ARE YOU UNCOVERING THE MANY FACES OF PSEUDOBULBAR AFFECT (PBA)?

Actor portrayals.

NUEDEXTA is the **only FDA-approved treatment** proven to reduce PBA episodes[1]

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.

Please see full Important Safety Information on page 11 and FULL PRESCRIBING INFORMATION.

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

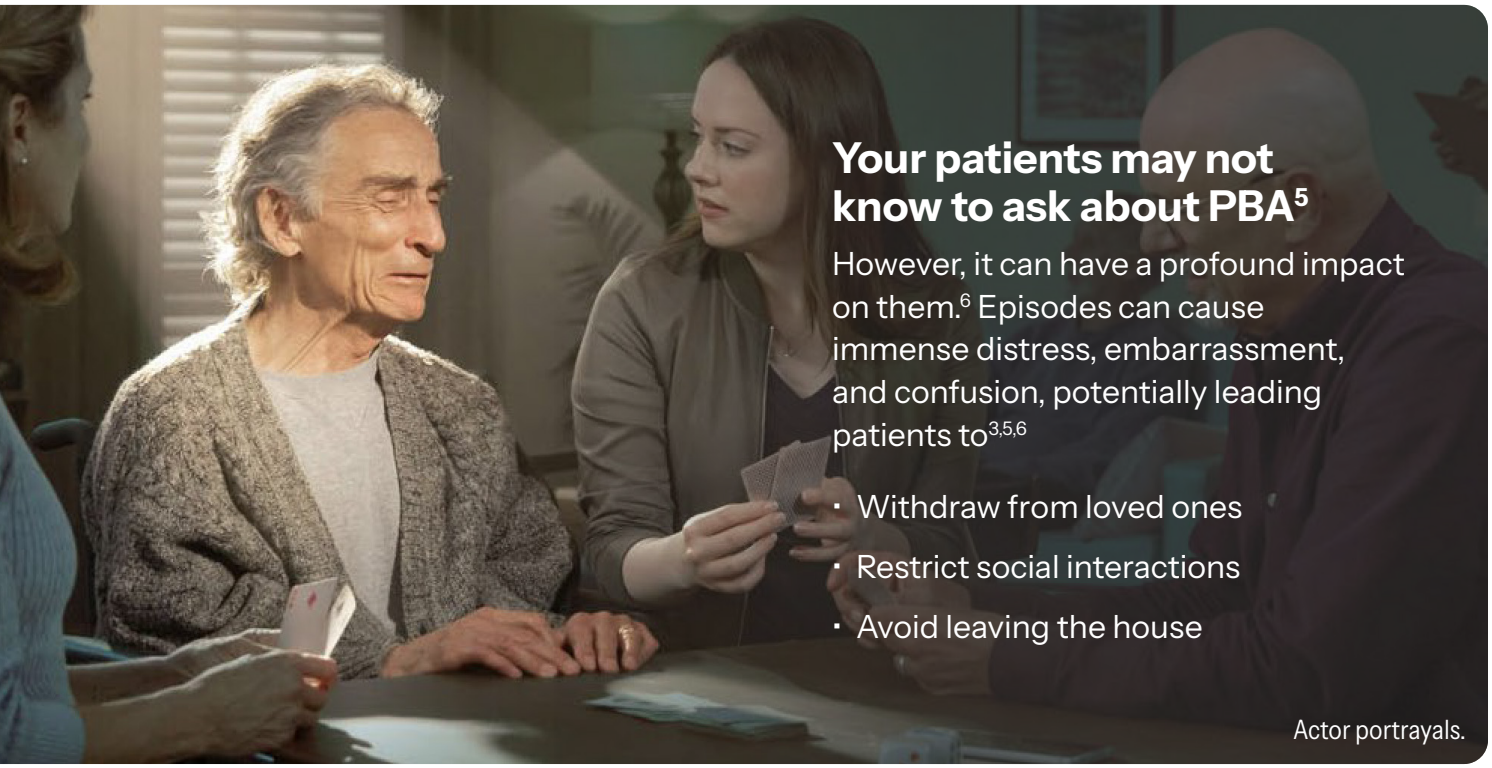
PBA: a neurologic disorder that can be mistaken for depression[2]

Listen closely for the PBA characteristics your patient may be describing[1,3,4]:

- **Uncontrollable** *"I can't control it."*
- **Sudden** *"It comes out of the blue."*
- **Frequent** *"I cry more than I used to."*
- **Disconnected from their actual mood** *"I laugh when it's not funny."*
- **Exaggerated** *"My reactions are over the top."*

While PBA and depression are commonly comorbid, **PBA is not a mood disorder**.[2]

It's a **distinct neurologic condition** caused by other neurologic conditions.[2]



ARE YOUR PATIENTS SUFFERING IN SILENCE?

When was the last time you diagnosed PBA?

~37%* of your patients with a primary neurologic condition may be suffering from PBA[2]

46%*
OF PATIENTS WITH **MULTIPLE SCLEROSIS**[2]

52%*
OF PATIENTS WITH **TRAUMATIC BRAIN INJURY**[2]

29%*
OF PATIENTS WITH **ALZHEIMER DISEASE**[2]

Actor portrayals.

PBA also affects many patients with stroke, amyotrophic lateral sclerosis, and Parkinson's disease. PBA is not limited to these underlying conditions.[2]

*Based on the PRISM Registry including 5290 patients with stroke, amyotrophic lateral sclerosis, multiple sclerosis, traumatic brain injury, Alzheimer disease, and Parkinson's disease. Patients with PBA symptoms were defined as having a CNS-LS score of ≥13.[2]

CNS-LS=Center for Neurologic Study-Lability Scale.

A simple question can help uncover PBA in your patients with a primary neurologic condition

3 STEPS TO HELP ASSESS FOR PBA

PBA can only be diagnosed following a complete assessment by a qualified healthcare provider.

1 Pose a question about their behavior[5]

"Do you ever cry or laugh but it feels odd because you're not actually sad or amused?"

2 Differentiate between PBA and depression[1,4,7]

	Crying in depression	Crying in PBA
How often and for how long?	Onset and duration **defined by mood**	Happens **frequently** and **suddenly** and may be brief
Can they control it?	Mostly **controllable;** stops when mood changes	**Uncontrollable** and involuntary
Does it match their mood?	**Consistent** with mood	**Inconsistent** with or **disproportionate** to mood

3 Document your confirmed diagnosis with ICD-10 code F48.2[8*]

CONSIDER TREATMENT WITH NUEDEXTA IF YOU CONFIRM THAT YOUR PATIENT HAS PBA[1]

*ICD-10 diagnosis codes are provided for informational purposes only and do not guarantee that billing codes will be appropriate or that coverage and reimbursement will result. Providers should consult with their payers for all relevant coverage, coding, and reimbursement requirements. It is the sole responsibility of the provider to select proper codes and ensure the accuracy of all claims used in seeking reimbursement. This resource is not intended as legal advice or as a substitute for a provider's independent professional judgment.

Please see full Important Safety Information on page 11 and FULL PRESCRIBING INFORMATION.

“For me, having a diagnosis and then having a treatment, it’s made such a difference in terms of the reduction in episodes.”

MARY BETH

PATIENT LIVING WITH PBA

IMPORTANT SAFETY INFORMATION (cont’d)

CONTRAINDICATIONS (cont’d):

- **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.

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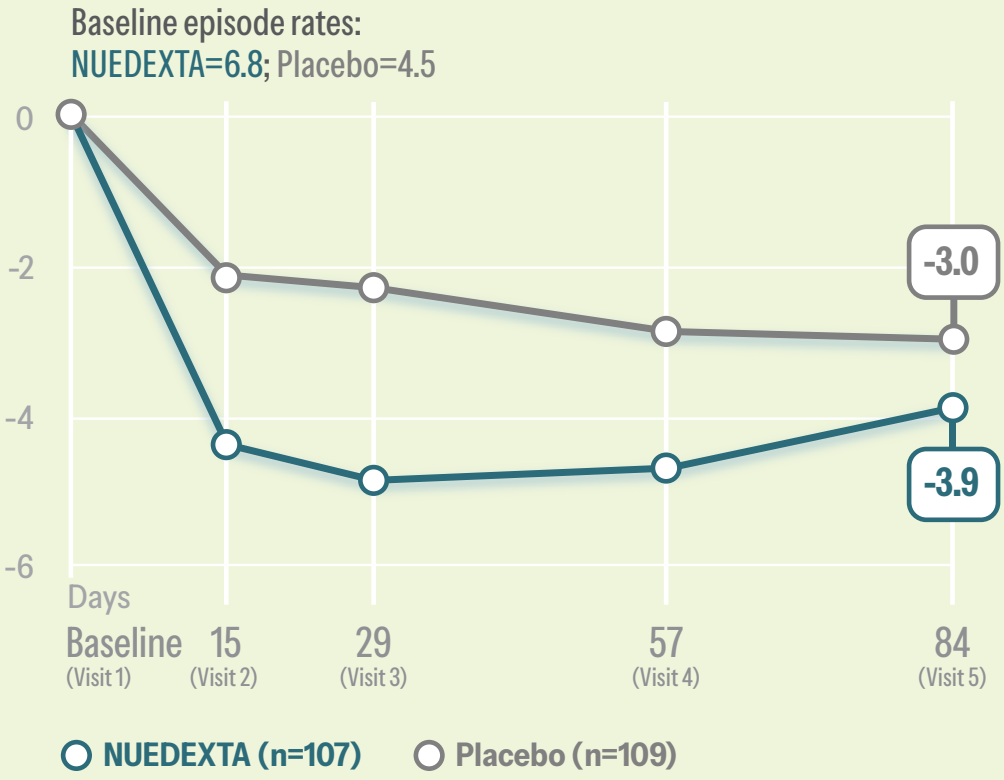
PRIMARY ENDPOINT: STAR TRIAL

NUEDEXTA significantly reduced PBA episodes of laughing and crying[1]

REDUCTION IN DAILY PBA EPISODES (MEAN CHANGE FROM BASELINE)[1,9]



AT WEEK 12

3.9

FEWER DAILY EPISODES*

*P=0.0048 vs placebo.[9]

Study design: The pivotal trial was a 12-week, randomized, placebo-controlled study of 326 patients with amyotrophic lateral sclerosis (n=197) or multiple sclerosis (n=129) and clinically significant PBA. Patients received NUEDEXTA dextromethorphan 20 mg/quinidine 10 mg (n=107), placebo (n=109), or dextromethorphan 30 mg/quinidine 10 mg (unapproved dose [n=110]) twice daily (once daily in week 1). The baseline daily PBA episode rates were 6.8 in the NUEDEXTA dextromethorphan 20 mg/quinidine 10 mg group and 4.5 in the placebo group.[1,9]

IMPORTANT SAFETY INFORMATION (cont'd)

CONTRAINDICATIONS (cont'd)

- **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.

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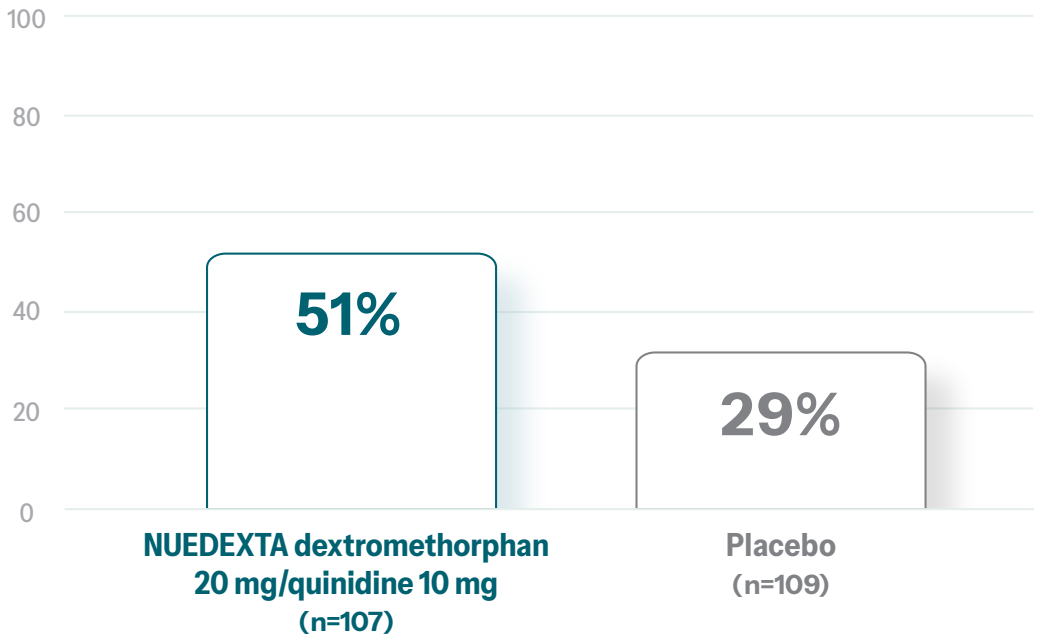
SECONDARY ENDPOINT: STAR TRIAL

Remission rates for patients treated with NUEDEXTA vs placebo[9]

PERCENT OF PATIENTS WITH ZERO EPISODES DURING THE FINAL TWO WEEKS[9]*



Statistical significance cannot be drawn.

*Remission was defined by the absence of episodes throughout the final 2 weeks of the study.[9]

IMPORTANT SAFETY INFORMATION (cont'd)

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.

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STAR TRIAL

NUEDEXTA has a demonstrated safety profile[1]

Adverse reaction with an incidence of ≥3% and ≥2x placebo in NUEDEXTA-treated patients by system organ class and preferred term

ADVERSE REACTION	NUEDEXTA dextromethorphan 20 mg/quinidine 10 mg (n=107)	Placebo (n=109)
Diarrhea	13%	6%
Dizziness	10%	5%
Cough	5%	2%
Vomiting	5%	1%
Asthenia	5%	2%
Peripheral edema	5%	1%
Urinary tract infection	4%	1%
Influenza	4%	1%
Increased gamma-glutamyltransferase	3%	0%
Flatulence	3%	1%

- **These are not all the risks from use of NUEDEXTA**[1]
- Adverse events were generally mild to moderate and consistent across studies[1,4]
- NUEDEXTA is not an antipsychotic medication or a controlled substance[1,10]

Adverse reactions leading to discontinuation: The most commonly reported (incidence ≥2% and greater than placebo) were muscle spasticity (3%), respiratory failure (1%), abdominal pain (2%), asthenia (2%), dizziness (2%), fall (1%), and muscle spasms (2%).[1]

IMPORTANT SAFETY INFORMATION (cont'd)

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.

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OPEN-LABEL TRIAL: PRISM II

PRIMARY ENDPOINT

Patient-reported PBA symptom score changed by -7.7[4]

Patients were asked to rate the frequency and severity over their PBA episodes (as assessed by CNS-LS score)

Day	Score, mean (SD)
0 (n=298)	**20.4 (4.4)**
30 (n=297)	**15.0 (5.0)**
90/final visit (n=261)	**12.8 (5.0)**

SECONDARY ENDPOINT

Weekly episode rate changed from 12 to 2[4]

Weekly median PBA episode rate*

Day	Episodes
0 (n=298)	**12**
30 (n=297)	**4**
90/final visit (n=261)	**2**

The most common adverse reactions were diarrhea (5.4%), headache (4.1%), urinary tract infection (2.7%), dizziness (2.5%), nausea (1.6%), fall (1.6%), fatigue (1.4%), somnolence (1.4%), dry mouth (1.1%), gastroesophageal reflux disease (1.1%), agitation (1.1%), and peripheral edema (1.1%). **These are not all the risks from use of NUEDEXTA**.[4]

Study limitation: Open-label study without active placebo or comparator, utilizing self-reported measures. The CNS-LS has not been validated in stroke, dementia, or traumatic brain injury. Results require cautious interpretation.[4]

Study design: A 90-day, open-label trial of 367 patients with stroke, dementia, or traumatic brain injury. Patients received 1 capsule of NUEDEXTA per day during week 1 and were titrated to 1 capsule twice a day for week 2 through day 90.[4]

CNS-LS is a self-administered questionnaire, designed to be completed by the patient with a 7-item rating scale that measures perceived frequency and severity of PBA episodes. It was validated as a screening tool in amyotrophic lateral sclerosis and multiple sclerosis populations. A CNS-LS score of ≥13 may suggest but does not confer a PBA diagnosis.[2,4,9]

*Measured as PBA episode counts over the 7 days prior to each visit (baseline, day 30, and day 90).[4]

IMPORTANT SAFETY INFORMATION (cont'd)

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

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Otsuka supports patients with comprehensive coverage and cost savings

BROAD INSURANCE COVERAGE

81% OF COMMERCIALLY INSURED PATIENTS **PAY ≤$30**[11]

84% OF MEDICARE PART D PATIENTS **PAY ≤$15**[11]

Learn about **cost reduction options** for your eligible patients by visiting the **website here**

COPAY CARD SAVINGS

Eligible patients may pay as little as $0* for a 90-day prescription with commercial insurance

*Restrictions apply. Eligible patients may pay as little as $0 for a 90-day supply of NUEDEXTA or $20 for a 30-day supply of NUEDEXTA with a maximum savings of $1335 per use and an annual maximum savings of $2670 per calendar year. Benefit cap applies regardless of copay amount.

REFERENCES: 1. Nuedexta. Package insert. Otsuka America Pharmaceutical, Inc.; 2022. **2.** Brooks BR, Crumpacker D, Fellus J, Kantor D, Kaye RE. PRISM: a novel research tool to assess the prevalence of pseudobulbar affect symptoms across neurological conditions. *PLoS One*. 2013;8(8):e72232. doi:10.1371/journal.pone.0072232 **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. doi:10.1586/ern.11.68 **4.** 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. doi:10.1186/s12883-016-0609-0 **5.** Suavé WM. Recognizing and treating pseudobulbar affect. *CNS Spectr*. 2016;21(S1):34-44. doi:10.1017/S1092852916000791. **6.** Colamonico J, Formella A, Bradley W. Pseudobulbar affect: burden of illness in the USA. *Adv Ther*. 2012;29(9):775-798. doi:10.1007/s12325-012-0043-7 **7.** Kekere V, Qureshi D, Thanju A, Fouron P, Olupona T. Pseudobulbar affect mimicking depression: a case report. *Cureus*. 2022;14(6):e26235. doi:10.7759/cureus.26235 **8.** Centers for Disease Control and Prevention. ICD-10-CM tabular list of diseases and injuries. Accessed March 7, 2024. https://ftp.cdc.gov/pub/health_statistics/nchs/publications/ICD10CM/2022/icd10cm-tabular-2022-April-1.pdf **9.** Pioro EP, Brooks BR, Cummings J, et al. Dextromethorphan plus ultra low-dose quinidine reduces pseudobulbar affect. *Ann Neurol*. 2010;68(5):693-702. doi:10.1002/ana.22093 **10.** Drug Enforcement Administration. Controlled substances. Diversion Control Division. Accessed March 7, 2024. https://www.deadiversion.usdoj.gov/schedules/orangebook/c_cs_alpha.pdf **11.** Data on file (NUE-007).

IMPORTANT SAFETY INFORMATION (cont'd)

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.

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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 FULL PRESCRIBING INFORMATION.

MARY BETH
PATIENT LIVING WITH PBA

CAROL
PATIENT LIVING WITH PBA

SEQUENA
PATIENT LIVING WITH PBA

WHEN WAS THE LAST TIME YOU DIAGNOSED AND TREATED A PATIENT WITH PBA?

NUEDEXTA provided significant reduction in PBA episodes[1]

Adverse events were generally mild to moderate[1,4]

NUEDEXTA has broad insurance coverage and copay savings for eligible patients[11]

IMPORTANT SAFETY INFORMATION (cont'd)

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