



Corporate Release

U.S. FDA approves Carnexiv™ (carbamazepine) injection as intravenous replacement therapy for oral carbamazepine formulations

- *Carbamazepine has been one of the recommended treatment standards for people with epilepsyⁱ*
- *Carnexiv is the first FDA-approved intravenous carbamazepine option in the U.S.*
- *Healthcare professionals will now be able to provide continuity of care for certain patients with epilepsy when oral carbamazepine cannot be administered*

Valby, Denmark, 7 October 2016 - H. Lundbeck A/S (Lundbeck) today announced that the U.S. Food and Drug Administration (FDA) has approved Carnexiv™ (carbamazepine) injection as a short-term replacement therapy for oral carbamazepine formulations in adults with certain seizure types when oral administration is temporarily not feasible. Carnexiv has received orphan drug designation from the U.S. FDA for this indication and will be the first available intravenous (IV) formulation of the antiepileptic drug (AED) carbamazepine. Lundbeck plans to make Carnexiv commercially available in the U.S. in early 2017.

Carnexiv is a short-term (≤7 days) intravenous replacement therapy for oral carbamazepine formulations that provides continuity of care for adult patients who are unable to take carbamazepine by mouth and have the following seizure types:

- Partial seizures with complex symptomatology
- Generalized tonic-clonic seizures
- Mixed seizure patterns which include the above, or other partial or generalized seizures

As with the oral carbamazepine formulation, there is a risk of serious dermatologic reactions during treatment with Carnexiv, including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), as well as a risk of aplastic anemia and agranulocytosis.

Partial seizures and generalized tonic-clonic seizures can often be difficult to controlⁱⁱ. As a result, many patients with epilepsy are on a daily regimen of one or more AEDs that has been carefully adjusted to obtain a therapeutic response. Switching or an abrupt discontinuation of AEDs can lead to seizure reoccurrence or breakthrough seizures^{iii, iv}.

“Carbamazepine is very difficult to make as an aqueous-based injectable formulation, which means that doctors have not had an IV formulation of the drug available when needed. This approval is the result of years of work to create a novel and stable injection formulation to support patients who need an alternative to oral carbamazepine,” said James Cloyd, PharmD, director of the Center for Orphan Drug Research at the University of Minnesota College of Pharmacy. *“We’re proud to partner with Lundbeck*



and appreciate the company's dedication to overcoming development challenges and making this therapy option available for patients and clinicians.”

Researchers at the University of Minnesota College of Pharmacy helped conduct early clinical proof-of-concept studies, which were instrumental in developing the formulation of Carnexiv, making intravenous administration possible. James Cloyd, PharmD, Angela Birnbaum, PhD, and Ilo E. Leppik, MD at the University of Minnesota partnered closely with Lundbeck during the clinical trial, orphan product and approval process for Carnexiv.

About Carnexiv

Carnexiv is an intravenous antiepileptic drug developed in the U.S. by Lundbeck and approved for use in the U.S. Carnexiv is a short-term (≤ 7 days) replacement therapy for oral carbamazepine for patients who are unable to take medication by mouth. When switching from oral carbamazepine, the total daily dosage of Carnexiv should be 70% of the total daily dose of oral carbamazepine, divided equally into four separate 30-minute infusions separated by 6 hours. At the end of the intravenous replacement period, patients should be switched back to their previous oral carbamazepine total daily dose and frequency as soon as clinically appropriate.

Indications and Usage

CARNEXIV (carbamazepine) injection is indicated as replacement therapy for oral carbamazepine formulations, when oral administration is temporarily not feasible, in adults with the following seizure types:

- Partial seizures with complex symptomatology
- Generalized tonic-clonic seizures
- Mixed seizure patterns which include the above, or other partial or generalized seizures

Limitations of Usage

CARNEXIV is not indicated for the treatment of absence seizures (including atypical absence). Carbamazepine has been associated with increased frequency of generalized convulsions in these patients.

Important Safety Information

**WARNING: SERIOUS DERMATOLOGIC REACTIONS
and APLASTIC ANEMIA AND AGRANULOCYTOSIS**
See full prescribing information for complete boxed warning.

Serious Dermatologic Reactions

- **Serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), have occurred with carbamazepine. Discontinue CARNEXIV if these reactions occur**
- **Patients of Asian ancestry have a 10-fold greater risk of TEN/SJS, compared to other populations. Avoid use of CARNEXIV in genetically at-risk patients, including those positive for the HLA-B*1502 allele**

Aplastic Anemia and Agranulocytosis

- **Aplastic anemia and agranulocytosis can occur with CARNEXIV**
- **Obtain complete CBC prior to initiation of CARNEXIV. Consider discontinuing CARNEXIV if significant bone marrow depression develops**

Contraindications: Bone Marrow Depression, Hypersensitivity, and Concomitant Drugs

- Patients with bone marrow depression or a known hypersensitivity to carbamazepine or tricyclic antidepressants. If patient or immediate family member has history of hypersensitivity, consider benefits and risks and closely monitor for symptoms
- Concomitant use with boceprevir, nefazodone, and delavirdine or other non-nucleoside reverse transcriptase inhibitors
- Use of monoamine oxidase inhibitors (MAOIs) within the past 14 days before beginning carbamazepine treatment

Toxic Epidermal Necrolysis (TEN), Stevens-Johnson syndrome (SJS), HLA-B*1502 Allele, and Aplastic Anemia and Agranulocytosis (see Boxed Warning)

Renal Impairment

CARNEXIV should generally not be used in patients with moderate or severe renal impairment. Closely monitor patients with renal impairment.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

DRESS, also known as multiorgan hypersensitivity, has occurred with carbamazepine. These events can be fatal or life-threatening. Advise patients to report signs and symptoms such as fever, rash, lymphadenopathy, and/or facial swelling immediately, and discontinue CARNEXIV if an alternative etiology cannot be established.

Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs), including CARNEXIV, increase the risk of suicidal thoughts or behavior. Monitor patients for the emergence or worsening of depression, any unusual changes in mood or behavior, or suicidal thoughts, behavior, or thoughts of self-harm; and instruct families and caregivers to report behaviors of concern immediately.



Pregnancy Registry and Nursing Mothers

- CARNEXIV can cause fetal harm when administered to a pregnant woman. If used during pregnancy, or if the patient becomes pregnant while taking CARNEXIV, inform the patient of the potential risk to the fetus and carefully consider both the potential risks and benefits of treatment. Encourage patients to call the toll-free number 1-888-233-2334 to enroll in the Pregnancy Registry or visit <http://www.aedpregnancyregistry.org/>.
- Discontinue CARNEXIV or discontinue nursing, taking into consideration the importance of the drug to the mother.

Abrupt Discontinuation and Seizure Risk

Do not discontinue CARNEXIV abruptly because of the risk of seizures, status epilepticus, and other withdrawal signs/symptoms.

Hyponatremia

Hyponatremia can result from treatment with CARNEXIV, and in many cases appears to be caused by the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The risk of SIADH appears to be dose-related. Elderly patients and patients treated with diuretics are at a greater risk. Consider discontinuing CARNEXIV in patients with symptomatic hyponatremia.

Neurologic Function

Carbamazepine has the potential to impair judgment, cognition, motor function, and motor coordination, and it may also cause dizziness, ataxia, and drowsiness. Caution patients about operating hazardous machinery, including automobiles, until they are reasonably certain that carbamazepine does not affect them adversely.

Hepatic Toxicity

Hepatic effects, ranging from slight elevations in liver enzymes to rare cases of hepatic failure, have been reported, and may progress despite drug discontinuation. Rare instances of vanishing bile duct syndrome have also been reported. Evaluate liver function before and during treatment, particularly in patients with a history of liver disease. Discontinue CARNEXIV based on clinical judgment in the case of active liver disease, or with newly occurring or worsening clinical or laboratory evidence of liver dysfunction or hepatic damage. Avoid using CARNEXIV in patients with a history of hepatic porphyria.

Increased Intraocular Pressure

Carbamazepine has mild anticholinergic activity. Consider assessing intraocular pressure before initiating and periodically during therapy in patients with a history of increased intraocular pressure.

Hepatic Porphyrria

Avoid using CARNEXIV in patients with a history of hepatic porphyria, as acute attacks have been reported in such patients and CARNEXIV increases porphyrin precursors in rodents.

Drug Interactions

Carbamazepine may reduce plasma concentrations of concomitant medications metabolized by CYP1A2, 2B6, 2C9/19 and 3A4; closely monitor carbamazepine levels and make appropriate dose



adjustments. CYP3A4 inhibitors can increase plasma carbamazepine levels. CYP3A4 inducers can decrease carbamazepine levels.

Adverse Reactions

The most common adverse reactions with CARNEXIV (incidence $\geq 2\%$) were dizziness, somnolence, blurred vision, diplopia, headache, infusion-related reaction, infusion site pain, and anemia. The most common adverse reactions with oral carbamazepine were dizziness, drowsiness, unsteadiness, nausea, and vomiting.

Important Dosing Information

Use of CARNEXIV for more than 7 days has not been studied and is not recommended. At the end of intravenous (IV) replacement therapy, switch patients back to oral carbamazepine at their previous total daily oral dose and frequency as soon as clinically appropriate.

Please see the [full Prescribing Information, including Boxed Warning for serious dermatologic reactions and aplastic anemia and agranulocytosis](#), for complete details; or go to www.CARNEXIV-US.com for more information.

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About H. Lundbeck A/S

H. Lundbeck A/S (LUN.CO, LUN DC, HLUYY) is a global pharmaceutical company specialized in psychiatric and neurological disorders. For more than 70 years, we have been at the forefront of research within neuroscience. Our key areas of focus are depression, schizophrenia, Parkinson's disease and Alzheimer's disease.

An estimated 700 million people worldwide are living with psychiatric and neurological disorders and far too many suffer due to inadequate treatment, discrimination, a reduced number of working days, early retirement and other unnecessary consequences. Every day, we strive for improved treatment and a better life for people living with psychiatric and neurological disorders – we call this Progress in Mind.

Our approximately 5,000 employees in 55 countries are engaged in the entire value chain throughout research, development, manufacturing, marketing and sales. Our pipeline consists of several late-stage development programmes and our products are available in more than 100 countries. We have research centres in China and Denmark and production facilities in China, Denmark, France and Italy. Lundbeck generated core revenue of DKK 14.6 billion in 2015 (EUR 2 billion; USD 2.2 billion).



For additional information, we encourage you to visit our corporate site www.lundbeck.com and connect with us on Twitter at @Lundbeck.

Safe Harbor/Forward-Looking Statements

The above information contains forward-looking statements that provide our expectations or forecasts of future events such as new product introductions, product approvals and financial performance.

Such forward-looking statements are subject to risks, uncertainties and inaccurate assumptions. This may cause actual results to differ materially from expectations and it may cause any or all of our forward-looking statements here or in other publications to be wrong. Factors that may affect future results include interest rate and currency exchange rate fluctuations, delay or failure of development projects, production problems, unexpected contract breaches or terminations, government-mandated or market-driven price decreases for Lundbeck's products, introduction of competing products, Lundbeck's ability to successfully market both new and existing products, exposure to product liability and other lawsuits, changes in reimbursement rules and governmental laws and related interpretation thereof, and unexpected growth in costs and expenses.

Certain assumptions made by Lundbeck are required by Danish Securities Law for full disclosure of material corporate information. Some assumptions, including assumptions relating to sales associated with product that is prescribed for unapproved uses, are made taking into account past performances of other similar drugs for similar disease states or past performance of the same drug in other regions where the product is currently marketed. It is important to note that although physicians may, as part of their freedom to practice medicine in the US, prescribe approved drugs for any use they deem appropriate, including unapproved uses, at Lundbeck, promotion of unapproved uses is strictly prohibited.

ⁱ Glauser T, Ben-Menachem E, et al. ILAE Treatment Guidelines: Evidence-based Analysis of Antiepileptic Drug Efficacy and Effectiveness as Initial Monotherapy for Epileptic Seizures and Syndromes. *Epilepsia*. 2006. 47(7):1094-1120.

ⁱⁱ Mattson R, Cramer J, et al. A comparison of valproate with carbamazepine for the treatment of complex partial seizures and secondarily generalized tonic-clonic seizures in adults. *N Engl J Med*. 1992. 327(11):765-71.

ⁱⁱⁱ Finamore JM, Sperling MR, et al. Seizure outcome after switching antiepileptic drugs: A matched, prospective study. *Epilepsia*. 2016:1-7.

^{iv} Wang SP, Mintzer ST, et al. Seizure recurrence and remission after switching antiepileptic drugs. *Epilepsia* 2013. 54: 187-193