

Assay Was One Part of Diagnosis

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in conjunction with, and not in lieu of, current standard diagnostic procedures, to aid the physician in the diagnosis of definite non-AD versus probable AD, possible AD or MCI [mild cognitive impairment].” Nymox CEO Paul Averbach, M.D., emphasized that the test should not be considered a stand-alone diagnostic, but, rather, “a measurement that adds useful information” and “moves the diagnosis along.” He said the test was particularly useful for primary care physicians, although it is intended for use by specialists as well. The FDA usually follows the recommendations of its advisory panels, which are not binding. A statement issued by Nymox after the panel’s vote said that the company will continue to pursue approval of the test kit and would work with the FDA to meet possible requirements for more data resulting from the panel’s suggestions.

The panel’s vote was based on the results of a prospective study of 200 patients presenting to one of nine cognitive/memories disorder centers for an evaluation by experts in AD and related cognitive disorders. The aim of the study was to show that the NTP test had a high degree of correlation with the results of a comprehen-

sive specialist exam using National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) criteria for diagnosing probable AD.

Patients had the urine NTP measurement and, based on a comprehensive evaluation that included a neurocognitive assessment, a Mini Mental State Examination, and structural imaging with CT, MRI, or other scans, were classified as having probable AD, possible AD MCI, or definite non-AD.

Patients categorized as “definite non-AD” were determined to have conditions that included age-related memory decline, pseudodementia due to depression, and metabolic disorders. An elevated NTP was set at above 22 mcg/mL, with a normal level at 22 mcg/mL or less; the test was performed on a first morning urine sample.

Nearly 80% (156 patients) had probable AD, possible AD, or MCI and were lumped together in the category of “not definite non-AD” in the study. Of the 57 patients with probable AD, 51 had an elevated NTP level and 6 had a normal level. Of the 56 with possible AD, 21 had an

elevated NTP level and 35 had a normal level. The 43 patients with MCI were split, with 22 having an elevated level and 21 having a normal level. Only 4 of the 44 patients with definite non-AD had an elevated NTP level.

The sensitivity of the test—the proportion of patients in the “not definite non-AD” category who had an elevated NTP measurement—was 60% (94 of 156 patients), according to the company’s analysis of the results.

The specificity of the test—the proportion of those with definite non-AD with a normal NTP measurement—was 91% (40 of 44 patients).

The positive predictive value—the percentage of patients with elevated NTP in the “not definite non-AD” category—was nearly 96% (94 of 98 patients).

The negative predictive value—the percentage of subjects with normal NTP who were in the definite non-AD category—was nearly 40% (40 of 102), according to Nymox.

Brain biopsy results confirming the diagnosis in a subject with clinically probable AD and an elevated NTP test were available in only one patient, a 39-year-old man with a family history of early-onset AD who died 2 years after diagnosis. This case was one of the clinical examples cited by the company to illustrate the usefulness of the test, particularly for primary care physicians.

Company documents included the case of a 73-year-old woman, with a 4- to 6-month history of forgetfulness, problems performing activities of daily living, and an elevated NTP of 33 mcg/mL. She was diagnosed with probable AD and over the next 2 years, declined significantly and was institutionalized, despite treatment. In another case, a 72-year-old man whose cognitive function had declined for 1-2 years and who had diffuse atrophy, prominent ventricles, and white matter lesions on MRI, but a normal neurologic exam and a normal NTP level of 19.4, was determined as falling in the definite non-AD category, and was normal over 2 years of follow-up.

But Ranjit Mani, M.D., a neurologist and medical reviewer in the FDA’s division of neuropharmacologic drug products, Rockville, Md., pointed out that while the results demonstrated that the

NTP level can help discriminate between probable AD and a patient with definite non-AD, a significant number of patients in the possible AD and MCI categories had NTP levels on both sides of the cutoff. This indicates that the test may have little value in distinguishing these two groups from the other two groups, raising the concern over the value of the test in clinical practice.

Panelist Joseph Parisi, M.D., professor of pathology at the Mayo Clinic, Rochester, Minn., raised the issue of whether NTP served as a reliable biomarker of the disease.

“Ideally, a biomarker should have some kind of relationship to disease pathogenesis, and I don’t think we have data to support that point.” He also found the data on the test’s sensitivity and specificity conflicting.

Other concerns raised by Dr. Mani and panel members included the intrasubject biologic variability seen in a small number of subjects who had more than one test and the high proportion of NTP measurements in the four diagnostic categories that clustered around the cutoff point. Some uncertainty remained as to whether urine NTP levels could be elevated in patients with other neurodegenerative diseases.

Neurologist Avindra Nath, M.D., Ph.D., of Johns Hopkins University, Baltimore, a panelist, said he was not entirely convinced that the study was adequate to justify its intended use, citing the small sample and the lack of longitudinal data on the patients.

A longitudinal study could answer some outstanding questions, such as the outcome of patients with “possible” AD, he added. He and other panelists observed that primary care physicians would likely refer any patient with memory problems to a specialist, regardless of the NTP result.

One of the two panelists who voted against the motion of nonapproval for the test, Oscar L. Lopez, M.D., associate professor of neurology at the University of Pittsburgh, remarked that the test probably would be useful for primary care physicians in rural areas who have no close access to specialists, although he added that the test results would not provide much information for the specialist who can make the diagnosis without the test. ■

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terminology. These categories are used in the listing below. The frequencies presented represent the proportion of the 911 individuals exposed to REQUIP who experienced events of the type cited on at least one occasion while receiving REQUIP. All reported events that occurred at least twice (or once for serious or potentially serious events), except those already listed, trivial events, and terms too vague to be meaningful, are included without regard to determination of a causal relationship to REQUIP, except that events very unlikely to be drug-related have been deleted. Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring in at least 1/100 patients and infrequent adverse events are those occurring in 1/100 to 1/1,000 patients. **Blood and Lymphatic System Disorders:** Infrequent: Anemia, lymphadenopathy. **Cardiac Disorders:** Frequent: Palpitations. Infrequent: Acute coronary syndrome, angina pectoris, angina unstable, bradycardia, cardiac failure, cardiovascular disorder, coronary artery disease, myocardial infarction, sick sinus syndrome, tachycardia. **Congenital, Familial, and Genetic Disorders:** Infrequent: Pigmented nevus. **Ear and Labyrinth Disorders:** Infrequent: Ear pain, middle ear effusion, tinnitus. **Endocrine Disorders:** Infrequent: Goiter, hypothyroidism. **Eye Disorders:** Infrequent: Blepharitis, conjunctival hemorrhage, conjunctivitis, eye irritation, eye pain, keratoconjunctivitis sicca, vision blurred, visual acuity reduced, visual disturbance. **Gastrointestinal Disorders:** Frequent: Abdominal pain, constipation, gastroesophageal reflux disease, stomach discomfort, toothache. Infrequent: Abdominal adhesions, abdominal discomfort, abdominal distension, abdominal pain lower, duodenal ulcer, dysphagia, eructation, flatulence, gastric disorder, gastric hemorrhage, gastric polyps, gastric ulcer, gastritis, gastrointestinal pain, hematemesis, hemorrhoids, hiatus hernia, intestinal obstruction, irritable bowel syndrome, loose stools, mouth ulceration, pancreatitis acute, peptic ulcer, rectal hemorrhage, reflux esophagitis. **General Disorders and Administration Site Conditions:** Frequent: Asthenia, chest pain, influenza-like illness, rigors. Infrequent: Chest discomfort, feeling cold, feeling hot, hunger, lethargy, malaise, edema, pain, pyrexia. **Hepatobiliary Disorders:** Infrequent: Cholecystitis, cholelithiasis, ischemic hepatitis. **Immune System Disorders:** Infrequent: Hypersensitivity. **Infections and Infestations:** Frequent: Bronchitis, gastroenteritis, gastroenteritis viral, lower respiratory tract infection, rhinitis, tooth abscess, urinary tract infection. Infrequent: Appendicitis, bacterial infection, bladder infection, bronchitis acute, candidiasis, cellulitis, cystitis, diarrhea infectious, diverticulitis, ear infection, folliculitis, fungal infection, gastrointestinal infection, herpes simplex, infected cyst, laryngitis, localized infection, mastitis, otitis externa, otitis media, pharyngitis, pneumonia, postoperative infection, respiratory tract infection, tonsillitis, tooth infection, vaginal candidiasis, vaginal infection, vaginal mycosis, viral infection, viral upper respiratory tract infection, wound infection. **Injury, Poisoning, and Procedural Complications:** Infrequent: Concussion. Infrequent: Concussion, lower limb fracture, post procedural hemorrhage, road traffic accident. **Investigations:** Infrequent: Blood cholesterol increased, blood iron decreased, blood pressure increased, blood urine present, hemoglobin decreased, heart rate increased, protein urine present, weight decreased, weight increased. **Metabolic and Nutrition Disorders:** Infrequent: Anorexia, decreased appetite, diabetes mellitus non-insulin-dependent, fluid retention, gout, hypercholesterolemia. **Musculoskeletal and Connective Tissue Disorders:** Frequent: Muscle spasms, musculoskeletal stiffness, myalgia, neck pain, osteoarthritis, tendonitis. Infrequent: Arthritis, aseptic necrosis bone, bone pain, bone spur, bursitis, groin pain, intervertebral disc degeneration, intervertebral disc protrusion, joint stiffness, joint swelling, localized osteoarthritis, monoarthritis, muscle contracture, muscle tightness, muscle twitching, osteoporosis, rotator cuff syndrome, sacroiliitis, synovitis. **Neoplasms Benign, Malignant, and Unspecified:** Infrequent: Anaplastic thyroid cancer, angiomylipoma, basal cell carcinoma, breast cancer, gastric cancer, gastrointestinal stromal tumor, malignant melanoma, prostate cancer, skin papilloma, squamous cell carcinoma, uterine leiomyoma. **Nervous System Disorders:** Frequent: Hypoesthesia, migraine. Infrequent: Amnesia, aphasia, ataxia, balance disorder, benign intracranial hypertension, burning sensation, carpal tunnel syndrome, disturbance in attention, dizziness postural, dysgeusia, dyskinesia, head discomfort, hyperesthesia, hypersomnia, lethargy, loss of consciousness, memory impairment, migraine with aura, migraine without aura, neuralgia, sciatica, sedation, sinus headache, sleep apnea syndrome, syncope vasovagal, tension headache, transient ischemic attack, tremor. **Psychiatric Disorders:** Frequent: Anxiety, depression, irritability, sleep disorder. Infrequent: Abnormal dreams, agitation, bruxism, confusional state, depressed mood, disorientation, early morning awakening, libido decreased, loss of libido, mood swings, nervousness, nightmare, panic attack, stress symptoms, tension. **Renal and Urinary Disorders:** Infrequent: Dysuria, hematuria, hypertonic bladder, micturition disorder, nephrolithiasis, nocturia, pollakiuria, proteinuria, urinary retention. **Reproductive System and Breast Disorders:** Frequent: Erectile dysfunction. Infrequent: Breast cyst, dysmenorrhea, menorrhagia, pelvic peritoneal adhesions, postmenopausal hemorrhage, premenstrual syndrome, prostatitis. **Respiratory, Thoracic and Mediastinal Disorders:** Frequent: Asthma, pharyngolaryngeal pain. Infrequent: Dry throat, dyspnea, epistaxis, hemoptysis, hoarseness, interstitial lung disease, nasal mucosal disorder, nasal polyps, respiratory tract congestion, rhinorrhea, sinus congestion, sneezing, wheezing, yawning. **Skin and Subcutaneous Tissue Disorders:** Frequent: Night sweats, rash. Infrequent: Acne, actinic keratosis, alopecia, cold sweat, dermatitis allergic, dermatitis contact, eczema, exanthem, face edema, photosensitivity reaction, pruritus, psoriasis, rash pruritic, skin lesion, urticaria. **Vascular Disorders:** Frequent: Hot flush, hypertension, hypotension. Infrequent: atherosclerosis, circulatory collapse, flushing, hematoma, thrombosis, varicose vein.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: REQUIP is not a controlled substance.

Physical and Psychological Dependence: Animal studies and human clinical trials with REQUIP did not reveal any potential for drug-seeking behavior or physical dependence.

OVERDOSAGE

In the Parkinson’s disease program, there have been patients who accidentally or intentionally took more than their prescribed dose of ropinirole. The largest overdose reported in the Parkinson’s disease clinical trials was 435 mg taken over a 7-day period (62.1 mg/day). Of patients who received a dose greater than 24 mg/day, reported symptoms included adverse events commonly reported during dopaminergic therapy (nausea, dizziness), as well as visual hallucinations, hyperhidrosis, claustrophobia, chorea, palpitations, asthenia, and nightmares. Additional symptoms reported for doses of 24 mg or less or for overdoses of unknown amount included vomiting, increased coughing, fatigue, syncope, vasovagal syncope, dyskinesia, agitation, chest pain, orthostatic hypotension, somnolence, and confusional state.

Overdose Management: It is anticipated that the symptoms of overdose with REQUIP will be related to its dopaminergic activity. General supportive measures are recommended. Vital signs should be maintained if necessary. Removal of any unabsorbed material (e.g., by gastric lavage), should be considered.

Dosing Consideration for Parkinson’s Disease and RLS: If a significant interruption in therapy with REQUIP has occurred, retreatment of therapy may be warranted.

gsk GlaxoSmithKline

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Research Triangle Park, NC 27709

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May 2005

BRS-RQ:11

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RQP275R0

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July 2005

Hypertension May Impair Memory

Impaired cerebral blood flow may contribute to the mild deficits in memory and other cognitive functions in people with hypertension, compared with their normotensive peers, according to J.R. Jennings, Ph.D., of the University of Pittsburgh, and associates.

The researchers assessed regional cerebral blood flow using MRI and PET brain scans in 37 hypertensive and 59 normotensive subjects (median age 60 years) who performed a battery of memory and sensorimotor tasks. The blood flow response to performance demands was sig-

nificantly blunted in certain areas of the brain in hypertensive subjects, who also showed mild deficits in performance, compared with the normotensive subjects (Neurology 2005;64:1358-65).

“Our results are far from conclusive but suggest that vascular factors may play a role” in mild memory and cognitive deficits seen in hypertensive people, the researchers said. Moreover, the findings show that common systemic diseases such as hypertension can have unanticipated effects on brain function, they added.

—Mary Ann Moon