NUEDEXTA®
(dextromethorphan HBr and quinidine sulfate) capsules 20 mg / 10 mg

The Science Behind NUEDEXTA

On-screen text: The Science Behind NUEDEXTA® (dextromethorphan HBR and quinidine sulfate 20mg/10mg)

October 2023 18US23EBP0118

VO: Life with a neurologic disorder or brain injury and Pseudobulbar Affect can be stressful.

On-screen text: Pseudobulbar Affect (PBA)

VO: Uncontrollable PBA episodes of laughing and/or crying can have a substantial impact on your patient's life. But treatment can help reduce these episodes.

On-screen text: Treatment can help.

VO: NUEDEXTA is the first and only FDA-approved treatment for PBA.

On-screen text: NUEDEXTA®
The first and only FDA-approved treatment for PBA
*FDA = U.S. Food and Drug Administration

VO: NUEDEXTA is a combination of two well-characterized components: dextromethorphan and quinidine

On-screen text: Dextromethorphan HBr (20 mg)
Quinidine sulfate (10 mg) - ultra-low dose

VO: It is important to note that while NUEDEXTA is generally well tolerated, it should not be used concomitantly with other drugs containing quinidine, quinine, or mefloquine.

On-screen text: Should not be used concomitantly with other drugs containing:

- Quinidine
- Quinine
- Mefloquine

VO: Dextromethorphan is a non-competitive NMDA receptor antagonist and a sigma-1 receptor agonist. Quinidine is a metabolic inhibitor that increases dextromethorphan's bioavailability and prolongs its elimination half-life so that it stays active longer.

On-screen text: Dextromethorphan
NMDA receptor antagonist
Sigma-1 receptor agonist

Quinidine
Metabolic inhibitor

VO: While the exact mechanism by which dextromethorphan exerts its therapeutic effects in patients with Pseudobulbar Affect is unknown, dextromethorphan is believed to target glutamate signaling in two key ways. Glutamate is one of the major neurotransmitters thought to be involved in PBA.

On-screen text: The exact mechanism by which dextromethorphan exerts its therapeutic effects in patients with Pseudobulbar Affect is unknown.

VO: First, it binds to the sigma-1 receptors, which is believed to inhibit the release of glutamate. This helps prevent too much glutamate from reaching neural receptors.

On-screen text: The exact mechanism by which dextromethorphan exerts its therapeutic effects in patients with Pseudobulbar Affect is unknown.

VO: Second, dextromethorphan binds to the NMDA receptor to reduce the amount of glutamate that is able to attach. With fewer activation points available, the NMDA response can be regulated when too much glutamate is released.

On-screen text: The exact mechanism by which dextromethorphan exerts its therapeutic effects in patients with Pseudobulbar Affect is unknown.

VO: NUEDEXTA is clinically proven to reduce PBA episodes.

On-screen text: NUEDEXTA logo
Clinically proven to reduce PBA episodes

VO: In the NUEDEXTA Pivotal trial, a randomized, placebo-controlled study, patients on NUEDEXTA had an average of 3.9 fewer episodes per day, compared to 6.8 at baseline, at Week 12.

On-screen text: The Pivotal Trial (N=326)
A randomized, placebo-controlled study of amyotrophic lateral sclerosis and multiple sclerosis patients.

November 2023 18US23EBP0119

NUEDEXTA Patients at Week 12 [Down Arrow] 3.9 fewer episodes per day from 6.8 at baseline*

Footnote: *Compared to 3 fewer episodes per day from a 4.5 baseline for placebo (P=.005)

Source: Pioro EP, Brooks BR, Cummings J, et al. Dextromethorphan plus ultra-low quinidine reduces pseudobulbar affect. *Ann Neurol*. 2010;68(5):693-702.

VO: According to a post-hoc analysis, patients on NUEDEXTA experienced an 82 percent reduction in episodes after 12 weeks.

On-screen text: Post hoc analysis: Episode rate reduction from baseline in 12-week Pivotal trial.

- Week 1: 44% fewer episodes
- Week 4: 70% fewer episodes
- Week 12: 82% fewer episodes

Source: Data on file. (NUE-002).

VO: When prescribing NUEDEXTA, keep in mind that it is contraindicated in patients with a history of NUEDEXTA-, quinine-, mefloquine-, or quinidine-induced thrombocytopenia, hepatitis, bone-marrow depression, lupus-like syndrome, or known hypersensitivity to dextromethorphan (for example, rash or hives).

On-screen text: Contraindicated in patients with a history of:
- NUEDEXTA-, quinine-, mefloquine-, or quinidine-induced
- Hepatitis,
- Bone-marrow depression,
- Lupus-like syndrome
- Hypersensitivity to dextromethorphan (e.g., rash or hives)

VO: Treating PBA with NUEDEXTA can help reduce their PBA episodes and make a difference for those in your care. To learn more about PBA and NUEDEXTA – and to access NUEDEXTA's full prescribing information, go to NUEDEXTAHCP[dot]com.

On-screen text: You can make a difference for your patients.
Access NUEDEXTA's full prescribing information at NUEDEXTAHCP.com

VO: Visit our website to watch part one in this series, PBA and the Brain.

On-screen text: Learn more at NUEDEXTAHCP.com

November 2023 18US23EBP0119

NUEDEXTA®
(dextromethorphan HBr and quinidine sulfate) capsules 20 mg / 10 mg

Onscreen Text and Narrator:

INDICATION and IMPORTANT SAFETY INFORMATION for NUEDEXTA® (dextromethorphan HBr and quinidine sulfate)

INDICATION:

NUEDEXTA is indicated for the treatment of pseudobulbar affect (PBA).

PBA occurs secondary to a variety of otherwise unrelated neurologic conditions, and is characterized by involuntary, sudden, and frequent episodes of laughing and/or crying. PBA episodes typically occur out of proportion or incongruent to the underlying emotional state. PBA is a specific condition, distinct from other types of emotional lability that may occur in patients with neurologic disease or injury.

IMPORTANT SAFETY INFORMATION:

CONTRAINDICATIONS:

- **Quinidine and Related Drugs:** NUEDEXTA contains quinidine and should not be used concomitantly with other drugs containing quinidine, quinine, or mefloquine.
- **Hypersensitivity:** NUEDEXTA is contraindicated in patients with a history of NUEDEXTA-, quinine-, mefloquine-, or quinidine-induced thrombocytopenia, hepatitis, bone-marrow depression, lupus-like syndrome, or known hypersensitivity to dextromethorphan (e.g., rash, hives).
- **MAOIs:** NUEDEXTA is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs), or in patients who have taken MAOIs within the preceding 14 days, due to the risk of serious and possibly fatal drug interactions, including serotonin syndrome. Allow at least 14 days after stopping NUEDEXTA before starting an MAOI.
- **Cardiovascular:** NUEDEXTA is contraindicated in patients with a prolonged QT interval, congenital long QT syndrome, history suggestive of torsades de pointes, heart failure, patients receiving drugs that both prolong QT interval and are metabolized by CYP2D6 (e.g., thioridazine and pimozide), patients with complete atrioventricular (AV) block without implanted pacemaker, or at high risk of complete AV block.

Thrombocytopenia and Other Hypersensitivity Reactions: Quinidine can cause immune-mediated thrombocytopenia that can be severe or fatal. Non-specific symptoms, such as lightheadedness, chills, fever, nausea, and vomiting, can precede or occur with thrombocytopenia. NUEDEXTA should be discontinued immediately if thrombocytopenia occurs.

Hepatotoxicity: Hepatitis, including granulomatous hepatitis, has been reported in patients receiving quinidine, generally during the first few weeks of therapy. Discontinue immediately if this occurs.

Otsuka
Otsuka America Pharmaceutical, Inc.

November 2023 18US23EBP0119

Cardiac Effects: NUEDEXTA causes dose-dependent QTc prolongation. QT prolongation can cause torsades de pointes–type ventricular tachycardia, with the risk increasing as the degree of prolongation increases. When initiating NUEDEXTA in patients at risk for QT prolongation and torsades de pointes, electrocardiographic (ECG) evaluation of QT interval should be conducted at baseline and 3 to 4 hours after the first dose. Some risk factors include use with CYP3A4 inhibitors or drugs that prolong QT interval, electrolyte abnormalities, bradycardia, or left ventricular hypertrophy or dysfunction. If patients taking NUEDEXTA experience symptoms that could indicate the occurrence of cardiac arrhythmias (e.g., syncope or palpitations), NUEDEXTA should be discontinued, and the patient further evaluated.

Concomitant Use of CYP2D6 Substrates: NUEDEXTA inhibits CYP2D6 and may interact with other drugs metabolized by CYP2D6. Adjust dose of CYP2D6 substrates as needed.

Dizziness: NUEDEXTA may cause dizziness. Take precautions to reduce the risk of falls.

Serotonin Syndrome: Use of NUEDEXTA with selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants increases the risk of "serotonin syndrome."

Anticholinergic Effects of Quinidine: Monitor for worsening in myasthenia gravis.

Adverse Reactions: The most common adverse reactions (incidence of ⩾3% and two-fold greater than placebo) in patients taking NUEDEXTA are diarrhea, dizziness, cough, vomiting, asthenia, peripheral edema, urinary tract infection, influenza, increased gamma-glutamyltransferase, and flatulence.

These are not all the risks for use of NUEDEXTA.

To report SUSPECTED ADVERSE REACTIONS, contact Otsuka America Pharmaceutical, Inc. at 1-800-438-9927 or FDA at 1-800-FDA-1088 (www.fda.gov/medwatch).

Please see **FULL PRESCRIBING INFORMATION** at NUEDEXTAHCP.com.

References: 1. Ahmed A, Simmons Z. Pseudobulbar affect: prevalence and management. *Ther Clin Risk Manag*. 2013;9(1):483-489. **2.** NUEDEXTA [package insert]. Rockville, MD: Otsuka America Pharmaceutical, Inc. **3.** Miller A, Pratt H, Schiffer RB. Pseudobulbar affect: the spectrum of clinical presentations, etiologies and treatments. *Expert Rev Neurother.* 2011;11(7):1077-1088. **4.** Purves D. Emotions. In: Purves D, Augustine G, Fitzpatrick D, Hall WC, LaMantia AS, White LE, eds. *Neuroscience.* 5th ed. Sunderland, MA: Sinauer Associates; 2011:647-667. **5.** Pankevich DE, Davis M, Altevogt BM; for the Institute of Medicine Forum on Neuroscience and Nervous System Disorders. Glutamate-Related Biomarkers in Drug Development for Disorders of the Nervous System: Workshop Summary. Washington, DC: The National Academies Press; 2011. **6.** Nguyen L,

November 2023 18US23EBP0119

Lucke-Wold BP, Mookerjee SA, et al. Role of sigma-1 receptors in neurodegenerative diseases. *J Pharmacol Sci.* 2015;127(1):17-29. **7.** Werling LL, Lauterbach EC, Calef U. Dextromethorphan as a potential neuroprotective agent with unique mechanisms of action. *Neurologist.* 2007;13(5):272-293. **8.** Schadel M, Wu D, Otton SV, Kalow W, Sellers EM. Pharmacokinetics of dextromethorphan and metabolites in humans: influence of the CYP2D6 phenotype and quinidine inhibition. *J Clin Psychopharmacol.* 1995;15(4):263-269. **9.** Pioro EP, Brooks BR, Cummings J, et al. Dextromethorphan plus ultra-low quinidine reduces pseudobulbar affect. *Ann Neurol*. 2010;68(5):693-702. **10.** Hammond FM, Alexander DN, Cutler AJ, et al. PRISM II: an open-label study to assess effectiveness of dextromethorphan/quinidine for pseudobulbar affect in patients with dementia, stroke or traumatic brain injury. *BMC Neurol*. 2016;16:89.

October 2023 18US23EBP0118

End Slate: NUEDEXTA logo
Visit NUEDEXTAHCP.com

November 2023 18US23EBP0119