

Medicinal product no longer authorised

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

NUEDEXTA 15 mg/9 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains dextromethorphan hydrobromide monohydrate, equivalent to 15.41 mg dextromethorphan and quinidine sulfate dihydrate, equivalent to 8.69 mg quinidine.

Excipient with known effect:

Each hard capsule contains 119.1 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule

Brick red gelatin capsule, size 1, with “DMQ / 20-10” printed in white ink on the capsule.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

NUEDEXTA is indicated for the symptomatic treatment of pseudobulbar affect (PBA) in adults (see section 4.4). Efficacy has only been studied in patients with underlying Amyotrophic Lateral Sclerosis or Multiple Sclerosis (see section 5.1).

4.2 Posology and method of administration

Posology

The recommended starting dose is NUEDEXTA 15 mg/9 mg once daily. The recommended dose titration schedule is outlined below:

- Week 1 (day 1-7):
The patient should take one NUEDEXTA 15 mg/9 mg capsule once daily, in the morning, for the initial 7 days.
- Weeks 2-4 (day 8-28):
The patient should take one NUEDEXTA 15 mg/9 mg capsule, two times per day, one in the morning and one in the evening, 12-hours apart, for 21 days.
- From Week 4 on:
If the clinical response with NUEDEXTA 15 mg/9 mg is adequate, the dose taken in weeks 2-4 should be continued.

If the clinical response with NUEDEXTA 15 mg/9 mg is inadequate, NUEDEXTA 23 mg/9 mg should be prescribed, taken two times per day, one in the morning and one in the evening, 12 hours apart.

The maximum daily dose from week 4 onwards is NUEDEXTA 23 mg/9 mg, twice daily.

In case a dose is missed, patients should not take an additional dose, but take the prescribed next dose at the usual time. No more than 2 capsules should be taken in any 24-hour period, with 12 hours between each dose.

Special populations

Elderly patients

Clinical studies did not include a sufficient number of patients aged ≥ 65 years to conclusively determine whether they respond differently in terms of efficacy and safety. A population pharmacokinetic analysis revealed similar pharmacokinetics in patients < 65 years and those ≥ 65 years of age (see section 5.2).

Patients with renal and hepatic impairment

Dose adjustment is not required in patients with mild to moderate renal or hepatic impairment (see section 4.4). However, as there was a trend toward increased incidence of adverse reactions in patients with moderate hepatic impairment, additional monitoring of adverse reactions is advised in these patients. In patients with severe hepatic impairment (Child-Pugh C) or severe renal impairment (Creatinine Clearance < 30 mL/min/1.73m²), the potential risks associated with the use of this medicine should be assessed against the medical need (see section 5.2).

CYP2D6 genotype

Dose adjustment is not required in patients with a non-functional CYP2D6 enzyme, referred to as poor metabolisers (PMs). Dose adjustment is not required in patients with increased CYP2D6 activity, referred to as ultra-rapid metabolisers (UMs), see section 5.2. In the event of inadequate clinical response, see recommended dose titration schedule.

Paediatric population

There is no relevant use of NUEDEXTA in the paediatric population for the symptomatic treatment of pseudobulbar affect.

Method of administration

The capsules should be taken orally at about the same time each day. When taking two capsules within 24 hours, the recommended dose interval is 12 hours. The capsules can be taken either with or without food.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

Patients with a history of quinidine-, quinine-, mefloquine-induced thrombocytopenia, hepatitis, bone marrow depression or lupus-like syndrome (see section 4.4).

Patients receiving concomitant treatment with quinidine, quinine, or mefloquine (see section 4.5).

Patients with a prolonged QT interval, congenital long QT syndrome or a history suggestive of torsades de pointes ventricular tachycardia (see section 4.4).

Patients receiving concomitant treatment with thioridazine, a medicinal product that both significantly prolongs QT interval and is primarily metabolized by CYP2D6. Interaction with NUEDEXTA may result in an increased effect on QT interval (see sections 4.4 and 4.5).

Patients with complete atrioventricular (AV) block without implanted pacemakers, or in patients who are at high risk of complete AV block (see section 4.4).

Patients taking monoamine oxidase inhibitors (MAOIs) or who have taken MAOIs within the preceding 14 days due to the risk of serious and possibly fatal drug interactions, including serotonin syndrome. Treatment with an MAOI should not be initiated until at least 14 days after stopping NUEDEXTA (see section 4.5).

4.4 Special warnings and precautions for use

Nuedexta is suitable only for the treatment of PBA, not for other causes of emotional lability. PBA is a consequence of neurological diseases affecting the brain, or brain, injury and is defined by episodes of involuntary, uncontrollable emotional expressions of laughing and/or crying that are incongruous or disproportionate to the patient's emotional state or mood. Before treatment with Nuedexta is initiated patients must be fully evaluated to confirm the diagnosis of PBA. Central to the diagnosis are the presence of an underlying neurological condition known to cause PBA, and confirmation that the episodes of emotional expression do not reflect the patient's emotional state or mood.

Thrombocytopenia

Quinidine at higher doses than in NUEDEXTA can cause immune-mediated thrombocytopenia that can be severe or fatal. The risk of thrombocytopenia in association with the lower dose of quinidine in NUEDEXTA is unknown. Non-specific symptoms, such as light-headedness, chills, fever, nausea, and vomiting, can precede or occur with thrombocytopenia. NUEDEXTA should be discontinued immediately if thrombocytopenia occurs, unless the thrombocytopenia is clearly not drug-related. Likewise, this medicinal product should not be restarted in sensitised patients, because more rapid and more severe thrombocytopenia than the original episode can occur. It should not be used if immune-mediated thrombocytopenia from structurally related active substances including quinine and mefloquine is suspected, as cross-sensitivity can occur. Quinidine-associated thrombocytopenia usually, but not always, resolves within a few days of discontinuation of the sensitising medicinal product.

Other hypersensitivity reactions

Quinidine at higher doses has also been associated with a lupus-like syndrome involving polyarthritis, sometimes with a positive antinuclear antibody test. Other associations include rash, bronchospasm, lymphadenopathy, haemolytic anaemia, vasculitis, uveitis, angioedema, agranulocytosis, the sicca syndrome, myalgia, elevation in serum levels of skeletal-muscle enzymes, and pneumonitis. Dextromethorphan can also be associated with hypersensitivity reactions, including urticaria, angioedema, and shortness of breath.

Hepatotoxicity

Hepatitis, including granulomatous hepatitis, has been reported in patients receiving quinidine, generally during the first few weeks of therapy. Fever may be a presenting symptom, and thrombocytopenia or other signs of hypersensitivity may also occur. NUEDEXTA should be discontinued if hepatitis occurs unless it is clearly not treatment related. Most cases remit when quinidine is withdrawn.

Cardiac effects

NUEDEXTA has the potential to cause QTc prolongation and hence torsades de pointes-type ventricular tachycardia. Hypokalemia and hypomagnesaemia should be corrected prior to initiation of therapy, and serum potassium and serum magnesium levels should be monitored during treatment if clinically indicated. When initiating treatment with NUEDEXTA in patients at risk of QT prolongation, electrocardiographic (ECG) evaluation of the QT interval should be conducted at

baseline and at 2 hours after the first dose administered in the fasted state (approximates to quinidine T_{max}). This includes patients with a family history of QT abnormality, concomitant medicinal products that prolong the QT interval, and patients with left ventricular hypertrophy (LVH) and/or left ventricular dysfunction (LVD). LVH and LVD are more likely to be present in patients with chronic hypertension, known coronary artery disease or history of stroke.

Concomitant medicinal products that both prolong the QT interval and are primarily metabolised by CYP2D6 (see below) are of particular potential concern. The concomitant use of thioridazine is contraindicated (see section 4.3). Caution is required when administering NUEDEXTA in combination with flecainide, chlorpromazine and haloperidol. The effect of the combination on the patient's QTc interval should be evaluated with pre- and post-dose ECGs.

ECG should be re-evaluated if risk factors for QTc prolongation change significantly during treatment with NUEDEXTA. If patients experience symptoms that could indicate the occurrence of cardiac arrhythmias, e.g. syncope or palpitations, NUEDEXTA should be discontinued pending further evaluation of the patient.

Concomitant use of CYP2D6 substrates/inhibitors

The quinidine in NUEDEXTA inhibits CYP2D6 in patients in whom CYP2D6 is not otherwise genetically absent or of low activity ("CYP2D6 Poor Metabolisers" see "Pharmacogenomics" in section 5.2). Because of this effect on CYP2D6, accumulation of parent drug substances and/or failure of active metabolite formation may affect the safety and/or the efficacy of medicinal products used concomitantly with NUEDEXTA that are metabolised by CYP2D6 (see section 4.5). Medicinal products that are dependent on CYP2D6 metabolism, especially those with a relatively narrow therapeutic index, should generally be avoided during treatment with NUEDEXTA, and patients must be instructed accordingly. When concomitant use of a CYP2D6 substrate drug is considered necessary, the dose of the CYP2D6 substrate should be reduced as appropriate according to the pharmacokinetics of the substrate involved (see section 4.5). A review of the patient's current medicines is an essential part of the evaluation of patients for whom treatment with NUEDEXTA is proposed.

Serotonin syndrome

When NUEDEXTA is used with other serotonergic medicines, the risk of "serotonin syndrome" may be increased due to pharmacodynamic interaction. Symptoms of serotonin syndrome include altered mental status, hypertension, restlessness, myoclonus, hyperthermia, hyperreflexia, diaphoresis, shivering, and tremor. Treatment should be discontinued if these symptoms occur. Combination with MAOIs is contraindicated (see section 4.3). Tricyclic antidepressants (TCAs e.g. desipramine, nortriptyline, imipramine, amitriptyline) are metabolised by CYP2D6 and therefore are also subject to pharmacokinetic interaction with quinidine. Given the pharmacodynamic and pharmacokinetic interactions, concomitant use of NUEDEXTA and TCAs is not recommended due to the elevated risk of serotonin syndrome (see section 4.5). Caution should be exercised if patients are treated with concomitant selective serotonin reuptake inhibitors (SSRIs).

Dizziness

NUEDEXTA may cause dizziness (see section 4.8). Precautions to reduce the risk of falls should be taken, particularly for patients with motor impairment affecting gait or a history of falls.

Anticholinergic effects of quinidine

Patients should be monitored for worsening clinical condition in myasthenia gravis and other conditions that may be adversely affected by anticholinergic effects.

Drug abuse and dependence

Dextromethorphan is a low-affinity uncompetitive NMDA antagonist and sigma-1 receptor agonist that has not been systematically studied in animals or humans for its potential for abuse, tolerance, or physical dependence. However, cases of dextromethorphan abuse have been reported, predominately in adolescents.

Due to the possibility of dextromethorphan abuse, physicians should evaluate patients for a history of drug abuse, and observe such patients closely for signs of misuse or abuse (e.g. development of tolerance, increases in dose, drug-seeking behaviour).

In addition, the maintenance of the clinical effect of NUEDEXTA in the patient should be regularly monitored in the long-term against its tolerability, in order to ascertain the continued benefit of the product.

Lactose warning

NUEDEXTA contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

MAOIs

NUEDEXTA must not be used with monoamine oxidase inhibitors (MAOIs), such as phenelzine and moklobemide, or in patients who have taken MAOIs within the preceding 14 days due to the risk of serotonin syndrome (see section 4.3).

CYP3A4 inhibitors

Quinidine is metabolised by CYP3A4. Concomitant administration of medicines that inhibit CYP3A4 can be expected to increase plasma levels of quinidine, which could increase risk relating to QTc prolongation. Strong and moderate CYP3A4 inhibitors should be avoided during treatment with NUEDEXTA. They include, but are not limited to, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, and verapamil. If concomitant treatment with strong or moderate CYP3A4 inhibitors is considered necessary, it is recommended that electrocardiographic (ECG) evaluation of the QT interval be carried out before NUEDEXTA is administered and at appropriate time point(s) subsequently.

Liver enzyme inducers

Quinidine is metabolised by CYP3A4. Potent CYP3A4 inducers (e.g. rifampicin, phenytoin, phenobarbital, carbamazepine, St John's wort/*Hypericum perforatum*) may accelerate the metabolism of quinidine, resulting in lower plasma concentrations and hence decreased inhibition of CYP2D6. This may lead to lower potentially subtherapeutic plasma concentrations of dextromethorphan and decreased efficacy of NUEDEXTA.

CYP2D6 substrates

Quinidine is a potent inhibitor of CYP2D6. Treatment with NUEDEXTA may therefore result in elevated plasma levels and accumulation of co-administered medicinal products that undergo extensive CYP2D6 metabolism. CYP2D6 substrates include certain beta-blockers such as metoprolol, antipsychotics such as haloperidol, perphenazine and aripiprazole, antidepressants such as nortriptyline, imipramine, amitriptyline and desipramine, the chemotherapeutic tamoxifen, and the noradrenaline transporter inhibitor atomoxetine. Thioridazine, a CYP2D6 substrate that also prolongs the QT interval is contraindicated (see section 4.3). Concomitant use of flecainide, chlorpromazine or haloperidol, CYP2D6 substrates that also prolong QT interval, requires caution (see section 4.4).

In the case of pro-drugs whose actions are mediated by the CYP2D6-produced metabolites (for example, codeine and hydrocodone, whose analgesic and antitussive effects appear to be mediated by morphine and hydromorphone, respectively), efficacy may be substantially reduced by NUEDEXTA due to inhibition of CYP2D6 and hence impaired formation of the active metabolite.

Drug interactions with desipramine and paroxetine have been studied in controlled clinical trials with a higher dose combination of dextromethorphan/quinidine (dextromethorphan 23 mg/ quinidine 26 mg) than in this medicinal product; study results are described below. No other drug interactions with CYP2D6 substrates have been systematically investigated.

Desipramine (CYP2D6 substrate)

The tricyclic antidepressant desipramine is metabolized primarily by CYP2D6. A drug-drug interaction study was conducted between a higher combination dose of dextromethorphan/quinidine (dextromethorphan 23 mg/quinidine 26 mg) and desipramine 25 mg. The combination dose of dextromethorphan/quinidine increased steady state desipramine levels approximately 8-fold. Concomitant use of NUEDEXTA and TCAs is not recommended (see section 4.4).

Paroxetine (CYP2D6 inhibitor and substrate)

The selective serotonin reuptake inhibitor (SSRI) paroxetine is metabolized primarily by CYP2D6 and is also a potent CYP2D6 inhibitor. In a drug-drug interaction study, a higher combination dose of dextromethorphan/quinidine (dextromethorphan 23 mg/quinidine 26 mg) was added to paroxetine at steady state. Paroxetine exposure (AUC_{0-24}) increased by 1.7 fold and C_{max} increased by 1.5 fold. If NUEDEXTA and paroxetine are prescribed concomitantly, the initial dose of paroxetine should be reduced. The dose of paroxetine can then be adjusted based on clinical response, however, dosage above 35 mg/day is not recommended.

NMDA receptor antagonists (memantine)

Both dextromethorphan and memantine are antagonists of the *N*-methyl-D-aspartate (NMDA) receptor which could theoretically result in an additive effect at NMDA receptors and potentially an increased incidence of adverse reactions. A drug-drug interaction study was conducted between a higher combination dose of dextromethorphan/quinidine (dextromethorphan 23 mg/quinidine 26 mg) and memantine 20 mg/day. There was no significant difference in the plasma concentrations of dextromethorphan and dextrorphan before and after the administration of memantine, and there was no effect on the plasma concentrations of memantine before and after the administration of dextromethorphan/quinidine. Plasma concentrations of quinidine increased 20-30% when memantine was added. No pharmacodynamic interactions were apparent.

Digoxin and other P-glycoprotein substrates

Quinidine is an inhibitor of P-glycoprotein. Concomitant administration of quinidine with digoxin, a P-glycoprotein substrate, results in serum digoxin levels that may be as much as doubled. Plasma digoxin concentrations should be closely monitored in patients taking NUEDEXTA concomitantly, and the digoxin dose reduced, as necessary. Other P-gp substrates for which a dose reduction may be considered include ticagrelor and dabigatran-etexilate.

Alcohol

Caution should be used when this medicinal product is taken in combination with alcohol or other centrally acting medicinal products that might increase the risk of adverse reactions such as somnolence and dizziness.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of NUEDEXTA in pregnant women. Studies in animals (rats and rabbits) have shown developmental toxicity, including teratogenicity and embryolethality (see section 5.3).

As this medicinal product may cause foetal harm, it is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

Quinidine is excreted in human milk and it is unknown whether dextromethorphan is excreted in human milk. A risk to the newborns/infants cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from NUEDEXTA therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

In pre-clinical studies no effect on fertility was observed in male and female rats (see section 5.3).

4.7 Effects on ability to drive and use machines

NUEDEXTA has no or negligible influence on the ability to drive and use machines. Patients should be warned about the potential for CNS-related effects like somnolence, dizziness and syncope or impaired vision (see section 4.8), and advised not to drive or operate machinery if these symptoms occur.

4.8 Undesirable effects

Summary of the safety profile

The safety of NUEDEXTA was investigated in a double-blind, randomized, placebo-controlled, multicenter study over 12 weeks in 326 PBA patients with underlying ALS (60%) or MS (40%) and in a follow-up open-label extension phase with a patient subgroup of this study (253 patients) for an additional 84 days.

The most commonly reported adverse reactions are gastrointestinal disorders (such as diarrhoea, nausea), nervous system disorders (such as dizziness, headache, somnolence) and fatigue.

Serious adverse reactions have been reported for NUEDEXTA; these are muscle spasticity, respiratory depression and decreased oxygen saturation in the blood.

Ten patients discontinued study treatment due to ADRs, one of these patients due to a serious ADR (worsening muscle spasticity).

Tabulated summary of adverse reactions

The adverse reactions considered at least possibly related to treatment with NUEDEXTA in the placebo-controlled and the open-label extension phase of the above mentioned clinical study are listed below by body system organ class and frequency.

- very common ($\geq 1/10$)
- common ($\geq 1/100$ to $< 1/10$)
- uncommon ($\geq 1/1,000$ to $< 1/100$)
- rare ($\geq 1/10,000$ to $< 1/1,000$)
- very rare ($< 1/10,000$)

System Organ Class	Frequency	Adverse Reaction
Metabolism and nutrition disorders	Uncommon	Decreased appetite
	Rare	Anorexia
Psychiatric disorders	Uncommon	Anxiety
	Rare	<ul style="list-style-type: none">• Bruxism, Confusional state, Depressed mood, Depression, Disorientation, Early morning awakening, Flat affect, Hallucination, Impulsive behaviour, Indifference, Insomnia, Restlessness, Sleep disorder
Nervous system disorders	Common	Dizziness, Headache, Somnolence

	Uncommon	Dysgeusia, Hypersomnia, Muscle spasticity, Syncope, Fall
	Rare	Balance disorder, Coordination abnormal, Dysarthria, Motor dysfunction, Paraesthesia, Paraparesis, Sedation
Eye disorders	Rare	Diplopia, Vision blurred
Ear and labyrinth disorders	Uncommon	Motion sickness, Tinnitus
Cardiac disorders	Uncommon	Atrioventricular block first degree, Electrocardiogram QT prolonged
	Rare	<ul style="list-style-type: none"> Myocardial infarction, Palpitations, Ventricular extrasystoles
Respiratory, thoracic and mediastinal disorders	Rare	<ul style="list-style-type: none"> Epistaxis, Pharyngolaryngeal pain, Respiratory depression, Rhinorrhoea, Yawning
Gastrointestinal disorders	Common	Diarrhoea, Nausea
	Uncommon	Abdominal pain, Constipation, Dry mouth, Flatulence, Stomach discomfort, Vomiting
	Rare	<ul style="list-style-type: none"> Abnormal faeces, Dyspepsia, Gastritis, Hypoaesthesia oral, Paraesthesia oral, Proctalgia, Tongue dry
Hepatobiliary disorders	Uncommon	Increased hepatic enzymes (GGT, AST, ALT)
	Rare	Cholelithiasis, blood bilirubin increased, Liver function test abnormal,
Skin and subcutaneous tissue disorders	Uncommon	Rash
	Rare	Erythema, Hyperhidrosis, Hypoaesthesia facial, Night sweats
Musculoskeletal and connective tissue disorders	Uncommon	Muscle spasms
	Rare	Musculoskeletal stiffness, Myalgia, Neck pain, Pain in extremity
Renal and urinary disorders	Rare	Pollakiuria
Reproductive system and breast disorders	Rare	Sexual dysfunction
General disorders and administration site conditions	Common	Fatigue
	Uncommon	Asthenia, Irritability
	Rare	Chest discomfort, Chest pain, Chills, Feeling hot, Gait disturbance, Influenza like illness, Pyrexia, Oxygen saturation decreased
Injury, poisoning and procedural complications	Rare	Skeletal injury

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

4.9 Overdose

Evaluation and treatment of overdose is based on experience with the individual components, dextromethorphan and quinidine. Metabolism of dextromethorphan is inhibited by quinidine, such that adverse reactions of overdose due to NUEDEXTA might be more severe or more persistent compared to overdose of dextromethorphan alone.

During development of this medicinal product, dose combinations of dextromethorphan/quinidine containing up to 6-times higher dextromethorphan dose and 12-times higher quinidine dose were studied. The most common adverse reactions were mild to moderate nausea, dizziness, and headache.

Dextromethorphan

Adverse reactions of dextromethorphan overdose include nausea, vomiting, stupor, coma, respiratory depression, seizures, tachycardia, hyperexcitability, and toxic psychosis. Other adverse reactions include ataxia, nystagmus, dystonia, blurred vision, and changes in muscle reflexes.

Dextromethorphan may increase the risk of serotonin syndrome, and this risk is increased by overdose, particularly if taken with other serotonergic agents, SSRIs or tricyclic antidepressants.

Quinidine

The most important effects of acute overdoses are ventricular arrhythmias and hypotension. Other signs and symptoms of overdose may include vomiting, diarrhoea, tinnitus, high-frequency hearing loss, vertigo, blurred vision, diplopia, photophobia, headache, confusion and delirium.

While therapeutic doses of quinidine for treatment of cardiac arrhythmia or malaria are generally ≥ 10 -fold higher than the dose of quinidine in this medicinal product, potentially fatal cardiac arrhythmia, including torsades de pointes, can occur at quinidine exposures that are possible from NUEDEXTA overdose.

Treatment of overdose

Quinidine

The treatment of cardiac effects (haemodynamically unstable polymorphic ventricular tachycardia (including torsades de pointes)) is either immediate cardioversion or immediate overdrive pacing. Other antiarrhythmics with Class I (procainamide) or Class III activities should (if possible) be avoided. Treatment of hypotension and of other signs and symptoms should be directed at symptomatic and supportive measures. Administration of activated charcoal in conventional dose of 1 g/kg, administered every 2 to 6 hours as a slurry with 8 mL/kg of tap water may enhance the systemic elimination of quinidine; this measure should be avoided if an ileus is present. Methods as to acidify the urine and dialysis are of no demonstrated benefit. Drugs that delay elimination of quinidine (cimetidine, carbonic anhydrase inhibitors, thiazide diuretics) should be withdrawn unless absolutely required.

Dextromethorphan

Treatment of dextromethorphan overdose should be directed at symptomatic and supportive measures. Gastric lavage may be of use.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other nervous system drugs; ATC code: N07XX59

Dextromethorphan hydrobromide is the pharmacologically active ingredient that acts on the central nervous system (CNS). Quinidine sulfate is a specific inhibitor of CYP2D6-dependent oxidative metabolism used to increase the systemic bioavailability of dextromethorphan.

Mechanism of action

The exact mechanism by which dextromethorphan exerts therapeutic effects in patients with pseudobulbar affect is unknown. Quinidine increases plasma levels of dextromethorphan by competitively inhibiting cytochrome P450 2D6 (CYP2D6), which catalyses a major biotransformation pathway for dextromethorphan.

Pharmacodynamic effects

Dextromethorphan is a sigma-1 receptor agonist and an uncompetitive NMDA receptor antagonist. In addition it shows affinity for the serotonin transporter (SERT) and for the 5-HT1B/D receptor. Through its binding to the NMDA, sigma-1, SERT and 5-HT1B/D receptors, dextromethorphan is thought to have a modulatory effect on neurotransmission involving glutamate, monoamines (including serotonin), as well as ion channel function.

Clinical efficacy and safety

The efficacy of dextromethorphan/quinidine for the treatment of PBA was demonstrated in three randomised, controlled, double-blind, multicentre clinical trials in PBA subjects with underlying amyotrophic lateral sclerosis (ALS) or multiple sclerosis (MS). Eligible patients had a diagnosis of PBA defined by episodes of involuntary, uncontrollable emotional expressions of laughing and/or crying that are incongruous or disproportionate to their emotional state or mood.

In all studies, the efficacy endpoints were “Count of episodes of laughing and crying” (PBA episodes) and subject scores on the Center for Neurologic Studies - Lability Scale (CNS-LS), a validated 7-item, self-administered questionnaire that provides a quantitative measure of the frequency and severity of PBA. CNS-LS scores range from a minimum of 7 (no symptoms) to a maximum of 35.

- Pivotal study (07-AVR-123)

In this placebo-controlled 12-week study, 326 PBA subjects with underlying ALS or MS were randomized to receive NUEDEXTA 15 mg / 9 mg (n=107), NUEDEXTA 23 mg / 9 mg (n=110), or placebo (n=109) for 12 weeks.

Subjects were 25 to 80 years of age with a mean age of approximately 51 years. Approximately 74% were Caucasian, 4% were Black, 1% were Asian and 19% were of Hispanic origin. 60% of subjects had underlying ALS and 40% of subjects had underlying MS. All subjects had clinically relevant PBA symptoms, quantified as CNS-LS score of 13 or more.

Mean baseline daily PBA episode rates (calculated from the total number of episodes reported for up to 7 pre-treatment days) were 4.7 in the NUEDEXTA 23 mg/9 mg group, 6.8 in the NUEDEXTA 15 mg/9 mg group, and 4.5 in the placebo group.

Mean baseline CNS-LS scores were 19.8 in the NUEDEXTA 23 mg /9 mg group, 21.0 in the NUEDEXTA 15 mg /9 mg group, and 19.9 in the placebo group.

To evaluate long-term data, 253 subjects who completed the double-blind study phase had the option of entering an open-label extension phase, receiving NUEDEXTA 23 mg /9 mg for another 84 days.

The frequency of PBA episodes as measured by “Count of Episodes” in both NUEDEXTA treatment groups decreased significantly throughout the course of the study by an incremental reduction of 47% and 49% relative to placebo, respectively (p <0.0001 for both comparisons).

The least-squares mean CNS-LS scores were significantly reduced at the end of treatment in both treatment groups compared to placebo (8.2 point reduction for NUEDEXTA 23 mg /9 mg, 7.5 point reduction for NUEDEXTA 15 mg /9 mg, 5.7 point reduction for placebo). The p-value for NUEDEXTA 23 mg /9 mg vs placebo was p=0.0002 and for NUEDEXTA 15 mg /9 mg vs placebo was p=0.008.

The 12-week open-label phase of the study (during which all subjects received NUEDEXTA 23 mg / 9 mg) showed persistence of the effect observed in the placebo controlled period.

- Studies with Higher Dose Combinations of dextromethorphan / quinidine

Two additional phase III studies were conducted using a higher dose combination of dextromethorphan 23 mg/quinidine 26 mg. The higher dose of quinidine used in these studies would have resulted in approximately a 1.6 fold greater exposure to of dextromethorphan than with NUEDEXTA 23 mg/ 9 mg.

The first was a 4-week study in PBA subjects with underlying ALS, and the second was a 12-week study in subjects with underlying MS. In both studies the primary outcome measure, CNS-LS, and the secondary outcome measure, “count of episodes of laughing and crying”, were statistically significantly decreased by the dextromethorphan/quinidine combination.

A 12 month open-label safety study, also using the higher dose combination of dextromethorphan 23 mg /quinidine 26 mg, included 553 subjects with PBA associated with thirty-four different neurological conditions. Approximately 30% of study participants carried diagnoses other than ALS and MS, including stroke, traumatic brain injury, Parkinson’s disease, Alzheimer’s disease and other dementia, primary lateral sclerosis, progressive bulbar palsy, and progressive supranuclear palsy. Only safety data were collected in this study; no new safety signals were identified.

- Studies to Assess Cardiac Effects

The effect of NUEDEXTA 23 mg / 9 mg (for 7 consecutive doses) on QTc prolongation was evaluated in a randomised, double-blind (except for moxifloxacin), placebo- and positive-controlled (400 mg moxifloxacin) crossover thorough QT study in 50 fasted normal healthy men and women with CYP2D6 extensive metabolizer (EM) genotype. Mean changes in QTcF were 6.8 ms for NUEDEXTA 23 mg/ 9 mg and 9.1 ms for the reference positive control (moxifloxacin). The maximum mean (95% upper confidence bound) difference from placebo after baseline correction was 10.2 (12.6) ms. This test dose is adequate to represent the steady state exposure in patients with CYP2D6 extensive metabolizer phenotype.

The effects of supra-therapeutic doses of dextromethorphan /quinidine (23 mg /26 mg and 46 mg / 53 mg, for 7 consecutive doses) on QTc prolongation were evaluated in a randomised, placebo-controlled, double-blind, crossover design with an additional open-label positive control (400 mg moxifloxacin) arm in 36 healthy volunteers. The maximum mean (95% upper confidence bound) differences from placebo after baseline-correction were 10.2 (14.6) and 18.4 (22.7) ms following dextromethorphan/quinidine doses of 23 mg /26 mg and 46 mg /53 mg, respectively. The supra-therapeutic doses are adequate to represent quinidine exposure increases due to drug-drug interactions and organ dysfunctions.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with NUEDEXTA in all subsets of the paediatric population in PBA (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Following single and repeated combination doses of NUEDEXTA 23 mg / 9 mg, subjects had an approximately 20-fold increase in dextromethorphan exposure compared to subjects given dextromethorphan without quinidine.

Following repeated doses of NUEDEXTA 23 mg / 9 mg and NUEDEXTA 15 mg / 9 mg, maximal plasma concentrations (C_{max}) of dextromethorphan are reached approximately 3 to 4 hours after dosing and maximal plasma concentrations of quinidine are reached approximately 2 hours after dosing.

In extensive metabolizers, mean C_{max} and AUC_{0-12} values of dextromethorphan and dextrorphan increased as doses of dextromethorphan increased from 15 mg to 23 mg and mean C_{max} and AUC_{0-12} values of quinidine were similar.

The mean plasma C_{max} of quinidine following NUEDEXTA 15 mg / 9 mg twice daily in subjects with PBA was 1 to 3% of the therapeutic concentrations associated with antiarrhythmic efficacy (2 to 5 $\mu\text{g/mL}$).

NUEDEXTA may be taken without regard to meals as food does not affect the exposure of dextromethorphan and quinidine significantly.

Distribution

After administration of the combination product, protein binding remains essentially the same as that after administration of the individual components; dextromethorphan is approximately 60-70% protein bound, and quinidine is approximately 80-89% protein bound.

Biotransformation and elimination

Dextromethorphan is rapidly metabolized by CYP2D6 to its primary metabolite, dextrorphan, which is rapidly glucuronidated and renally eliminated. The quinidine component of NUEDEXTA serves to selectively inhibit CYP2D6-dependent oxidative metabolism of dextromethorphan, thus increasing dextromethorphan plasma concentrations. In the presence of quinidine, CYP3A4-dependent oxidative metabolism is believed to play a greater role in dextromethorphan elimination.

After administration of NUEDEXTA 23 mg/9 mg to 14 extensive metabolizers, the elimination half-life of dextromethorphan was 18.8 hours and the elimination half-life of quinidine was 9.6 hours.

Quinidine is metabolized by CYP3A4. There are several hydroxylated metabolites of quinidine. The major metabolite is 3-hydroxyquinidine, which is considered to be at least half as pharmacologically active as quinidine with respect to cardiac effects such as QT prolongation. There are currently limited data on the magnitude of the effect of CYP3A4 inhibitors on the pharmacokinetic parameters of quinidine and its metabolites, including the potential for accumulation at steady state.

When the urine pH is less than 7, about 20% of administered quinidine appears unchanged in the urine, but this fraction drops to as little as 5% when the urine is more alkaline. Renal clearance involves both glomerular filtration and active tubular secretion, moderated by (pH-dependent) tubular reabsorption.

Linearity/non-linearity

Plasma concentrations of dextromethorphan and dextrorphan are proportional to dextromethorphan dose in the presence of a fixed dose of quinidine such as that contained in NUEDEXTA. Quinidine plasma concentrations are proportional to quinidine dose.

In vitro CYP P450 interaction studies

The potential for dextromethorphan and quinidine to inhibit or induce cytochrome P450 *in vitro* were evaluated in human microsomes. Dextromethorphan did not inhibit (<20% inhibition) any of the tested isoenzymes: CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4 in human liver microsomes at concentrations up to 5 μM . Quinidine did not inhibit (<30% inhibition) CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2E1, or CYP3A4 in human microsomes at concentrations up to 5 μM . Quinidine inhibited CYP2D6 with a half maximal inhibitory concentration (IC_{50}) of less than 0.05 μM . Neither dextromethorphan nor quinidine induced CYP1A2, CYP2B6 or CYP3A4 in human hepatocytes at concentrations up to 4.8 μM .

In vitro transporter interaction studies

Based on the results of transporter inhibition studies drug-drug interactions related to dextromethorphan inhibition of P-gp, OATP1B1, OATP1B3, OCT2, OAT1, OAT3 or BSEP are not expected during treatment with NUEDEXTA. Dextromethorphan has been shown to be a

mild/moderate inhibitor of the OCT1 transporter *in vitro*. The clinical relevance of this observation to drugs that are OCT1 substrates, such as metformin, is unknown.

Based on literature citations, drug-drug interactions as a result of quinidine inhibition of OATP1B1, OCT1, OCT2, OAT3, BSEP, MATE1, and MATE2-K are not expected.

Special Populations

Elderly patients

The pharmacokinetics of dextromethorphan/quinidine have not been investigated systematically in elderly subjects (aged >65 years) although such subjects were included in the clinical programme (14% ≥65 years, 2% ≥75 years).

A population pharmacokinetic analysis of 170 subjects (148 subjects <65 years old and 22 subjects ≥65 years old) administered dextromethorphan 23 mg / quinidine 26 mg revealed similar pharmacokinetics in subjects <65 years and those ≥65 years of age.

Gender

A population pharmacokinetic analysis based on data from 109 subjects (75 male; 34 female) showed no apparent gender differences in the pharmacokinetics of dextromethorphan/quinidine.

Race

A population pharmacokinetic analysis of race with 109 subjects (21 Caucasian; 71 Hispanic; 18 Black) revealed no apparent racial differences in the pharmacokinetics of dextromethorphan/quinidine.

Renal impairment

In a study of a combination dose of dextromethorphan 23 mg / quinidine 26 mg twice daily in 12 subjects with mild (CLCR 50-80 mL/min) or moderate (CLCR 30-50 mL/min) renal impairment (6 each) compared to 9 healthy subjects (matched in gender, age, and weight range to impaired subjects), subjects showed little difference in quinidine or dextromethorphan pharmacokinetics compared to healthy subjects. Dose adjustment is therefore not required in mild or moderate renal impairment. Dextromethorphan / quinidine has not been studied in patients with severe renal impairment.

Hepatic impairment

In a study of a combination dose of dextromethorphan 23 mg / quinidine 26 mg twice daily in 12 subjects with mild or moderate hepatic impairment (as indicated by the Child-Pugh method; 6 each) compared to 9 healthy subjects (matched in gender, age, and weight range to impaired subjects), subjects with moderate hepatic impairment showed similar dextromethorphan AUC and C_{max} and clearance compared to healthy subjects. Mild to moderate hepatic impairment had little effect on quinidine pharmacokinetics. Quinidine clearance is unaffected, although there is an increased volume of distribution that leads to an increase in the elimination half-life. Patients with moderate hepatic impairment showed an increased frequency of adverse reactions. Therefore, dosage adjustment is not required in patients with mild and moderate hepatic impairment, although additional monitoring for adverse reactions should be considered in patients with moderate hepatic impairment. Dose increase, if warranted, should be undertaken with caution in these patients. Neither dextromethorphan alone nor dextromethorphan/quinidine has been evaluated in patients with severe hepatic impairment.

Pharmacogenomics

The quinidine component is intended to inhibit CYP2D6 so that higher exposure to dextromethorphan can be achieved compared to when dextromethorphan is given alone. Approximately 7-8% of individuals of Caucasian descent, 3-6% of Black African descent, 2-3% of Arab descent and 1-2% of Asian descent generally lack the capacity to metabolize CYP2D6 substrates and are classified as Poor Metabolizer (PMs). The quinidine component is not expected to contribute to the effectiveness of NUDEXTA in PMs, but adverse reactions of the quinidine component are still possible.

Approximately 1-10% of individuals of Caucasian descent, 5-30% of Black African descent, 12-40% of Arab descent and 1% of Asian descent exhibit increased metabolic activity for CYP2D6 substrates and are classified as Ultra-rapid Metabolizer (UMs). In such UM patients, dextromethorphan is rapidly metabolised, leading to lower, potentially subtherapeutic concentrations.

Paediatric population

The pharmacokinetics of dextromethorphan/quinidine in paediatric patients has not been studied (see section 5.1).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for a genotoxicity or carcinogenic potential, nor for fertility impairment.

In embryo-fetal and developmental toxicity studies (rats and rabbits) with dextromethorphan hydrobromide/quinidine sulfate, abnormalities were observed at mid and high dose with reduced ossification from the lowest dose in rats which is approximately 1 and 50 times the human dose of 30/18 mg/day on a mg/m² basis, respectively. The no effect dose in rabbits is 2 and 60 times higher than the RHD.

In the pre and post-natal developmental study, slight developmental delay was seen in offspring at the mid- and high-doses. Pup survival and pup weight were slightly decreased from the lowest dose corresponding approximately to 1 and 50 times the human dose of 30/18 mg/kg on a mg/m² basis, for dextromethorphan hydrobromide and quinidine sulfate, respectively.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content

Croscarmellose sodium
Cellulose, microcrystalline
Silica, colloidal anhydrous
Lactose monohydrate
Magnesium stearate

Capsule shell

Gelatin
Titanium dioxide (E171)
Red iron oxide (E172)

Printing ink

Shellac glaze (20% esterified)
Propylene glycol
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

High density polyethylene (HDPE) bottle with a child resistant polypropylene cap. Each bottle is packed in a carton.

Pack size: 60 capsules

Blister of a PVC based clear film with aluminium foil seal. Each blister is packed in a sleeve.

Pack size: 13 capsules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Jenson Pharmaceutical Services Limited
Carradine House, 237 Regents Park Road
N3 3LF London
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/833/001

EU/1/13/833/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>

1. NAME OF THE MEDICINAL PRODUCT

NUEDEXTA 23 mg/9 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains dextromethorphan hydrobromide monohydrate, equivalent to 23.11 mg dextromethorphan and quinidine sulfate dihydrate, equivalent to 8.69 mg quinidine.

Excipient with known effect:

Each hard capsule contains 109.2 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule

Brick red gelatin capsule, size 1, with “DMQ / 30-10” printed in white ink on the capsule and three white bands around the circumference.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

NUEDEXTA is indicated for the symptomatic treatment of pseudobulbar affect (PBA) in adults (see section 4.4). Efficacy has only been studied in patients with underlying Amyotrophic Lateral Sclerosis or Multiple Sclerosis (see section 5.1).

4.2 Posology and method of administration

Posology

The recommended starting dose is NUEDEXTA 15 mg/9 mg once daily. The recommended dose titration schedule is outlined below:

- Week 1 (day 1-7):
The patient should take one NUEDEXTA 15 mg/9 mg capsule once daily, in the morning, for the initial 7 days.
- Weeks 2-4 (day 8-28):
The patient should take one NUEDEXTA 15 mg/9 mg capsule, two times per day, one in the morning and one in the evening, 12-hours apart, for 21 days.
- From Week 4 on:
If the clinical response with NUEDEXTA 15 mg/9 mg is adequate, the dose taken in weeks 2-4 should be continued.

If the clinical response with NUEDEXTA 15 mg/9 mg is inadequate, NUEDEXTA 23 mg/9 mg should be prescribed, taken two times per day, one in the morning and one in the evening, 12 hours apart.

The maximum daily dose from week 4 onwards is NUEDEXTA 23 mg/9 mg, twice daily.

In case a dose is missed, patients should not take an additional dose, but take the prescribed next dose at the usual time. No more than 2 capsules should be taken in any 24-hour period, with 12 hours between each dose.

Special populations

Elderly patients

Clinical studies did not include a sufficient number of patients aged ≥ 65 years to conclusively determine whether they respond differently in terms of efficacy and safety. A population pharmacokinetic analysis revealed similar pharmacokinetics in patients < 65 years and those ≥ 65 years of age (see section 5.2).

Patients with renal and hepatic impairment

Dose adjustment is not required in patients with mild to moderate renal or hepatic impairment (see section 4.4). However, as there was a trend toward increased incidence of adverse reactions in patients with moderate hepatic impairment, additional monitoring of adverse reactions is advised in these patients. In patients with severe hepatic impairment (Child-Pugh C) or severe renal impairment (Creatinine Clearance < 30 mL/min/1.73m²), the potential risks associated with the use of this medicine should be assessed against the medical need (see section 5.2).

CYP2D6 genotype

Dose adjustment is not required in patients with a non-functional CYP2D6 enzyme, referred to as poor metabolisers (PMs). Dose adjustment is not required in patients with increased CYP2D6 activity, referred to as ultra-rapid metabolisers (UMs), see section 5.2. In the event of inadequate clinical response, see recommended dose titration schedule.

Paediatric population

There is no relevant use of NUEDEXTA in the paediatric population for the symptomatic treatment of pseudobulbar affect.

Method of administration

The capsules should be taken orally at about the same time each day. When taking two capsules within 24 hours, the recommended dose interval is 12 hours. The capsules can be taken either with or without food.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

Patients with a history of quinidine-, quinine-, mefloquine-induced thrombocytopenia, hepatitis, bone marrow depression or lupus-like syndrome (see section 4.4).

Patients receiving concomitant treatment with quinidine, quinine, or mefloquine (see section 4.5).

Patients with a prolonged QT interval, congenital long QT syndrome or a history suggestive of torsades de pointes ventricular tachycardia (see section 4.4).

Patients receiving concomitant treatment with thioridazine, a medicinal product that both significantly prolongs QT interval and is primarily metabolized by CYP2D6. Interaction with NUEDEXTA may result in an increased effect on QT interval (see sections 4.4 and 4.5).

Patients with complete atrioventricular (AV) block without implanted pacemakers, or in patients who are at high risk of complete AV block (see section 4.4).

Patients taking monoamine oxidase inhibitors (MAOIs) or who have taken MAOIs within the preceding 14 days due to the risk of serious and possibly fatal drug interactions, including serotonin syndrome. Treatment with an MAOI should not be initiated until at least 14 days after stopping NUEDEXTA (see section 4.5).

4.3 Special warnings and precautions for use

Nuedexta is suitable only for the treatment of PBA, not for other causes of emotional lability. PBA is a consequence of neurological diseases affecting the brain, or brain, injury and is defined by episodes of involuntary, uncontrollable emotional expressions of laughing and/or crying that are incongruous or disproportionate to the patient's emotional state or mood. Before treatment with Nuedexta is initiated patients must be fully evaluated to confirm the diagnosis of PBA. Central to the diagnosis are the presence of an underlying neurological condition known to cause PBA, and confirmation that the episodes of emotional expression do not reflect the patient's emotional state or mood.

Thrombocytopenia

Quinidine at higher doses than in NUEDEXTA can cause immune-mediated thrombocytopenia that can be severe or fatal. The risk of thrombocytopenia in association with the lower dose of quinidine in NUEDEXTA is unknown. Non-specific symptoms, such as light-headedness, chills, fever, nausea, and vomiting, can precede or occur with thrombocytopenia. NUEDEXTA should be discontinued immediately if thrombocytopenia occurs, unless the thrombocytopenia is clearly not drug-related. Likewise, this medicinal product should not be restarted in sensitised patients, because more rapid and more severe thrombocytopenia than the original episode can occur. It should not be used if immune-mediated thrombocytopenia from structurally related active substances including quinine and mefloquine is suspected, as cross-sensitivity can occur. Quinidine-associated thrombocytopenia usually, but not always, resolves within a few days of discontinuation of the sensitising medicinal product.

Other hypersensitivity reactions

Quinidine at higher doses has also been associated with a lupus-like syndrome involving polyarthritis, sometimes with a positive antinuclear antibody test. Other associations include rash, bronchospasm, lymphadenopathy, haemolytic anaemia, vasculitis, uveitis, angioedema, agranulocytosis, the sicca syndrome, myalgia, elevation in serum levels of skeletal-muscle enzymes, and pneumonitis. Dextromethorphan can also be associated with hypersensitivity reactions, including urticaria, angioedema, and shortness of breath.

Hepatotoxicity

Hepatitis, including granulomatous hepatitis, has been reported in patients receiving quinidine, generally during the first few weeks of therapy. Fever may be a presenting symptom, and thrombocytopenia or other signs of hypersensitivity may also occur. NUEDEXTA should be discontinued if hepatitis occurs unless it is clearly not treatment related. Most cases remit when quinidine is withdrawn.

Cardiac effects

NUEDEXTA has the potential to cause QTc prolongation and hence torsades de pointes-type ventricular tachycardia. Hypokalemia and hypomagnesaemia should be corrected prior to initiation of therapy, and serum potassium and serum magnesium levels should be monitored during treatment if clinically indicated. When initiating treatment with NUEDEXTA in patients at risk of QT prolongation, electrocardiographic (ECG) evaluation of the QT interval should be conducted at

baseline and at 2 hours after the first dose administered in the fasted state (approximates to quinidine T_{max}). This includes patients with a family history of QT abnormality, concomitant medicinal products that prolong the QT interval, and patients with left ventricular hypertrophy (LVH) and/or left ventricular dysfunction (LVD). LVH and LVD are more likely to be present in patients with chronic hypertension, known coronary artery disease or history of stroke.

Concomitant medicinal products that both prolong the QT interval and are primarily metabolised by CYP2D6 (see below) are of particular potential concern. The concomitant use of thioridazine is contraindicated (see section 4.3). Caution is required when administering NUEDEXTA in combination with flecainide, chlorpromazine and haloperidol. The effect of the combination on the patient's QTc interval should be evaluated with pre- and post-dose ECGs.

ECG should be re-evaluated if risk factors for QTc prolongation change significantly during treatment with NUEDEXTA. If patients experience symptoms that could indicate the occurrence of cardiac arrhythmias, e.g. syncope or palpitations, NUEDEXTA should be discontinued pending further evaluation of the patient.

Concomitant use of CYP2D6 substrates/inhibitors

The quinidine in NUEDEXTA inhibits CYP2D6 in patients in whom CYP2D6 is not otherwise genetically absent or of low activity ("CYP2D6 Poor Metabolisers" see "Pharmacogenomics" in section 5.2). Because of this effect on CYP2D6, accumulation of parent drug substances and/or failure of active metabolite formation may affect the safety and/or the efficacy of medicinal products used concomitantly with NUEDEXTA that are metabolised by CYP2D6 (see section 4.5). Medicinal products that are dependent on CYP2D6 metabolism, especially those with a relatively narrow therapeutic index, should generally be avoided during treatment with NUEDEXTA, and patients must be instructed accordingly. When concomitant use of a CYP2D6 substrate drug is considered necessary, the dose of the CYP2D6 substrate should be reduced as appropriate according to the pharmacokinetics of the substrate involved (see section 4.5). A review of the patient's current medicines is an essential part of the evaluation of patients for whom treatment with NUEDEXTA is proposed.

Serotonin syndrome

When NUEDEXTA is used with other serotonergic medicines, the risk of "serotonin syndrome" may be increased due to pharmacodynamic interaction. Symptoms of serotonin syndrome include altered mental status, hypertension, restlessness, myoclonus, hyperthermia, hyperreflexia, diaphoresis, shivering, and tremor. Treatment should be discontinued if these symptoms occur. Combination with MAOIs is contraindicated (see section 4.3). Tricyclic antidepressants (TCAs e.g. desipramine, nortriptyline, imipramine, amitriptyline) are metabolised by CYP2D6 and therefore are also subject to pharmacokinetic interaction with quinidine. Given the pharmacodynamic and pharmacokinetic interactions, concomitant use of NUEDEXTA and TCAs is not recommended due to the elevated risk of serotonin syndrome (see section 4.5). Caution should be exercised if patients are treated with concomitant selective serotonin reuptake inhibitors (SSRIs).

Dizziness

NUEDEXTA may cause dizziness (see section 4.8). Precautions to reduce the risk of falls should be taken, particularly for patients with motor impairment affecting gait or a history of falls.

Anticholinergic effects of quinidine

Patients should be monitored for worsening clinical condition in myasthenia gravis and other conditions that may be adversely affected by anticholinergic effects.

Drug abuse and dependence

Dextromethorphan is a low-affinity uncompetitive NMDA antagonist and sigma-1 receptor agonist that has not been systematically studied in animals or humans for its potential for abuse, tolerance, or physical dependence. However, cases of dextromethorphan abuse have been reported, predominately in adolescents.

Due to the possibility of dextromethorphan abuse, physicians should evaluate patients for a history of drug abuse, and observe such patients closely for signs of misuse or abuse (e.g. development of tolerance, increases in dose, drug-seeking behaviour).

In addition, the maintenance of the clinical effect of NUEDEXTA in the patient should be regularly monitored in the long-term against its tolerability, in order to ascertain the continued benefit of the product.

Lactose warning

NUEDEXTA contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

MAOIs

NUEDEXTA must not be used with monoamine oxidase inhibitors (MAOIs), such as phenelzine and moklobemide, or in patients who have taken MAOIs within the preceding 14 days due to the risk of serotonin syndrome (see section 4.3).

CYP3A4 inhibitors

Quinidine is metabolised by CYP3A4. Concomitant administration of medicines that inhibit CYP3A4 can be expected to increase plasma levels of quinidine, which could increase risk relating to QTc prolongation. Strong and moderate CYP3A4 inhibitors should be avoided during treatment with NUEDEXTA. They include, but are not limited to, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, and verapamil. If concomitant treatment with strong or moderate CYP3A4 inhibitors is considered necessary, it is recommended that electrocardiographic (ECG) evaluation of the QT interval be carried out before NUEDEXTA is administered and at appropriate time point(s) subsequently.

Liver enzyme inducers

Quinidine is metabolised by CYP3A4. Potent CYP3A4 inducers (e.g. rifampicin, phenytoin, phenobarbital, carbamazepine, St John's wort/*Hypericum perforatum*) may accelerate the metabolism of quinidine, resulting in lower plasma concentrations and hence decreased inhibition of CYP2D6. This may lead to lower, potentially subtherapeutic plasma concentrations of dextromethorphan and decreased efficacy of NUEDEXTA.

CYP2D6 substrates

Quinidine is a potent inhibitor of CYP2D6. Treatment with NUEDEXTA may therefore result in elevated plasma levels and accumulation of co-administered medicinal products that undergo extensive CYP2D6 metabolism. CYP2D6 substrates include certain beta-blockers such as metoprolol, antipsychotics such as haloperidol, perphenazine and aripiprazole, antidepressants such as nortriptyline, imipramine, amitriptyline and desipramine, the chemotherapeutic tamoxifen, and the noradrenaline transporter inhibitor atomoxetine. Thioridazine, a CYP2D6 substrate that also prolongs the QT interval is contraindicated (see section 4.3). Concomitant use of flecainide, chlorpromazine or haloperidol, CYP2D6 substrates that also prolong QT interval, requires caution (see section 4.4).

In the case of pro-drugs whose actions are mediated by the CYP2D6-produced metabolites (for example, codeine and hydrocodone, whose analgesic and antitussive effects appear to be mediated by morphine and hydromorphone, respectively), efficacy may be substantially reduced by NUEDEXTA due to inhibition of CYP2D6 and hence impaired formation of the active metabolite.

Drug interactions with desipramine and paroxetine have been studied in controlled clinical trials with a higher dose combination of dextromethorphan/quinidine (dextromethorphan 23 mg/ quinidine 26 mg) than in this medicinal product; study results are described below. No other drug interactions with CYP2D6 substrates have been systematically investigated.

Desipramine (CYP2D6 substrate)

The tricyclic antidepressant desipramine is metabolized primarily by CYP2D6. A drug-drug interaction study was conducted between a higher combination dose of dextromethorphan/quinidine (dextromethorphan 23 mg/quinidine 26 mg) and desipramine 25 mg. The combination dose of dextromethorphan/quinidine increased steady state desipramine levels approximately 8-fold. Concomitant use of NUEDEXTA and TCAs is not recommended (see section 4.4).

Paroxetine (CYP2D6 inhibitor and substrate)

The selective serotonin reuptake inhibitor (SSRI) paroxetine is metabolized primarily by CYP2D6 and is also a potent CYP2D6 inhibitor. In a drug-drug interaction study, a higher combination dose of dextromethorphan/quinidine (dextromethorphan 23 mg/quinidine 26 mg) was added to paroxetine at steady state. Paroxetine exposure (AUC_{0-24}) increased by 1.7 fold and C_{max} increased by 1.5 fold. If NUEDEXTA and paroxetine are prescribed concomitantly, the initial dose of paroxetine should be reduced. The dose of paroxetine can then be adjusted based on clinical response, however, dosage above 35 mg/day is not recommended.

NMDA receptor antagonists (memantine)

Both dextromethorphan and memantine are antagonists of the *N*-methyl-D-aspartate (NMDA) receptor which could theoretically result in an additive effect at NMDA receptors and potentially an increased incidence of adverse reactions. A drug-drug interaction study was conducted between a higher combination dose of dextromethorphan/quinidine (dextromethorphan 23 mg/quinidine 26 mg) and memantine 20 mg/day. There was no significant difference in the plasma concentrations of dextromethorphan and dextrorphan before and after the administration of memantine, and there was no effect on the plasma concentrations of memantine before and after the administration of dextromethorphan/quinidine. Plasma concentrations of quinidine increased 20-30% when memantine was added. No pharmacodynamic interactions were apparent.

Digoxin and other P-glycoprotein substrates

Quinidine is an inhibitor of P-glycoprotein. Concomitant administration of quinidine with digoxin, a P-glycoprotein substrate, results in serum digoxin levels that may be as much as doubled. Plasma digoxin concentrations should be closely monitored in patients taking NUEDEXTA concomitantly, and the digoxin dose reduced, as necessary. Other P-gp substrates for which a dose reduction may be considered include ticagrelor and dabigatran-etexilate.

Alcohol

Caution should be used when this medicinal product is taken in combination with alcohol or other centrally acting medicinal products that might increase the risk of adverse reactions such as somnolence and dizziness.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of NUEDEXTA in pregnant women. Studies in animals (rats and rabbits) have shown developmental toxicity, including teratogenicity and embryolethality (see section 5.3).

As this medicinal product may cause foetal harm, it is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

Quinidine is excreted in human milk and it is unknown whether dextromethorphan is excreted in human milk. A risk to the newborns/infants cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from NUEDEXTA therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

In pre-clinical studies no effect on fertility was observed in male and female rats (see section 5.3).

4.7 Effects on ability to drive and use machines

NUEDEXTA has no or negligible influence on the ability to drive and use machines. Patients should be warned about the potential for CNS-related effects like somnolence, dizziness and syncope or impaired vision (see section 4.8), and advised not to drive or operate machinery if these symptoms occur.

4.8 Undesirable effects

Summary of the safety profile

The safety of NUEDEXTA was investigated in a double-blind, randomized, placebo-controlled, multicenter study over 12 weeks in 326 PBA patients with underlying ALS (60%) or MS (40%) and in a follow-up open-label extension phase with a patient subgroup of this study (253 patients) for an additional 84 days.

The most commonly reported adverse reactions are gastrointestinal disorders (such as diarrhoea, nausea), nervous system disorders (such as dizziness, headache, somnolence) and fatigue.

Serious adverse reactions have been reported for NUEDEXTA; these are muscle spasticity, respiratory depression and decreased oxygen saturation in the blood.

Ten patients discontinued study treatment due to ADRs, one of these patients due to a serious ADR (worsening muscle spasticity).

Tabulated summary of adverse reactions

The adverse reactions considered at least possibly related to treatment with NUEDEXTA in the placebo-controlled and the open-label extension phase of the above mentioned clinical study are listed below by body system organ class and frequency.

- very common ($\geq 1/10$)
- common ($\geq 1/100$ to $< 1/10$)
- uncommon ($\geq 1/1,000$ to $< 1/100$)
- rare ($\geq 1/10,000$ to $< 1/1,000$)
- very rare ($< 1/10,000$)

System Organ Class	Frequency	Adverse Reaction
Metabolism and nutrition disorders	Uncommon	Decreased appetite
	Rare	Anorexia
Psychiatric disorders	Uncommon	Anxiety
	Rare	<ul style="list-style-type: none">• Bruxism, Confusional state, Depressed mood, Depression, Disorientation, Early morning awakening, Flat affect, Hallucination, Impulsive behaviour, Indifference, Insomnia, Restlessness, Sleep disorder
Nervous system disorders	Common	Dizziness, Headache, Somnolence

	Uncommon	Dysgeusia, Hypersomnia, Muscle spasticity, Syncope, Fall
	Rare	Balance disorder, Coordination abnormal, Dysarthria, Motor dysfunction, Paraesthesia, Paraparesis, Sedation
Eye disorders	Rare	Diplopia, Vision blurred
Ear and labyrinth disorders	Uncommon	Motion sickness, Tinnitus
Cardiac disorders	Uncommon	Atrioventricular block first degree, Electrocardiogram QT prolonged
	Rare	<ul style="list-style-type: none"> Myocardial infarction, Palpitations, Ventricular extrasystoles
Respiratory, thoracic and mediastinal disorders	Rare	<ul style="list-style-type: none"> Epistaxis, Pharyngolaryngeal pain, Respiratory depression, Rhinorrhoea, Yawning
Gastrointestinal disorders	Common	Diarrhoea, Nausea
	Uncommon	Abdominal pain, Constipation, Dry mouth, Flatulence, Stomach discomfort, Vomiting
	Rare	<ul style="list-style-type: none"> Abnormal faeces, Dyspepsia, Gastritis, Hypoaesthesia oral, Paraesthesia oral, Proctalgia, Tongue dry
Hepatobiliary disorders	Uncommon	Increased hepatic enzymes (GGT, AST, ALT)
	Rare	Cholelithiasis, blood bilirubin increased, Liver function test abnormal,
Skin and subcutaneous tissue disorders	Uncommon	Rash
	Rare	Erythema, Hyperhidrosis, Hypoaesthesia facial, Night sweats
Musculoskeletal and connective tissue disorders	Uncommon	Muscle spasms
	Rare	Musculoskeletal stiffness, Myalgia, Neck pain, Pain in extremity
Renal and urinary disorders	Rare	Pollakiuria
Reproductive system and breast disorders	Rare	Sexual dysfunction
General disorders and administration site conditions	Common	Fatigue
	Uncommon	Asthenia, Irritability
	Rare	Chest discomfort, Chest pain, Chills, Feeling hot, Gait disturbance, Influenza like illness, Pyrexia, Oxygen saturation decreased
Injury, poisoning and procedural complications	Rare	Skeletal injury

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

4.9 Overdose

Evaluation and treatment of overdose is based on experience with the individual components, dextromethorphan and quinidine. Metabolism of dextromethorphan is inhibited by quinidine, such that adverse reactions of overdose due to NUEDEXTA might be more severe or more persistent compared to overdose of dextromethorphan alone.

During development of this medicinal product, dose combinations of dextromethorphan/quinidine containing up to 6-times higher dextromethorphan dose and 12-times higher quinidine dose were studied. The most common adverse reactions were mild to moderate nausea, dizziness, and headache.

Dextromethorphan

Adverse reactions of dextromethorphan overdose include nausea, vomiting, stupor, coma, respiratory depression, seizures, tachycardia, hyperexcitability, and toxic psychosis. Other adverse reactions include ataxia, nystagmus, dystonia, blurred vision, and changes in muscle reflexes.

Dextromethorphan may increase the risk of serotonin syndrome, and this risk is increased by overdose, particularly if taken with other serotonergic agents, SSRIs or tricyclic antidepressants.

Quinidine

The most important effects of acute overdoses are ventricular arrhythmias and hypotension. Other signs and symptoms of overdose may include vomiting, diarrhoea, tinnitus, high-frequency hearing loss, vertigo, blurred vision, diplopia, photophobia, headache, confusion and delirium.

While therapeutic doses of quinidine for treatment of cardiac arrhythmia or malaria are generally ≥ 10 -fold higher than the dose of quinidine in this medicinal product, potentially fatal cardiac arrhythmia, including torsades de pointes, can occur at quinidine exposures that are possible from NUEDEXTA overdose.

Treatment of overdose

Quinidine

The treatment of cardiac effects (haemodynamically unstable polymorphic ventricular tachycardia (including torsades de pointes)) is either immediate cardioversion or immediate overdrive pacing. Other antiarrhythmics with Class I (procainamide) or Class III activities should (if possible) be avoided. Treatment of hypotension and of other signs and symptoms should be directed at symptomatic and supportive measures. Administration of activated charcoal in conventional dose of 1 g/kg, administered every 2 to 6 hours as a slurry with 8 mL/kg of tap water may enhance the systemic elimination of quinidine; this measure should be avoided if an ileus is present. Methods as to acidify the urine and dialysis are of no demonstrated benefit. Drugs that delay elimination of quinidine (cimetidine, carbonic anhydrase inhibitors, thiazide diuretics) should be withdrawn unless absolutely required.

Dextromethorphan

Treatment of dextromethorphan overdose should be directed at symptomatic and supportive measures. Gastric lavage may be of use.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other nervous system drugs; ATC code: N07XX59

Dextromethorphan hydrobromide is the pharmacologically active ingredient that acts on the central nervous system (CNS). Quinidine sulfate is a specific inhibitor of CYP2D6-dependent oxidative metabolism used to increase the systemic bioavailability of dextromethorphan.

Mechanism of action

The exact mechanism by which dextromethorphan exerts therapeutic effects in patients with pseudobulbar affect is unknown. Quinidine increases plasma levels of dextromethorphan by competitively inhibiting cytochrome P450 2D6 (CYP2D6), which catalyses a major biotransformation pathway for dextromethorphan.

Pharmacodynamic effects

Dextromethorphan is a sigma-1 receptor agonist and an uncompetitive NMDA receptor antagonist. In addition it shows affinity for the serotonin transporter (SERT) and for the 5-HT1B/D receptor. Through its binding to the NMDA, sigma-1, SERT and 5-HT1B/D receptors, dextromethorphan is thought to have a modulatory effect on neurotransmission involving glutamate, monoamines (including serotonin), as well as ion channel function.

Clinical efficacy and safety

The efficacy of dextromethorphan/quinidine for the treatment of PBA was demonstrated in three randomised, controlled, double-blind, multicentre clinical trials in PBA subjects with underlying amyotrophic lateral sclerosis (ALS) or multiple sclerosis (MS). Eligible patients had a diagnosis of PBA defined by episodes of involuntary, uncontrollable emotional expressions of laughing and/or crying that are incongruous or disproportionate to their emotional state or mood.

In all studies, the efficacy endpoints were “Count of episodes of laughing and crying” (PBA episodes) and subject scores on the Center for Neurologic Studies - Lability Scale (CNS-LS), a validated 7-item, self-administered questionnaire that provides a quantitative measure of the frequency and severity of PBA. CNS-LS scores range from a minimum of 7 (no symptoms) to a maximum of 35.

- Pivotal study (07-AVR-123)

In this placebo-controlled 12-week study, 326 PBA subjects with underlying ALS or MS were randomized to receive NUEDEXTA 15 mg / 9 mg (n=107), NUEDEXTA 23 mg / 9 mg (n=110), or placebo (n=109) for 12 weeks.

Subjects were 25 to 80 years of age with a mean age of approximately 51 years. Approximately 74% were Caucasian, 4% were Black, 1% were Asian and 19% were of Hispanic origin. 60% of subjects had underlying ALS and 40% of subjects had underlying MS. All subjects had clinically relevant PBA symptoms, quantified as CNS-LS score of 13 or more.

Mean baseline daily PBA episode rates (calculated from the total number of episodes reported for up to 7 pre-treatment days) were 4.7 in the NUEDEXTA 23 mg/9 mg group, 6.8 in the NUEDEXTA 15 mg/9 mg group, and 4.5 in the placebo group.

Mean baseline CNS-LS scores were 19.8 in the NUEDEXTA 23 mg /9 mg group, 21.0 in the NUEDEXTA 15 mg /9 mg group, and 19.9 in the placebo group.

To evaluate long-term data, 253 subjects who completed the double-blind study phase had the option of entering an open-label extension phase, receiving NUEDEXTA 23 mg /9 mg for another 84 days.

The frequency of PBA episodes as measured by “Count of Episodes” in both NUEDEXTA treatment groups decreased significantly throughout the course of the study by an incremental reduction of 47% and 49% relative to placebo, respectively (p <0.0001 for both comparisons).

The least-squares mean CNS-LS scores were significantly reduced at the end of treatment in both treatment groups compared to placebo (8.2 point reduction for NUEDEXTA 23 mg /9 mg, 7.5 point reduction for NUEDEXTA 15 mg /9 mg, 5.7 point reduction for placebo). The p-value for NUEDEXTA 23 mg /9 mg vs placebo was p=0.0002 and for NUEDEXTA 15 mg /9 mg vs placebo was p=0.008.

The 12-week open-label phase of the study (during which all subjects received NUEDEXTA 23 mg / 9 mg) showed persistence of the effect observed in the placebo controlled period.

- Studies with Higher Dose Combinations of dextromethorphan / quinidine

Two additional phase III studies were conducted using a higher dose combination of dextromethorphan 23 mg/quinidine 26 mg. The higher dose of quinidine used in these studies would have resulted in approximately a 1.6 fold greater exposure to of dextromethorphan than with NUEDEXTA 23 mg/ 9 mg.

The first was a 4-week study in PBA subjects with underlying ALS, and the second was a 12-week study in subjects with underlying MS. In both studies the primary outcome measure, CNS-LS, and the secondary outcome measure, “count of episodes of laughing and crying”, were statistically significantly decreased by the dextromethorphan/quinidine combination.

A 12 month open-label safety study, also using the higher dose combination of dextromethorphan 23 mg /quinidine 26 mg, included 553 subjects with PBA associated with thirty-four different neurological conditions. Approximately 30% of study participants carried diagnoses other than ALS and MS, including stroke, traumatic brain injury, Parkinson’s disease, Alzheimer’s disease and other dementia, primary lateral sclerosis, progressive bulbar palsy, and progressive supranuclear palsy. Only safety data were collected in this study; no new safety signals were identified.

- Studies to Assess Cardiac Effects

The effect of NUEDEXTA 23 mg / 9 mg (for 7 consecutive doses) on QTc prolongation was evaluated in a randomised, double-blind (except for moxifloxacin), placebo- and positive-controlled (400 mg moxifloxacin) crossover thorough QT study in 50 fasted normal healthy men and women with CYP2D6 extensive metabolizer (EM) genotype. Mean changes in QTcF were 6.8 ms for NUEDEXTA 23 mg/ 9 mg and 9.1 ms for the reference positive control (moxifloxacin). The maximum mean (95% upper confidence bound) difference from placebo after baseline correction was 10.2 (12.6) ms. This test dose is adequate to represent the steady state exposure in patients with CYP2D6 extensive metabolizer phenotype.

The effects of supra-therapeutic doses of dextromethorphan /quinidine (23 mg /26 mg and 46 mg / 53 mg, for 7 consecutive doses) on QTc prolongation were evaluated in a randomised, placebo-controlled, double-blind, crossover design with an additional open-label positive control (400 mg moxifloxacin) arm in 36 healthy volunteers. The maximum mean (95% upper confidence bound) differences from placebo after baseline-correction were 10.2 (14.6) and 18.4 (22.7) ms following dextromethorphan/quinidine doses of 23 mg /26 mg and 46 mg /53 mg, respectively. The supra-therapeutic doses are adequate to represent quinidine exposure increases due to drug-drug interactions and organ dysfunctions.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with NUEDEXTA in all subsets of the paediatric population in PBA (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Following single and repeated combination doses of NUEDEXTA 23 mg / 9 mg, subjects had an approximately 20-fold increase in dextromethorphan exposure compared to subjects given dextromethorphan without quinidine.

Following repeated doses of NUEDEXTA 23 mg / 9 mg and NUEDEXTA 15 mg / 9 mg, maximal plasma concentrations (C_{max}) of dextromethorphan are reached approximately 3 to 4 hours after dosing and maximal plasma concentrations of quinidine are reached approximately 2 hours after dosing.

In extensive metabolizers, mean C_{max} and AUC_{0-12} values of dextromethorphan and dextrorphan increased as doses of dextromethorphan increased from 15 mg to 23 mg and mean C_{max} and AUC_{0-12} values of quinidine were similar.

The mean plasma C_{max} of quinidine following NUEDEXTA 15 mg / 9 mg twice daily in subjects with PBA was 1 to 3% of the therapeutic concentrations associated with antiarrhythmic efficacy (2 to 5 $\mu\text{g/mL}$).

NUEDEXTA may be taken without regard to meals as food does not affect the exposure of dextromethorphan and quinidine significantly.

Distribution

After administration of the combination product, protein binding remains essentially the same as that after administration of the individual components; dextromethorphan is approximately 60-70% protein bound, and quinidine is approximately 80-89% protein bound.

Biotransformation and elimination

Dextromethorphan is rapidly metabolized by CYP2D6 to its primary metabolite, dextrorphan, which is rapidly glucuronidated and renally eliminated. The quinidine component of NUEDEXTA serves to selectively inhibit CYP2D6-dependent oxidative metabolism of dextromethorphan, thus increasing dextromethorphan plasma concentrations. In the presence of quinidine, CYP3A4-dependent oxidative metabolism is believed to play a greater role in dextromethorphan elimination.

After administration of NUEDEXTA 23 mg/9 mg to 14 extensive metabolizers, the elimination half-life of dextromethorphan was 18.8 hours and the elimination half-life of quinidine was 9.6 hours.

Quinidine is metabolized by CYP3A4. There are several hydroxylated metabolites of quinidine. The major metabolite is 3-hydroxyquinidine, which is considered to be at least half as pharmacologically active as quinidine with respect to cardiac effects such as QT prolongation. There are currently limited data on the magnitude of the effect of CYP3A4 inhibitors on the pharmacokinetic parameters of quinidine and its metabolites, including the potential for accumulation at steady state.

When the urine pH is less than 7, about 20% of administered quinidine appears unchanged in the urine, but this fraction drops to as little as 5% when the urine is more alkaline. Renal clearance involves both glomerular filtration and active tubular secretion, moderated by (pH-dependent) tubular reabsorption.

Linearity/non-linearity

Plasma concentrations of dextromethorphan and dextrorphan are proportional to dextromethorphan dose in the presence of a fixed dose of quinidine such as that contained in NUEDEXTA. Quinidine plasma concentrations are proportional to quinidine dose.

In vitro CYP P450 interaction studies

The potential for dextromethorphan and quinidine to inhibit or induce cytochrome P450 *in vitro* were evaluated in human microsomes. Dextromethorphan did not inhibit (<20% inhibition) any of the tested isoenzymes: CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4 in human liver microsomes at concentrations up to 5 μM . Quinidine did not inhibit (<30% inhibition) CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2E1, or CYP3A4 in human microsomes at concentrations up to 5 μM . Quinidine inhibited CYP2D6 with a half maximal inhibitory concentration (IC_{50}) of less than 0.05 μM . Neither dextromethorphan nor quinidine induced CYP1A2, CYP2B6 or CYP3A4 in human hepatocytes at concentrations up to 4.8 μM .

In vitro transporter interaction studies

Based on the results of transporter inhibition studies drug-drug interactions related to dextromethorphan inhibition of P-gp, OATP1B1, OATP1B3, OCT2, OAT1, OAT3 or BSEP are not expected during treatment with NUEDEXTA. Dextromethorphan has been shown to be a mild/moderate inhibitor of the OCT1 transporter *in vitro*. The clinical relevance of this observation to drugs that are OCT1 substrates, such as metformin, is unknown.

Based on literature citations, drug-drug interactions as a result of quinidine inhibition of OATP1B1, OCT1, OCT2, OAT3, BSEP, MATE1, and MATE2-K are not expected.

Special Populations

Elderly patients

The pharmacokinetics of dextromethorphan/quinidine have not been investigated systematically in elderly subjects (aged >65 years) although such subjects were included in the clinical programme (14% ≥65 years, 2% ≥75 years).

A population pharmacokinetic analysis of 170 subjects (148 subjects <65 years old and 22 subjects ≥65 years old) administered dextromethorphan 23 mg / quinidine 26 mg revealed similar pharmacokinetics in subjects <65 years and those ≥65 years of age.

Gender

A population pharmacokinetic analysis based on data from 109 subjects (75 male; 34 female) showed no apparent gender differences in the pharmacokinetics of dextromethorphan/quinidine.

Race

A population pharmacokinetic analysis of race with 109 subjects (21 Caucasian; 71 Hispanic; 18 Black) revealed no apparent racial differences in the pharmacokinetics of dextromethorphan/quinidine.

Renal impairment

In a study of a combination dose of dextromethorphan 23 mg / quinidine 26 mg twice daily in 12 subjects with mild (CLCR 50-80 mL/min) or moderate (CLCR 30-50 mL/min) renal impairment (6 each) compared to 9 healthy subjects (matched in gender, age, and weight range to impaired subjects), subjects showed little difference in quinidine or dextromethorphan pharmacokinetics compared to healthy subjects. Dose adjustment is therefore not required in mild or moderate renal impairment. Dextromethorphan / quinidine has not been studied in patients with severe renal impairment.

Hepatic impairment

In a study of a combination dose of dextromethorphan 23 mg / quinidine 26 mg twice daily in 12 subjects with mild or moderate hepatic impairment (as indicated by the Child-Pugh method; 6 each) compared to 6 healthy subjects (matched in gender, age, and weight range to impaired subjects), subjects with moderate hepatic impairment showed similar dextromethorphan AUC and C_{max} and clearance compared to healthy subjects. Mild to moderate hepatic impairment had little effect on quinidine pharmacokinetics. Quinidine clearance is unaffected, although there is an increased volume of distribution that leads to an increase in the elimination half-life. Patients with moderate hepatic impairment showed an increased frequency of adverse reactions. Therefore, dosage adjustment is not required in patients with mild and moderate hepatic impairment, although additional monitoring for adverse reactions should be considered in patients with moderate hepatic impairment. Dose increase, if warranted, should be undertaken with caution in these patients. Neither dextromethorphan alone nor dextromethorphan/quinidine has been evaluated in patients with severe hepatic impairment.

Pharmacogenomics

The quinidine component is intended to inhibit CYP2D6 so that higher exposure to dextromethorphan can be achieved compared to when dextromethorphan is given alone. Approximately 7-8% of individuals of Caucasian descent, 3-6% of Black African descent, 2-3% of Arab descent and 1-2% of Asian descent generally lack the capacity to metabolize CYP2D6 substrates and are classified as Poor

Metabolizer (PMs). The quinidine component is not expected to contribute to the effectiveness of NUDEXTA in PMs, but adverse reactions of the quinidine component are still possible.

Approximately 1-10% of individuals of Caucasian descent, 5-30% of Black African descent, 12-40% of Arab descent and 1% of Asian descent exhibit increased metabolic activity for CYP2D6 substrates and are classified as Ultra-rapid Metabolizer (UMs). In such UM patients, dextromethorphan is rapidly metabolised, leading to lower, potentially subtherapeutic concentrations.

Paediatric population

The pharmacokinetics of dextromethorphan/quinidine in paediatric patients has not been studied (see section 5.1).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for a genotoxicity or carcinogenic potential, nor for fertility impairment.

In embryo-fetal and developmental toxicity studies (rats and rabbits) with dextromethorphan hydrobromide/quinidine sulfate, abnormalities were observed at mid and high dose with reduced ossification from the lowest dose in rats which is approximately 1 and 50 times the human dose of 30/18 mg/day on a mg/m² basis, respectively. The no effect dose in rabbits is 2 and 60 times higher than the RHD.

In the pre and post-natal developmental study, slight developmental delay was seen in offspring at the mid- and high-doses. Pup survival and pup weight were slightly decreased from the lowest dose corresponding approximately to 1 and 50 times the human dose of 30/18 mg/kg on a mg/m² basis, for dextromethorphan hydrobromide and quinidine sulfate, respectively.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content

Croscarmellose sodium
Cellulose, microcrystalline
Silica, colloidal anhydrous
Lactose monohydrate
Magnesium stearate

Capsule shell

Gelatin
Titanium dioxide (E171)
Red iron oxide (E172)

Printing ink

Shellac glaze (20% esterified)
Propylene glycol
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

High density polyethylene (HDPE) bottle with a child resistant polypropylene cap. Each bottle is packed in a carton.

Pack size: 60 capsules

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Jenson Pharmaceutical Services Limited
Carradine House, 237 Regents Park Road
N3 3LF London
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/833/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>

ANNEX II

- A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Medicinal product no longer authorised

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Jenson Pharmaceutical Services Ltd
Carradine House
237 Regents Park Road
N3 3LF London
UNITED KINGDOM

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

• Periodic Safety Update Reports

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

• Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

• Additional risk minimisation measures

Prior to launch in each Member State the Marketing Authorisation Holder (MAH) shall agree an educational programme with the National Competent Authority.

The MAH shall ensure that, following discussion and agreement with the National Competent Authorities in each Member State where Nuedexta is marketed, at launch and after launch, all

healthcare professionals who are expected to prescribe Nuedexta are provided with the following items:

- Summary of Product Characteristics (SmPC)
- Educational material for Healthcare Professionals (HCPs)
- Patient alert cards

The educational material for HCPs should assist them in the collection and assessment of relevant patient's details on pre-existing co-morbidities and concomitant medications prior to initiating Nuedexta therapy. Furthermore, educational material for HCPs should provide information on the following safety concerns and on the actions needed to reduce the risks:

- Off-label use
- Allergic reactions
- Cardiac effects (QT prolongation) including pre-existing cardiovascular conditions and clinically significant electrolyte imbalances
- Drug-drug interactions including involvement of CYP2D6 substrates and inhibitors
- Serotonin syndrome
- Co-administration of a strong CYP3A4 inhibitor
- Drug misuse and abuse

The patient alert card should be provided to all patients with instructions to carry it on them at all times. The card should contain details to alert any HCP treating the patient that they are being treated with Nuedexta and of the potential for interaction once a patient is on treatment with Nuedexta and another treatment is added.

Medicinal product no longer authorised

Medicinal product no longer authorised

ANNEX III
LABELLING AND PACKAGE LEAFLET

Medicinal product no longer authorised

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BOTTLE CARTON (60 hard capsules) – NUEDEXTA 15 mg/9 mg capsules

1. NAME OF THE MEDICINAL PRODUCT

NUEDEXTA 15 mg/9 mg hard capsules

dextromethorphan / quinidine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains dextromethorphan hydrobromide monohydrate, equivalent to 15.41 mg dextromethorphan and quinidine sulfate dihydrate, equivalent to 8.69 mg quinidine.

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

60 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Jenson Pharmaceutical Services Limited
Carradine House, 237 Regents Park Road
N3 3LF London
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/833/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

NUEDEXTA 15 mg/9 mg

Medicinal product no longer authorised

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL (60 hard capsules) – NUEDEXTA 15 mg/9 mg capsules

1. NAME OF THE MEDICINAL PRODUCT

NUEDEXTA 15 mg/9 mg hard capsules

dextromethorphan / quinidine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains dextromethorphan hydrobromide monohydrate, equivalent to 15.41 mg dextromethorphan and quinidine sulfate dihydrate, equivalent to 8.69 mg quinidine.

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

60 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Jenson Pharmaceutical Services Limited
Carradine House, 237 Regents Park Road
N3 3LF London
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/833/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Medicinal product no longer authorised

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BOTTLE CARTON (60 hard capsules) – NUEDEXTA 23 mg/9 mg capsules

1. NAME OF THE MEDICINAL PRODUCT

NUEDEXTA 23 mg/9 mg hard capsules

dextromethorphan / quinidine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains dextromethorphan hydrobromide monohydrate, equivalent to 23.4 mg dextromethorphan and quinidine sulfate dihydrate, equivalent to 8.69 mg quinidine.

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

60 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Jenson Pharmaceutical Services Limited
Carradine House, 237 Regents Park Road
N3 3LF London
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/833/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

NUEDEXTA 23 mg/9 mg

Medicinal product no longer authorised

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL (60 hard capsules) – NUEDEXTA 23 mg/9 mg capsules

1. NAME OF THE MEDICINAL PRODUCT

NUEDEXTA 23 mg/9 mg hard capsules

dextromethorphan / quinidine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains dextromethorphan hydrobromide monohydrate, equivalent to 23.11 mg dextromethorphan and quinidine sulfate dihydrate, equivalent to 8.69 mg quinidine.

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

60 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Jenson Pharmaceutical Services Limited
Carradine House, 237 Regents Park Road
N3 3LF London
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/833/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

/

Medicinal product no longer authorised

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**OUTER CARTON – NUEDEXTA 15 mg/9 mg capsules: PACK OF 13 CAPSULES****1. NAME OF THE MEDICINAL PRODUCT**

NUEDEXTA 15 mg/9 mg hard capsules

dextromethorphan / quinidine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains dextromethorphan hydrobromide monohydrate, equivalent to 15.41 mg dextromethorphan and quinidine sulfate dihydrate, equivalent to 8.69 mg quinidine.

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

13 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

To access capsules:

1. Squeeze and hold at tabs above and below (▼▲)
2. Pull out card to the right (➤)

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Jenson Pharmaceutical Services Limited
Carradine House, 237 Regents Park Road
N3 3LF London
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/833/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

NUEDEXTA 15 mg/9 mg

Medicinal product no longer authorised

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER SLEEVE (13 hard capsules) – NUEDEXTA 15 mg/9 mg capsules

1. NAME OF THE MEDICINAL PRODUCT

NUEDEXTA 15 mg/9 mg hard capsules

dextromethorphan / quinidine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Jenson Pharmaceutical Services Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

DAYS 1-7

Day 1

Day 2

Day 3

Day 4

Day 5

Day 6

Day 7

BEGINNING DAY 8

Day 8

Day 9

Day 10

Medicinal product no longer authorised

B. PACKAGE LEAFLET

Medicinal product no longer authorised

Package leaflet: information for the user

NUEDEXTA 15 mg/9 mg hard capsules
NUEDEXTA 23 mg/9 mg hard capsules
dextromethorphan / quinidine

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any side effects not listed in this leaflet.

What is in this leaflet

1. What NUEDEXTA is and what it is used for
2. What you need to know before you take NUEDEXTA
3. How to take NUEDEXTA
4. Possible side effects
5. How to store NUEDEXTA
6. Contents of the pack and other information

1. What NUEDEXTA is and what it is used for

NUEDEXTA is a combination of two active substances:

- Dextromethorphan acts on the brain.
- Quinidine increases the amount of dextromethorphan in your body, by blocking the breakdown of dextromethorphan by the liver.

NUEDEXTA is used for the treatment of pseudobulbar affect (PBA) in adults. PBA is a neurological condition characterized by involuntary and uncontrollable episodes of laughing and/or crying, which don't match your emotional state or mood.

NUEDEXTA can help reduce how often you have episodes of PBA.

2. What you need to know before you take NUEDEXTA

Do not take NUEDEXTA

- if you are allergic to dextromethorphan, quinidine or any of the other ingredients of this medicine (listed in section 6).
- if you have a history of low levels of blood cells caused by quinidine, quinine or mefloquine (this can cause a tendency to bleed or bruise more easily than normal)
- if you have a history of a liver disease (hepatitis) caused by quinidine
- if you have a history of a condition called lupus-like syndrome caused by quinidine (this can cause joint pains, skin rash, excessive skin sensitivity to sun and overall feeling of sickness).
- if you are already taking medicines containing quinidine, quinine, or mefloquine. These are medicines used to treat malaria or heart rhythm problems.
- if you have a heart problem called "complete heart block" or "long QT syndrome" or have had a problem with your heart called "torsades de pointes".
- if you take a medicine called thioridazine, which is used for mental illness but can also affect the heart.
- if you are taking, or have taken during the last two weeks, certain medicines for depression called monoamine oxidase inhibitors (MAOIs), such as phenelzine and moclobemide.

Please ask your doctor if you are not sure, if any of the above applies to you.

Warnings and precautions

Talk to your doctor before and after taking NUEDEXTA if:

- you or a family member currently have or have ever had any heart disease or problems. This medicine may cause changes in heart rhythm. If you have certain heart problems or are currently taking certain other medicines, NUEDEXTA may not be appropriate for you, or your doctor may want to monitor your heart activity when you start NUEDEXTA.
- you experience symptoms such as palpitations or fainting, which may be a sign of heart problems.
- you develop symptoms of an allergic reaction such as swelling of the throat or tongue, difficulty breathing, dizziness, fever, rash, or hives after taking this medicine.
- you experience symptoms such as bruising, bleeding under the skin, nosebleeds and/or bleeding gums, as this may be a sign of low levels of blood cells called platelets (thrombocytopenia).
- you experience symptoms, such as yellowing of the skin or eyes, dark urine, nausea or vomiting, loss of appetite, abdominal pain, and fever, as this may be a sign of drug-induced hepatitis (liver inflammation).
- you have a condition called myasthenia gravis (an autoimmune neuromuscular disease that causes muscle weakness and fatigability).
- you have problems with your liver or kidney. Depending on the severity of your problems, your doctor may carefully consider whether this medicine is suitable for you and monitor you more closely for potential side effects.
- you have a tendency to have falls. This medicine may cause dizziness and your doctor might need to discuss appropriate precautions to reduce the risk of falls.
- you have had at any time a serious condition called “serotonin syndrome”, which can be caused by certain medicines e.g. antidepressants. Symptoms of serotonin syndrome include agitation, high blood pressure, restlessness, muscle spasms and twitching, high body temperature, excessive sweating, shivering, and tremor.
- you have a history of drug abuse. Your doctor will monitor you closely for signs of NUEDEXTA misuse or abuse.

Stop taking NUEDEXTA and seek medical attention immediately if any of the above symptoms occur.

Children and adolescents

NUEDEXTA should not be used in children and adolescents below the age of 18 years.

Other medicines and NUEDEXTA

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

It is very important to tell your doctor if you are taking any of the medicines listed below, as these medicines should never be taken while you are taking NUEDEXTA:

- medicines containing quinidine, quinine, or mefloquine. These are medicines used to treat malaria or heart rhythm problems,
- thioridazine, a medicine used in the treatment of schizophrenia and psychosis, that may affect the heart,
- certain medicines for depression, called monoamine oxidase inhibitors (MAOIs- for example phenelzine and moklobemide). Do not take NUEDEXTA if you have taken these antidepressants during the last two weeks and allow at least 14 days after stopping NUEDEXTA before starting an MAOI.

Please tell your doctor if you are taking any of the following medicines, as your doctor will closely monitor you for side effects.:

- medicines used to treat fungal infections, such as ketoconazole, itraconazole, fluconazole
- medicines used to treat HIV infection and AIDS, such as atazanavir, indinavir, nelfinavir, ritonavir, saquinavir, amprenavir, fosamprenavir
- medicines used to treat bacterial infections, including tuberculosis, containing clarithromycin, telithromycin, erythromycin and rifampicin
- medicines used to treat various heart conditions, such as diltiazem, verapamil, digoxin, flecainide and beta-blockers (such as metoprolol)
- medicines used to prevent nausea and vomiting during chemotherapy and after surgery, such as aprepitant
- certain medicines used to treat depression, including nortriptyline, desipramine, paroxetine, imipramine and amitriptyline, nefazodone
- St John's wort, a herbal medicine used to treat depression
- medicines used to treat schizophrenia and other psychotic disorders, such as haloperidol, perphenazine, aripiprazole and chlorpromazine
- certain medicines used to prevent blood clots in patients with heart conditions and at risk of stroke, such as ticagrelor and dabigatran-etexilate
- tamoxifen, used to treat or prevent some cancers
- atomoxetine, used to treat attention-deficit hyperactivity disorder (ADHD)
- medicines to reduce pain and/or cough, such as codeine and hydrocodone
- medicines to treat epilepsy or fits, such as phenytoin, carbamazepine and phenobarbital

Your doctor will closely monitor you for side effects and/or may need to adjust the dose of the other medicine or NUEDEXTA.

NUEDEXTA with food, drink and alcohol

You should not drink grapefruit juice or eat grapefruit while you are taking NUEDEXTA as this can increase the likelihood of serious side effects.

Take care if you consume alcohol while you are taking NUEDEXTA as this might increase the risk of side effects such as dizziness and sleepiness.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, or if you are not using reliable contraception, ask your doctor for advice before taking this medicine.

As NUEDEXTA may cause harm to your unborn baby, its use is not recommended when you are pregnant or if you are a woman of childbearing potential not using contraception. Your doctor will discuss with you the risks and benefits of using this medicine in these situations.

It is not known whether the active substances of NUEDEXTA are expressed into human milk. Your doctor will decide if you should take this medicine while breast-feeding.

Driving and using machines

NUEDEXTA may cause dizziness. If this happens to you, do not drive or use machines.

NUEDEXTA contains lactose

If you have been told by your doctor that you have intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take NUEDEXTA

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Start of treatment (first 4 weeks):

Your doctor will start your treatment with NUEDEXTA 15 mg/9 mg capsules which should be taken by you as follows:

- For the first seven days of treatment: one capsule per day, taken in the morning.
- From the eighth day of treatment onwards: two capsules per day, one in the morning and one in the evening, 12 hours apart.

After 4 weeks:

Your doctor will assess you carefully. Depending on your response to the treatment, your doctor may either decide:

- to continue the treatment with NUEDEXTA 15 mg/9 mg capsules, or
- to give you a higher dose and to prescribe NUEDEXTA 23 mg/9 mg capsules to you.

Regardless of which strength of NUEDEXTA has been prescribed to you:

- continue the treatment with: two capsules per day (one capsule every 12 hours).

Use in older persons

No special dose adjustment of NUEDEXTA is required in older patients.

How to take NUEDEXTA

The capsule should be taken orally (by mouth) either with or without food at about the same time each day. When taking two capsules within 24 hours, you should leave about 12 hours between doses.

If you take more NUEDEXTA than you should

If you have taken more capsules than you should, speak to your doctor immediately.

Adverse reactions observed with this medicine may occur more often or may worsen and your doctor may perform some test and monitor you more closely.

Symptoms of dextromethorphan overdose include nausea, vomiting, stupor, coma, respiratory depression, seizures, increased heart rate, hyperexcitability, and toxic psychosis. Other effects include loss of coordinated movement (ataxia), involuntary eye movements (nystagmus), over contraction of the muscles (dystonia), blurred vision, and changes in muscle reflexes. Dextromethorphan may increase the risk of serotonin syndrome (see *Warnings and precautions and Possible side effects*).

Symptoms of quinidine overdose include irregular heartbeat and low blood pressure, and may also include vomiting, diarrhoea, ringing in the ears, high-frequency hearing loss, vertigo, blurred vision, double vision, increased sensitivity of the eyes to light, headache, confusion, and delirium (characterised by loss of attention, poor memory, disorientation, impaired speech).

If you forget to take NUEDEXTA

If you forget to take 1 or more capsules, you must not take a double dose to make up for the missed doses. Take your next dose at the usual time and make sure that approximately 12 hours passes between two doses.

If you stop taking NUEDEXTA

Do not stop taking this medicine without speaking to your doctor first, even if you begin to feel better. Stopping treatment may cause your symptoms to return.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Most side effects are mild to moderate. However, some side effects may be serious and require treatment.

Tell your doctor immediately if you experience severe symptoms including agitation, high blood pressure, restlessness, muscle spasms and twitching, high body temperature, excessive sweating, shivering, and tremor. These may be a sign of a serious condition called “serotonin syndrome”.

Tell your doctor immediately if you notice any of the following:

- excessive muscle stiffness (spasticity)
- excessively slow or shallow breathing (respiratory depression) and/or turning blue.

The most commonly reported side effects are gastrointestinal disorders (such as diarrhoea, nausea), nervous system disorders (such as dizziness, headache, somnolence) and fatigue.

If any of the above occur, stop taking the capsules and tell your doctor immediately

A list of all other side effects is provided below:

Common side effects

(may affect up to 1 in 10 people)

- diarrhoea, nausea
- dizziness, headache, drowsiness
- fatigue

Uncommon side effects

(may affect up to 1 in 100 people)

- decreased appetite
- anxiety
- distorted sense of taste (dysgeusia), sleepiness (hypersomnia), muscle spasticity, fainting (syncope), fall
- travel or motion sickness, ringing in the ears (tinnitus)
- heart problems, such as slow, fast or irregular heart beat, or altered results during an electrocardiogram (ECG – QT prolongation)
- abdominal pain, constipation, dry mouth, wind (flatulence), stomach discomfort, vomiting
- increased liver enzymes (GGT, AST, ALT)
- rash
- muscle spasms
- weakness (asthenia), irritability

Rare

(may affect up to 1 in 1,000 people)

- loss of appetite (anorexia)
- teeth grinding (bruxism), confusion, depressed mood, depression, disorientation (e.g. difficulty sensing time, direction, and recognition of people and places), early morning awakening, reduced emotional expressiveness (flat affect), hallucination, impulsive behaviour, indifference, insomnia, restlessness, disturbed sleep
- balance disorder, abnormal coordination, speech difficulties (dysarthria), movement dysfunction, pins and needles / tingling or numbness (paraesthesia), loss of feeling or function in the lower limbs (paraparesis), sedation
- double vision, blurred vision
- heart attack (myocardial infarction), heart palpitations
- nose bleeds, throat pain, excessively slow or shallow breathing (respiratory depression), runny nose, yawning
- abnormal faeces, indigestion, inflammation of the lining of the stomach (gastritis), numbness and abnormal sensation in the mouth, rectal pain, dry tongue
- gall stones, increased bilirubin levels in the blood, abnormal liver function test
- redness of the skin (erythema), excessive sweating (hyperhidrosis), loss of sensation or numbness of the face, night sweats
- musculoskeletal stiffness, muscle pain (myalgia), neck pain, pain in the limbs

- abnormally frequent daytime urination
- sexual dysfunction
- chest discomfort, chest pain, chills, feeling hot, gait disturbance (difficulty walking), flu-like illness, fever, decreased oxygen levels in the blood
- bone fractures (skeletal injury)

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store NUEDEXTA

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the bottle, blister and carton after EXP. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What NUEDEXTA contains

- The active substances are:
Each NUEDEXTA 15 mg/9 mg capsule contains dextromethorphan hydrobromide monohydrate, equivalent to 15.41 mg dextromethorphan and quinidine sulfate dihydrate, equivalent to 8.69 mg quinidine.

Each NUEDEXTA 23 mg/9 mg capsule contains dextromethorphan hydrobromide monohydrate, equivalent to 23.11 mg dextromethorphan and quinidine sulfate dihydrate, equivalent to 8.69 mg quinidine.
- The other ingredients are croscarmellose sodium, cellulose microcrystalline, silica colloidal, lactose monohydrate, magnesium stearate and gelatin, titanium dioxide (E171), red iron oxide (E172), printing ink (shellac glaze, propylene glycol, titanium dioxide (E171)).

What NUEDEXTA looks like and contents of the pack

Each bottle consists of high density polyethylene (HDPE) with a child resistant polypropylene cap and contains 60 hard capsules. Each bottle will be contained within a carton.

Only for NUEDEXTA 15 mg/9 mg: Blister packs consist of a PVC based clear film with aluminium foil seal and contains 13 hard capsules. Each blister is packed in a sleeve. This pack is intended to be used for the first 10 days of treatment.

Description:

- NUEDEXTA 15 mg/9 mg is a brick red gelatin capsule, size 1, with “DMQ / 20-10” printed in white ink on the capsule.
- NUEDEXTA 23 mg/9 mg is a brick red gelatin capsule, size 1, with “DMQ / 30-10” printed in white ink on the capsule and three white bands around the circumference.

Marketing Authorisation Holder and Manufacturer

Jenson Pharmaceutical Services Limited
Carradine House, 237 Regents Park Road
N3 3LF London
United Kingdom

This leaflet was last revised in {MM/YYYY}

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>

Medicinal product no longer authorised