OTSUKA AND PROTEUS® ANNOUNCE
THE FIRST U.S. FDA APPROVAL OF A DIGITAL MEDICINE SYSTEM:
ABILIFY MYCITE® (aripiprazole tablets with sensor)

- *ABILIFY MYCITE (aripiprazole tablets with sensor) is a drug-device combination product comprised of Otsuka's oral aripiprazole tablets embedded with an Ingestible Event Marker (IEM) sensor. The ABILIFY MYCITE System includes: ABILIFY MYCITE, the MYCITE® Patch (wearable sensor); the MYCITE APP (a smartphone application); and web-based portals for healthcare providers and caregivers*[1]
- *The system records medication ingestion and communicates it to the patient and healthcare provider. In addition, it can collect data on activity level, as well as self-reported rest and mood which, with patient consent, can be shared with the healthcare provider and selected members of the family and care team*[1]
- *The system provides an objective summary of drug ingestion over time, to help enhance collaboration with healthcare providers who treat patients with certain serious mental illnesses*[1,2,3]

Tokyo, Japan and Redwood City, Calif. – November 14, 2017 – Otsuka Pharmaceutical Co., Ltd. (Otsuka) and Proteus Digital Health (Proteus) today announce that the United States Food and Drug Administration (FDA) has granted the first approval of a digital medicine system, ABILIFY MYCITE® (aripiprazole tablets with sensor), a drug-device combination product comprised of Otsuka's oral aripiprazole tablets embedded with an Ingestible Event Marker (IEM) sensor. The ABILIFY MYCITE System includes: ABILIFY MYCITE, the MYCITE® Patch (a wearable sensor, developed by Proteus); the MYCITE® APP, a smartphone application (app), used with a compatible smartphone to display information for the patient; and web-based portals for healthcare providers and caregivers that display a summary of aripiprazole ingestion over time.[1] Only functions of the app related to tracking drug ingestion have been approved by the FDA. ABILIFY MYCITE, an atypical antipsychotic, is indicated in adults for the treatment of schizophrenia, for the treatment of acute manic and mixed episodes, and maintenance treatment of bipolar I disorder as monotherapy, and as adjunctive therapy to lithium or valproate, and the adjunctive treatment of major depressive disorder.[1] ABILIFY MYCITE is intended to track drug ingestion. The ability of ABILIFY MYCITE to improve patient compliance or modify aripiprazole dosage has not been established. The use of ABILIFY MYCITE to track drug ingestion in "real-time" or during an emergency is not recommended because detection may be delayed or not occur.

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death (1.6 to 1.7 times) compared to placebo-treated patients. ABILIFY MYCITE is not approved for the treatment of patients with dementia-related psychosis. Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults. Those on antidepressant therapy should be monitored closely for worsening, and for emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber. ABILIFY MYCITE is not approved for use in pediatric patients (see IMPORTANT SAFETY INFORMATION below).[1]

"The approval of ABILIFY MYCITE, the first digital medicine system, means that for the first time in my years of experience as a psychiatrist, there is an innovative way to provide individuals with serious mental illness, and selected

members of their families and care teams, with information on objective medication taking patterns to help inform the patient's illness management and personalized treatment plan. This information allows the opportunity for an open dialogue with the patient," said John Kane, MD, SVP, Behavioral Health Services, Northwell Health and Chair, Psychiatry, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell. "Until now, pharmacologic therapy for serious mental illness has been missing a systematic approach to objectively track and signal that a patient has taken their drug."

A person living with serious mental illness, in collaboration with his or her physician, decides whether this new digital medicine system may help them manage their approach to treatment.[1] The system has been designed for the individual with serious mental illness to allow them to record their daily medication intake and have a more informed dialogue with their healthcare team.[1] The system is intended to integrate into individuals' lives, and individuals indicate through the app which member(s) of their care team can access information about their medication ingestion, activity, and self-reported mood and rest.[1,4,5] For physicians, this information, assessed in collaboration with the individual, helps facilitate a more open dialogue.[1,6] The hope is to provide additional clarity to better inform decision-making for physicians and their patients. Patients can discontinue sharing some information from the system, or opt out of the program altogether, at any time.

Otsuka's approach for this first-of-its-kind treatment is novel for a pharmaceutical company. As such, the launch of the ABILIFY MYCITE system will be conducted in close collaboration with only a select number of health plans and providers, who will identify a limited number of appropriate adults with schizophrenia, bipolar I disorder, or major depressive disorder who may benefit from this new digital medicine system.[1] This limited rollout is purposeful, as having fewer people using the system initially means their prescribers, health plans, and Otsuka can focus on learning from these patients' experiences. Through ongoing feedback from those using the system every day, Otsuka will further enhance the experience for all prospective users of the ABILIFY MYCITE system. This initial limited rollout will be a crucial step in determining Otsuka's broader go-to-market plan.

Tatsuo Higuchi, president and representative director of Otsuka Pharmaceutical Co., Ltd., remarked, "This approval marks a potentially transformative juncture in our more than 25 years of experience in the field of mental health therapies. We remain committed to making a difference for individual patients and their care team by helping address the challenge of objectively measuring medication ingestion. Our rollout of the ABILIFY MYCITE system will be done in phases to obtain, and respond to, feedback from healthcare providers and their patients."

Andrew Thompson, president and chief executive officer of Proteus Digital Health said, "The time is right for the category of Digital Medicines to be available to appropriate patients with serious mental illness. Consumers already manage important tasks like banking, shopping, and communicating with friends and family by using their smart phones, as they go about their daily lives. With this FDA approval, Otsuka can help enable individuals with serious mental illness to engage with their care team about their treatment plan in a new way."

About the ABILIFY MYCITE® System

The ABILIFY MYCITE system is composed of the following components:

- ABILIFY MYCITE, the first FDA-approved digital medicine system, is comprised of an Otsuka aripiprazole tablet embedded at the point of manufacture with an IEM sensor. This IEM sensor is the size of a grain of sand, and is made up of ingredients found in food.[1] The IEM sensor activates when in contact with stomach fluid and communicates to a wearable sensor, called the MYCITE Patch. The IEM sensor is then digested and eliminated from the body.[1]
- The MYCITE Patch detects and records the date and time of the ingestion of the tablet, as well as, certain physiological data such as activity level, and communicates this and the tablet ingestion data to the MYCITE APP on a compatible mobile device.[1]
- The MYCITE APP allows individuals to review their objective medication ingestion and daily activity level, as well as enter their mood and rest.[1] They can also invite others to view their data.[1]
- Web-based dashboards are provided to healthcare providers and caregivers. These dashboards give the healthcare provider the ability to display the individual's drug ingestion patterns over time. With patient consent, selected members of the family and care team can also access this information, as well as, the individual's daily activity level and self-reported mood and rest.[1]

The ABILIFY MYCITE System is intended to track if ABILIFY MYCITE has been taken. It can take 30 minutes to 2 hours to detect ingestion of the tablet. Sometimes the system might not detect that the medication has been taken. If the MYCITE APP does not indicate that the ABILIFY MYCITE tablet was taken, do not repeat the dose.

Please visit www.ABILIFYMYCITE.com for more information and media resources.

INDICATIONS and IMPORTANT SAFETY INFORMATION for ABILIFY MYCITE® (aripiprazole tablets with sensor)

INDICATIONS

ABILIFY MYCITE, a drug-device combination product comprised of aripiprazole tablets embedded with an Ingestible Event Marker (IEM) sensor intended to track drug ingestion, is indicated in adults for the:

- Treatment of adults with schizophrenia
- Treatment of bipolar I disorder:
  - Acute treatment of manic and mixed episodes as monotherapy and as adjunct to lithium or valproate
  - Maintenance treatment as monotherapy and as adjunct to lithium or valproate
- Adjunctive treatment of adults with major depressive disorder

Limitations of Use:

- The ability of ABILIFY MYCITE to improve patient compliance or modify aripiprazole dosage has not been established
- The use of ABILIFY MYCITE to track drug ingestion in "real-time" or during an emergency is not recommended because detection may be delayed or not occur

IMPORTANT SAFETY INFORMATION

WARNING: INCREASED MORTALITY IN ELDERLY WITH DEMENTIA-RELATED PSYCHOSIS

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death (1.6 to 1.7 times) compared to placebo-treated patients. ABILIFY MYCITE is not approved for the treatment of patients with dementia-related psychosis.

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS

Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults. Those on antidepressant therapy should be monitored closely for worsening, and for emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber. The safety and effectiveness of ABILIFY MYCITE have not been established in pediatric patients.

Contraindication: Known hypersensitivity reaction to aripiprazole. Reactions have ranged from pruritus/urticaria to anaphylaxis.

Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients with Dementia-Related Psychosis: Increased incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, have been reported in clinical trials of elderly patients with dementia-related psychosis treated with aripiprazole.

Neuroleptic Malignant Syndrome (NMS): NMS is a potentially fatal symptom complex reported in association with administration of antipsychotic drugs, including ABILIFY MYCITE. Clinical signs of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability. Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. Manage NMS with immediate discontinuation of ABILIFY MYCITE, intensive symptomatic treatment, and monitoring.

Tardive Dyskinesia (TD): Risk of TD, and the potential to become irreversible, are believed to increase with duration of treatment and in total cumulative dose of antipsychotic drugs. TD can develop after a relatively brief treatment period, even at low doses, or after discontinuation. If antipsychotic treatment is withdrawn, TD may remit, partially or completely. Prescribing should be consistent with the need to minimize TD.

Metabolic Changes: Atypical antipsychotic drugs have caused metabolic changes including:

- **Hyperglycemia/Diabetes Mellitus:** Hyperglycemia, in some cases extreme and associated with ketoacidosis, hyperosmolar coma, or death, has been reported in patients treated with atypical antipsychotics including aripiprazole. Patients with diabetes mellitus should be regularly monitored for worsening of glucose control; those with risk factors for diabetes (e.g., obesity, family history of diabetes), should undergo baseline and periodic fasting blood glucose testing. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia should also undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.
- **Dyslipidemia:** Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.
- **Weight Gain:** Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

Pathological Gambling and Other Compulsive Behaviors: Intense urges, particularly for gambling, and the inability to control these urges have been reported while taking aripiprazole. Other compulsive urges have been reported less frequently. Prescribers should ask patients or their caregivers about the development of new or intense compulsive urges. Consider dose reduction or stopping ABILIFY MYCITE if such urges develop.

Orthostatic Hypotension: ABILIFY MYCITE may cause orthostatic hypotension and should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or conditions which would predispose them to hypotension.

Falls: Antipsychotics may cause somnolence, postural hypotension, motor and sensory instability, which may lead to falls causing fractures or other injuries. For patients with diseases, conditions, or medications that could exacerbate these effects, complete fall risk assessments when initiating treatment and recurrently during therapy.

Leukopenia, Neutropenia, and Agranulocytosis: Leukopenia, neutropenia and agranulocytosis have been reported with antipsychotics. Monitor complete blood count in patients with pre-existing low white blood cell count (WBC)/absolute neutrophil count or history of drug-induced leukopenia/neutropenia. Discontinue ABILIFY MYCITE at the first sign of a clinically significant decline in WBC and in severely neutropenic patients.

Seizures: ABILIFY MYCITE should be used with caution in patients with a history of seizures or with conditions that lower the seizure threshold.

Potential for Cognitive and Motor Impairment: ABILIFY MYCITE may impair judgment, thinking, or motor skills. Instruct patients to avoid operating hazardous machinery, including automobiles, until they are certain ABILIFY MYCITE does not affect them adversely.

Body Temperature Regulation: Use ABILIFY MYCITE with caution in patients who may experience conditions that increase body temperature (e.g., strenuous exercise, extreme heat, dehydration, or concomitant use with anticholinergics).

Dysphagia: Esophageal dysmotility and aspiration have been associated with ABILIFY MYCITE. Use caution in patients at risk for aspiration pneumonia.

Dosage adjustments and Cytochrome P450 Considerations: For patients with schizophrenia and bipolar I disorder taking ABILIFY MYCITE who are:

- Known CYP2D6 poor metabolizers, administer half the recommended dose
- Known CYP2D6 poor metabolizers taking concomitant strong CYP3A4 inhibitors (e.g., itraconazole, clarithromycin), administer a quarter the recommended dose.
- Taking strong CYP2D6 (e.g., quinidine, fluoxetine, paroxetine) or CYP3A4 inhibitors, administer half the recommended dose.
- Taking strong CYP2D6 and CYP3A4 inhibitors, administer a quarter the recommended dose. When co-administered drug is withdrawn, adjust ABILIFY MYCITE dosage to its original level.
- Taking strong CYP3A4 inducers (e.g., carbamazepine, rifampin), double recommended dose over 1 to 2 weeks. When co-administered drug is withdrawn, reduce ABILIFY MYCITE dosage to original level over 1 to 2 weeks.

Commonly Observed Adverse Reactions (incidence ≥5% and at least twice that for placebo) in adult patients:

- Schizophrenia: akathisia
- Bipolar mania (monotherapy): akathisia, sedation, restlessness, tremor, and extrapyramidal disorder
- Bipolar mania (adjunctive therapy with lithium or valproate): akathisia, insomnia, and extrapyramidal disorder
- Major depressive disorder (adjunctive treatment to antidepressant therapy): akathisia, restlessness, insomnia, constipation, fatigue, and blurred vision

Dystonia: Symptoms of dystonia may occur in susceptible individuals during the first days of treatment and at low doses.

Skin Irritation for MYCITE Patch: Symptoms of skin irritation localized at the site of the MYCITE Patch may occur. In clinical studies, 12.4% of patients (n=61) experienced skin rashes at the site of patch placement

Pregnancy: Neonates exposed to antipsychotic drugs, including ABILIFY MYCITE, during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms. Consider the benefits and risks of ABILIFY MYCITE and possible risks to the fetus when prescribing ABILIFY MYCITE to a pregnant woman. Advise pregnant women of potential fetal risk.

Lactation: Aripiprazole is present in human breast milk; however, there are insufficient data to assess the amount in human milk, effects on the breastfed infant, or effects on milk production. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for ABILIFY MYCITE and any potential adverse effects on the infant or from the underlying maternal condition.

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

Please see accompanying FULL PRESCRIBING INFORMATION, including **BOXED WARNING**.

About Otsuka Pharmaceutical Co., Ltd.

Otsuka Pharmaceutical is a global healthcare company with the corporate philosophy: "Otsuka-people creating new products for better health worldwide." Otsuka researches, develops, manufactures and markets innovative products, with a focus on pharmaceutical products for the treatment of diseases and nutraceutical products for the maintenance of everyday health.

In pharmaceuticals, Otsuka is a leader in the challenging area of mental health and also has research programs on several under-addressed diseases including tuberculosis, a significant global public health issue. These commitments illustrate how Otsuka is a "big venture" company at heart, applying a youthful spirit of creativity in everything it does.

Otsuka Pharmaceutical is a subsidiary of Otsuka Holdings Co., Ltd. headquartered in Tokyo, Japan. The Otsuka group of companies employed 45,000 people worldwide and had consolidated sales of approximately USD 11 billion (€ 9.9 billion) in 2016.

All Otsuka stories start by taking the road less travelled. Learn more about Otsuka Pharmaceutical Company on its global website at https://www.otsuka.co.jp/en. Learn more about Otsuka in the U.S. at www.otsuka-us.com and connect with us on Twitter at @OtsukaUS.

About Proteus Digital Health®

Proteus Digital Health is enabling a new category of therapy: Digital Medicines. These offerings include widely used drugs, formulated so they communicate when they have been swallowed; a wearable patch that detects medicines and captures physiologic response; mobile applications to support patient self-care and physician decision-making; and data analytics to serve the needs of health system managers. The company has more than 440 issued patents that protect this enabling technology, and regulatory clearances in the U.S., European Union and China.

Proteus Digital Health is privately held by investors that include Carlyle, Essex Woodlands, Kaiser Permanente®, Medtronic®, Novartis®, Otsuka®, Oracle®, and ON Semiconductor®. Further information is available at: www.proteus.com. Connect with us on Twitter @ProteusDH.

About the Proteus Digital Health® Ingestible Sensor and Wearable Sensor Patch

The Proteus ingestible sensor and wearable sensor patch have been cleared by the Food and Drug Administration (FDA) for use in the United States, CE marked per the Medical Device Directive for use in the European Union and approved by the China Food and Drug Administration (CFDA) for use in China. More information is available at www.proteus.com.

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