to your healthcare provider about the best birth control method to use.
- are pregnant or plan to become pregnant. **ONFI may harm your unborn baby.**
    - Tell your healthcare provider right away if you become pregnant while taking ONFI. You and your healthcare provider will decide if you should take ONFI while you are pregnant.
    - Children born to mothers receiving benzodiazepine medications (including ONFI) late in pregnancy may be at some risk of experiencing breathing problems, feeding problems, dangerously low body temperature, and withdrawal symptoms.

- If you become pregnant while taking ONFI, talk to your healthcare provider about registering with the North American Antiepileptic Drug Pregnancy Registry. You can register by calling 1-888-233-2334. 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.

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

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

How should I take ONFI?

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

What should I avoid while taking ONFI?

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

What are the possible side effects of ONFI?

ONFI may cause serious side effects, including:

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

The most common side effects of ONFI include:

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

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

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

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

How should I store ONFI?

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

Tablets

- Keep ONFI tablets in a dry place

Oral Suspension

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

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

General Information about the safe and effective use of ONFI.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use ONFI for a condition for which it was not

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

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

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

What are the ingredients in ONFI?

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

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

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

Marketed by: Lundbeck, Deerfield, IL 60015, U.S.A.

Lundbeck 

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11/2013

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

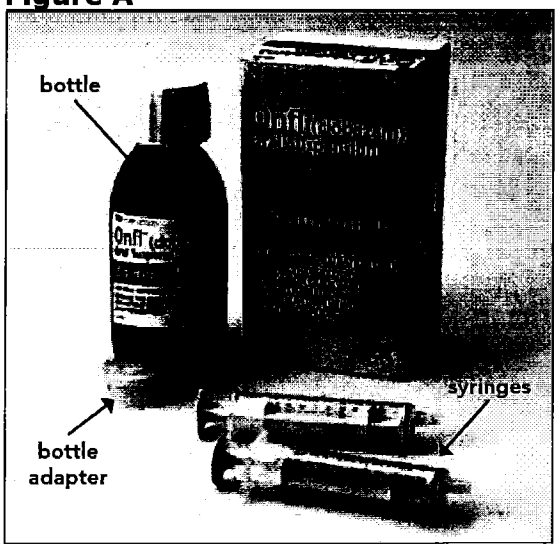
Read this Instructions for Use before using ONFI oral suspension and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your healthcare provider about your medical condition or treatment.

Prepare ONFI Oral Suspension Dose

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

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

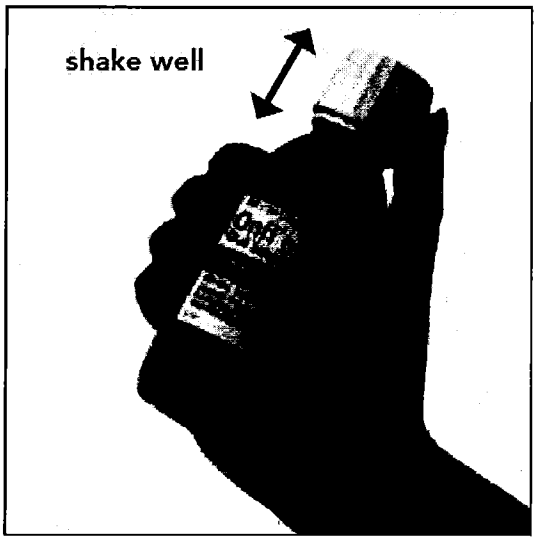
Figure A



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

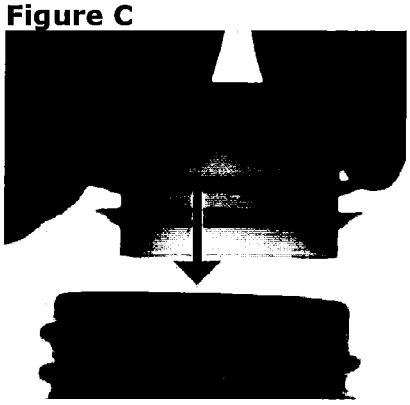
Step 2. Shake the bottle well before each use. **See Figure B**

Figure B



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

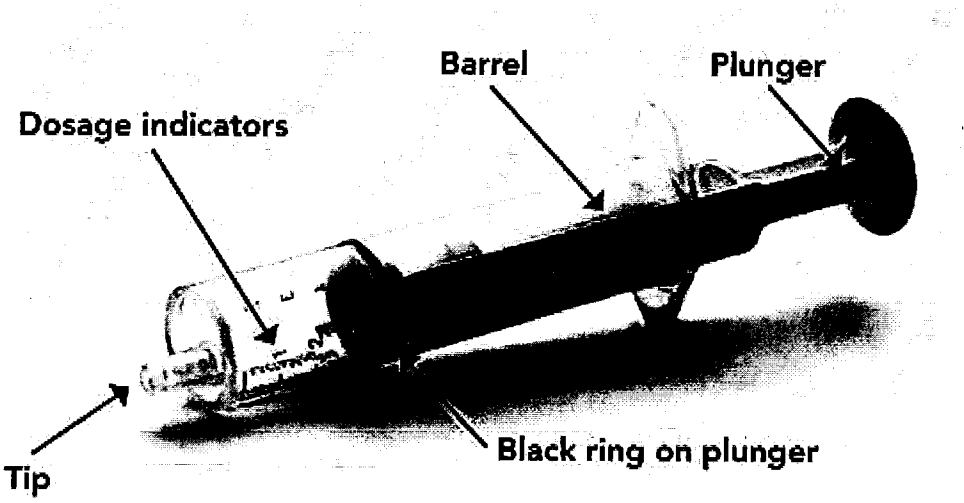
Figure C



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

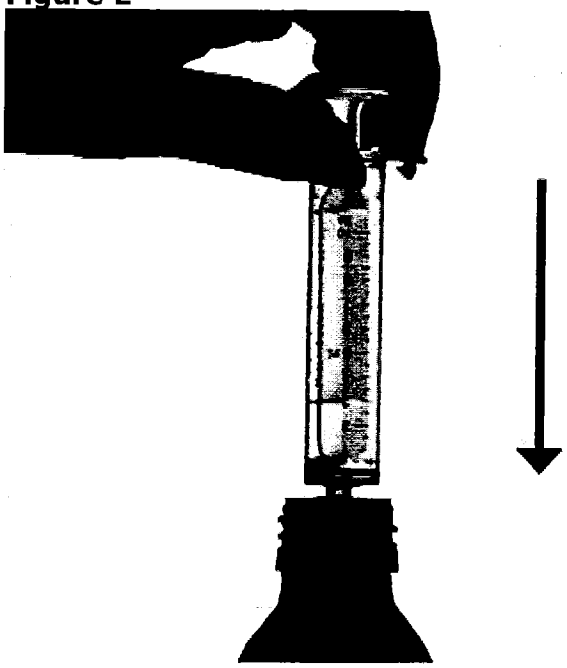
Step 4. Check your dose in milliliters (mL) as prescribed by your healthcare provider. Find this number on the syringe. Do not take more than the prescribed total dose in 1 day. **See Figure D**

Figure D



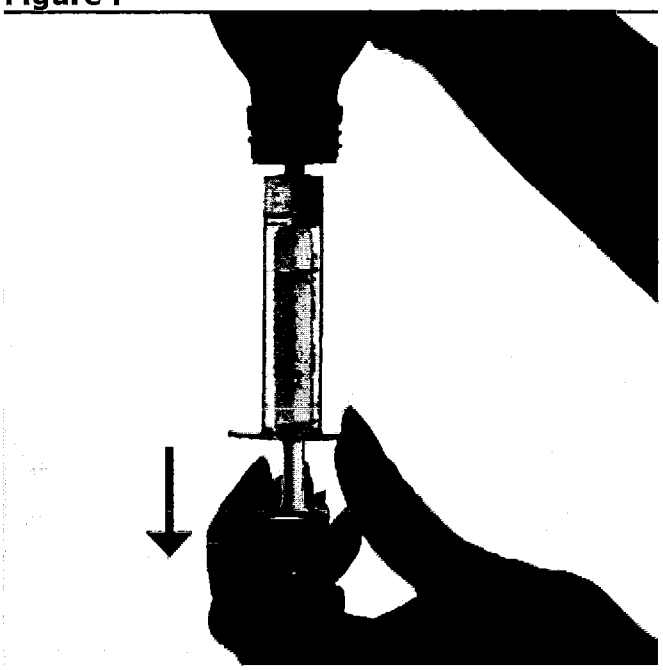
Step 5. Push the plunger all the way down and then insert the syringe into the upright bottle through the opening in the bottle adapter. **See Figure E**

Figure E



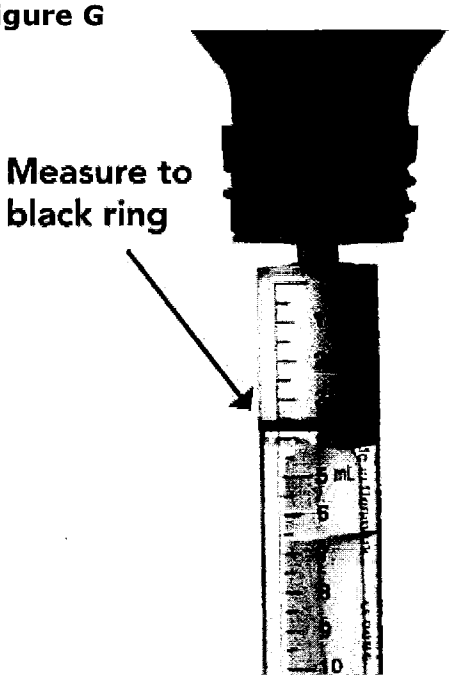
Step 6. With the syringe in place, turn the bottle upside down. Pull the plunger to the number of mLs needed (the amount of liquid medicine in Step 4). **See Figure F**

Figure F



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

Figure G



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

Figure H

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

Store 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.

Figure I

Step 9. Wash the oral syringe after each use.

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

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11/2013

JS 44 (Rev. 09/11)

CIVIL COVER SHEET

The JS 44 civil coversheet and the information contained herein neither replace nor supplement the filing and service of pleadngs or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States inSeptember 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. *(SEE INSTRUCTIONS ON NEXT PAGE OF THIS FORM.)*

I. (a) PLAINTIFFS
Madeline & Rogelio Escareno, as parents and on behalf of their minor child, Antonio Escareno

(b) County of Residence of First Listed Plaintiff Dallas County, TX
(EXCEPT IN U.S. PLAINTIFF CASES)

(c) Attorneys *(Firm Name, Address, and Telephone Number)*
Dunn Sheehan LLP
3400 Carlisle Street, Suite 200, Dallas, TX 75204
214.866.0077

DEFENDANTS
Lundbeck, LLC
Lundbeck Pharmaceuticals Services, LLC
H. Lundbeck A/S

County of Residence of First Listed Defendant Lake County, IL
(IN U.S. PLAINTIFF CASES ONLY)

NOTE: IN LAND CONDEMNATION CASES, USE THE LOCATION OF THE TRACT OF LAND INVOLVED.

Attorneys *(If Known)*

II. BASIS OF JURISDICTION *(Place an "X" in One Box Only)*

- ☐ 1 U.S. Government Plaintiff
- ☐ 3 Federal Question *(U.S. Government Not a Party)*
- ☐ 2 U.S. Government Defendant
- ☒ 4 Diversity *(Indicate Citizenship of Parties in Item III)*

III. CITIZENSHIP OF PRINCIPAL PARTIES *(Place an "X" in One Box for Plaintiff) (For Diversity Cases Only) and One Box for Defendant)*

	PTF	DEF		PTF	DEF
Citizen of This State	☒ 1	☐ 1	Incorporated *or* Principal Place of Business In This State	☐ 4	☐ 4
Citizen of Another State	☐ 2	☐ 2	Incorporated *and* Principal Place of Business In Another State	☐ 5	☒ 5
Citizen or Subject of a Foreign Country	☐ 3	☐ 3	Foreign Nation	☐ 6	☐ 6

IV. NATURE OF SUIT *(Place an "X" in One Box Only)*

CONTRACT
- ☐ 110 Insurance
- ☐ 120 Marine
- ☐ 130 Miller Act
- ☐ 140 Negotiable Instrument
- ☐ 150 Recovery of Overpayment & Enforcement of Judgment
- ☐ 151 Medicare Act
- ☐ 152 Recovery of Defaulted Student Loans (Excl. Veterans)
- ☐ 153 Recovery of Overpayment of Veteran's Benefits
- ☐ 160 Stockholders' Suits
- ☐ 190 Other Contract
- ☐ 195 Contract Product Liability
- ☐ 196 Franchise

REAL PROPERTY
- ☐ 210 Land Condemnation
- ☐ 220 Foreclosure
- ☐ 230 Rent Lease & Ejectment
- ☐ 240 Torts to Land
- ☐ 245 Tort Product Liability
- ☐ 290 All Other Real Property

TORTS

PERSONAL INJURY
- ☐ 310 Airplane
- ☐ 315 Airplane Product Liability
- ☐ 320 Assault, Libel & Slander
- ☐ 330 Federal Employers' Liability
- ☐ 340 Marine
- ☐ 345 Marine Product Liability
- ☐ 350 Motor Vehicle
- ☐ 355 Motor Vehicle Product Liability
- ☐ 360 Other Personal Injury
- ☐ 362 Personal Injury - Med. Malpractice

PERSONAL INJURY
- ☐ 365 Personal Injury - Product Liability
- ☒ 367 Health Care/ Pharmaceutical Personal Injury Product Liability
- ☐ 368 Asbestos Personal Injury Product Liability

PERSONAL PROPERTY
- ☐ 370 Other Fraud
- ☐ 371 Truth in Lending
- ☐ 380 Other Personal Property Damage
- ☐ 385 Property Damage Product Liability

CIVIL RIGHTS
- ☐ 440 Other Civil Rights
- ☐ 441 Voting
- ☐ 442 Employment
- ☐ 443 Housing/ Accommodations
- ☐ 445 Amer. w/Disabilities - Employment
- ☐ 446 Amer. w/Disabilities - Other
- ☐ 448 Education

PRISONER PETITIONS
- ☐ 510 Motions to Vacate Sentence

Habeas Corpus:
- ☐ 530 General
- ☐ 535 Death Penalty
- ☐ 540 Mandamus & Other
- ☐ 550 Civil Rights
- ☐ 555 Prison Condition
- ☐ 560 Civil Detainee - Conditions of Confinement

FORFEITURE/PENALTY
- ☐ 625 Drug Related Seizure of Property 21 USC 881
- ☐ 690 Other

LABOR
- ☐ 710 Fair Labor Standards Act
- ☐ 720 Labor/Mgmt. Relations
- ☐ 740 Railway Labor Act
- ☐ 751 Family and Medical Leave Act
- ☐ 790 Other Labor Litigation
- ☐ 791 Empl. Ret. Inc. Security Act

IMMIGRATION
- ☐ 462 Naturalization Application
- ☐ 463 Habeas Corpus - Alien Detainee (Prisoner Petition)
- ☐ 465 Other Immigration Actions

BANKRUPTCY
- ☐ 422 Appeal 28 USC 158
- ☐ 423 Withdrawal 28 USC 157

PROPERTY RIGHTS
- ☐ 820 Copyrights
- ☐ 830 Patent
- ☐ 840 Trademark

SOCIAL SECURITY
- ☐ 861 HIA (1395ff)
- ☐ 862 Black Lung (923)
- ☐ 863 DIWC/DIWW (405(g))
- ☐ 864 SSID Title XVI
- ☐ 865 RSI (405(g))

FEDERAL TAX SUITS
- ☐ 870 Taxes (U.S. Plaintiff or Defendant)
- ☐ 871 IRS—Third Party 26 USC 7609

OTHER STATUTES
- ☐ 375 False Claims Act
- ☐ 400 State Reapportionment
- ☐ 410 Antitrust
- ☐ 430 Banks and Banking
- ☐ 450 Commerce
- ☐ 460 Deportation
- ☐ 470 Racketeer Influenced and Corrupt Organizations
- ☐ 480 Consumer Credit
- ☐ 490 Cable/Sat TV
- ☐ 850 Securities/Commodities/ Exchange
- ☐ 890 Other Statutory Actions
- ☐ 891 Agricultural Acts
- ☐ 893 Environmental Matters
- ☐ 895 Freedom of Information Act
- ☐ 896 Arbitration
- ☐ 899 Administrative Procedure Act/Review or Appeal of Agency Decision
- ☐ 950 Constitutionality of State Statutes

V. ORIGIN *(Place an "X" in One Box Only)*

☒ 1 Original Proceeding ☐ 2 Removed from State Court ☐ 3 Remanded from Appellate Court ☐ 4 Reinstated or Reopened ☐ 5 Transferred from another district *(specify)* ☐ 6 Multidistrict Litigation

VI. CAUSE OF ACTION

Cite the U.S. Civil Statute under which you are filing *(Do not cite jurisdictional statutes unless diversity)*:
28 U.S.C. 1332

Brief description of cause:
Off-Label Promotion; Strict Products Liability & Failure to Warn; Defective Design & Manufacturing Defect; Fraud

VII. REQUESTED IN COMPLAINT:

☐ CHECK IF THIS IS A CLASS ACTION UNDER F.R.C.P. 23

DEMAND $ >$75,000.00 (greater than)

CHECK YES only if demanded in complaint:
JURY DEMAND: ☒ Yes ☐ No

VIII. RELATED CASE(S) PENDING OR CLOSED: *(See instructions):* JUDGE _____ DOCKET NUMBER _____

DATE
01/22/2014

SIGNATURE OF ATTORNEY OF RECORD
Conn Sheehan

FOR OFFICE USE ONLY

RECEIPT # _____ AMOUNT _____ APPLYING IFP _____ JUDGE _____ MAG. JUDGE _____