Drug Monograph

Drug Name: **Abilify MyCite® (aripiprazole with sensor) tablets**
Drug Class: **Antipsychotics, Second Generation**
Prepared For: MO HealthNet
Prepared By: Conduent

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms:	Abilify MyCite is available as oral tablets embedded with an Ingestible Event Marker (IEM) sensor containing 2 mg, 5 mg, 10 mg, 15 mg, 20 mg, and 30 mg of aripiprazole. Co-packaged with 7 MYCITE Patches (wearable sensors).
Manufacturer:	Distributed by: Otsuka America Pharmaceutical, Inc., Rockville, MD 20850.
Summary of Findings:	The efficacy of Abilify MyCite for the treatment of adults with schizophrenia, treatment of adults with manic and mixed episodes associated with bipolar I disorder, and adjunctive treatment of adults with major depressive disorder (MDD) has been established and is based on trials of aripiprazole. The main study of Abilify MyCite for approval was to determine usability and safety, in which the primary outcome measured was the proportion of participants who are able to pair and apply a patch independently and successfully by the end of the week 8 study visit as defined by a score of 91 to 100 on the Subject Ability to Use System Scale – Healthcare Professional Version (SAUSS-HCP). A participant was considered to have successfully and independently applied a patch if the SAUSS-HCP was at least 91 for at least one post-baseline score. An average of 55% of participants were able to successfully use the device.
Status Recommendation:	☒ Clinical Edit ☐ PDL ☐ Open Access ☐ Prior Authorization (PA) Required
Type of PA Criteria:	☒ Appropriate Indications ☐ Non-Preferred Agent ☐ No PA Required ☐ Preferred

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [1-4]

Schizophrenia is a mental disorder characterized by disruptions in thought processes, perceptions, emotional responsiveness and social interactions, and tends to be diagnosed in the late teens to early thirties. Symptoms include hallucinations, delusions, and thought disorders. Schizophrenia can be severe and disabling. Schizophrenia is one of the top 15 leading causes of disability worldwide. Prevalence of schizophrenia and other psychotic disorders are often combined due to complexities with diagnosis and is estimated to be about 3.5 million people in the US.

Bipolar I disorder is defined by manic episodes that last at least 7 days or by symptoms that are so severe that a person needs immediate hospital care. Usually depressive episodes occur and last at least 2 weeks. Manic symptoms include feeling very elated, lots of energy, having trouble sleeping, and conducting risky behaviors. Depressive symptoms include feeling down, little energy, decreased activity, and suicidal thoughts. Bipolar I disorder affects 5.7 million people in the US with onset in the late teens or early twenties.

MDD is one of the most common mental disorders in the US and is estimated to affect 17.3 million adults. Symptoms of MDD include a depressed mood or loss of interest or pleasure in daily activities, as well as problems with sleep, eating, energy, concentration and self-worth. MDD can result in severe impairments that interfere with or limit the ability to carry out life activities.

Medication non-adherence is a significant concern for patients with psychiatric disorders. Studies show 50% of patients with MDD and schizophrenia and 35% of patients with bipolar I are adherent with their prescribed medications. Non-adherence can cause exacerbation of their illness, re-hospitalization, poor psychosocial outcomes, relapses, reduced effectiveness of treatment and increased suicide and substance abuse.

Dosage Form [5]

Abilify MyCite is available as oral tablets embedded with an Ingestible Event Marker (IEM) sensor containing 2 mg, 5 mg, 10 mg, 15 mg, 20 mg, and 30 mg of aripiprazole.

Manufacturer [5]

Distributed by: Otsuka America Pharmaceutical, Inc., Rockville, MD 20850.

Indication(s) [5]

Abilify MyCite is indicated for the treatment of adults with 1) Schizophrenia, 2) Treatment of bipolar I disorder (acute treatment of adults with manic and mixed episodes as monotherapy and as adjunct to lithium or valproate; maintenance treatment of adults as monotherapy and as adjunct to lithium or valproate), and 3) Adjunctive treatment of adults with major depressive disorder.

Clinical Efficacy [5-8] (mechanism of action/pharmacology, comparative efficacy)

Abilify MyCite is an atypical antipsychotic. The mechanism of action in the treatment of schizophrenia, bipolar 1 disorder, or adjunctive treatment of major depressive disorder is unknown. However, the efficacy of aripiprazole could be mediated through a combination of partial agonist activity at D_2 and 5-HT_{1A} receptors and antagonist activity at 5-HT_{2A} receptors.

Pharmacokinetics:

Absorption	Bioavailability: 87% Time to peak plasma concentrations: 3-5 hours
Metabolism	Hepatic dehydrogenation, hydroxylation and N-dealkylation via CYP2D6 and CYP3A4
Excretion	Feces: 55% (~18% of total oral dose as unchanged drug) Urine: 25% (<1% of total oral dose as unchanged drug)
Half-life	Aripiprazole: 75 hours Dehydro-aripiprazole (active metabolite): 94 hours

Clinical Trials Experience:

STUDY 1 DESIGN	Open-label Study to Assess Usability of the Medical Information Device #1(MIND1) System in Adults with Schizophrenia on Oral Aripiprazole (n=67)
INCLUSION CRITERIA	• 18-65 years of age. • Primary current diagnosis of schizophrenia (as defined by DSM-V criteria). • Currently prescribed and on stable dose of oral aripiprazole for schizophrenia at single daily dose of 10, 15, 20 or 30 mg. • Able and willing to carry MIND1 System smartphone and complete all tasks, as well as adequately operate all devices. Caregiver or third-party assistance can be utilized if needed. • Possess the capacity to utilize the technology interfaces. • Not pregnant or breast-feeding or planning to become pregnant. • Skin on anterior chest above lower edge of rib cage that is free of any dermatological problems.
EXCLUSION CRITERIA	• Current DSM-V diagnosis other than schizophrenia that may impact ability to participate in study. • Currently on a long-acting injectable antipsychotic. • Incapable of using the MIND1 System technology, even with assistance. • Answer of “Yes” on the Columbia-Suicide Severity Rating Scale (C-SSRS) to Suicidal Ideation Item 4 and Suicidal Ideation Item 5 occurring within last 3 months, OR “Yes” to any of the 5 C-SSRS Suicidal Behavior Items occurring within last 1 year, OR presents a serious risk of suicide in the opinion of the investigator. • Received any investigational product within last 30 days, including MIND1 system. • History of medical condition that would increase risk of a significant adverse effect or interfere with assessments of safety or usability. • Diagnosis or history of seizures, neuroleptic malignant syndrome,

	or clinically significant tardive dyskinesia. • Known allergic, intolerant, or unresponsive to prior treatment with aripiprazole or other quinolinones. • History of hypersensitivity to antipsychotic agents. • Known allergy to adhesive tape or any pertinent components of the patch or IEM. • Sexually active women of childbearing potential who will not commit to utilizing 2 of the approved birth control methods or who will not remain abstinent during study and for 30 days following the last dose of study medication. • Sexually active males (unless sterile, defined as having had a bilateral orchiectomy) who will not commit to utilizing 2 of the approved birth control methods or who will not remain abstinent during the study and for 90 days following the last dose of study drug. • Current history (within the past month) of a substance use disorder which meets DSM-V criteria, or demonstrates a positive result on urine drug test during screen (excluding tobacco and cannabinoids). • Acutely psychotic or exhibit symptoms currently requiring hospitalization, in the opinion of the investigator. • Unwilling to refrain from use of topical products on the skin patch sites. • Unwilling or unable to complete evaluations included in the study (unwilling to be recorded or inability to distinguish colors).
TREATMENT REGIMEN	Patients discontinued their normally prescribed oral aripiprazole tablets and received aripiprazole tablets embedded with an IEM at the previously prescribed dose on a once-daily dosing schedule for 8 weeks.
RESULTS	The primary outcome measured was the proportion of participants who are able to pair and apply a patch independently and successfully by the end of the week 8 study visit as defined by a score of 91 to 100 on the SAUSS-HCP. A participant was considered to have successfully and independently applied a patch if the SAUSS-HCP was at least 91 for at least one post-baseline score. An average of 55% of participants were able to successfully use the device.
SAFETY	Discussed in the Adverse Effects section below.

STUDY 2 DESIGN	A multicenter, open-label, pilot study evaluating the functionality of an integrated call center for a digital medicine system to optimize monitoring of adherence to oral aripiprazole in adult patients with serious mental illness" (n=49)
INCLUSION CRITERIA	• 18-65 years of age • Primary diagnosis of bipolar I disorder, MDD, or schizophrenia defined by DSM-5 criteria • Receiving treatment with stable, once daily oral doses of

	aripiprazole in outpatient setting • Able to read and understand English • Willing to use and keep a study-provided smartphone containing the digital medicine system (DMS) software application with them at all times (with satisfactory mobile phone reception or Wi-Fi) • Caregiver assistance allowed • Area of undamaged skin on torso (free of any dermatologic problems, such as dermatitis or abrasions) • Patients who were prescribed concomitant antidepressants and/or psychotropic medications were required to have taken stable doses and regimens of those medications for at least 2 weeks and be deemed likely to remain on such therapy during study
EXCLUSION CRITERIA	• DSM-5 defined psychiatric diagnoses other than bipolar I disorder, MDD, or schizophrenia or any diagnosis/condition that might impair ability to participate • Patients with prominent negative symptoms • Borderline, antisocial, paranoid, schizoid, schizotypal, or histrionic personality disorders • Positive suicidal screen on item 4 or 5 of C-SSRS or deemed by investigator to be at serious risk of suicide • Underlying medical conditions that would put the patient at increased risk for adverse events • Unstable mood or acute psychotic symptoms at screening that would likely require hospitalizations
TREATMENT REGIMEN	Patients received the oral drug-device combination (aripiprazole + IEM) according to their stable prescribed dose for 8 weeks (during 2 phases), n=49. Scheduled outbound calls from the integrated call center were performed 48 hours after patients received DMS training at study sites and on day 8 to assess for any difficulties the patient may be having. Patients were also contacted between visits based on predefined triggers to assist in system compliance. The first phase was a 2-week prospective phase during which patients' DMS use was assessed. Patients who were engaged (% of patch wear by the patient) and worse the DMS patch $\geq$ 50% of the times during the 7 days before their 2 week visit continued into the 6-week observational phase.
RESULTS	Primary outcome was to evaluate the functionality of an integrated call center in optimizing the use of the DMS by adult patients receiving oral aripiprazole for treatment of bipolar I disorder, major depressive disorder, or schizophrenia. The call center was established to provide coordinated feedback to the patient and investigative site to optimize use of the DMS. After the initial 2-week prospective phase, 40 of the 49 patients were enrolled into the following 6-week observation phase and 77.6% completed the study. 8.2% of patients were inconsistent with patch wearing.
SAFETY	Discussed in the Adverse Effects section below.

Contraindications [5,6]

Hypersensitivity to aripiprazole or any component of the formulation.

Warnings and Precautions [5,6]

- Increased mortality in elderly patients with dementia-related psychosis
- Increased risk of suicidal thoughts and behaviors in pediatric, adolescent and young adult patients with major depressive disorder and other psychiatric disorders
- Cerebrovascular adverse reactions, including stroke, in elderly patients with dementia-related psychosis
- Neuroleptic malignant syndrome (NMS)
- Tardive dyskinesia
- Metabolic changes (weight gain, hyperglycemia, dyslipidemia)
- Pathological gambling and other compulsive behaviors
- Orthostatic hypotension
- Increased risk of falls
- Leucopenia, neutropenia, and agranulocytosis
- Seizures
- Potential for cognitive and motor impairment
- Impaired body temperature regulation
- Esophageal dysmotility and aspiration

Adverse Effects [7,8]

Most common, ≥ 4%	Study 1 (n = 67) %	Study 2 (n = 49) %
Rash	8	22.4
Pruritus	13	4.1
Upper respiratory tract infection	8	
Hypertension	8	
Increased appetite	6	
Somnolence	6	
Erythema	6	4.1
Dermatitis contact	5	
Erythema	5	
Rash erythematous	5	
Sinusitis		4.1

Drug Interactions [5,6]

- Strong CYP3A4 inhibitors (e.g., itraconazole, clarithromycin) or strong CYP2D6 inhibitors (e.g., quinidine, fluoxetine, paroxetine): concomitant use of aripiprazole with strong CYP3A4 or CYP2D6 inhibitors increases the exposure of aripiprazole

- Strong CYP3A4 inducers (e.g., carbamazepine, rifampin): concomitant use of aripiprazole with strong CYP3A4 inducers decreases the exposure of aripiprazole
- Antihypertensive drugs: aripiprazole has the potential to enhance the effect of certain antihypertensive agents due to its alpha adrenergic antagonism
- Benzodiazepines (e.g., lorazepam): intensity of sedation was greater with the combination of oral aripiprazole and lorazepam as compared to that observed with aripiprazole alone. The orthostatic hypotension observed was greater with the combination as compared to that observed with lorazepam alone

Dosage and Administration [5,6]

	Initial Dose	Recommended Dose	Maximum Dose
Schizophrenia	10-15 mg/day	10-15 mg/day	30 mg/day
Bipolar mania – adults: monotherapy	15 mg/day	15 mg/day	30 mg/day
Bipolar mania – adults: adjunct to lithium or valproate	10-15 mg/day	15 mg/day	30 mg/day
Major depressive disorder – adults: adjunct to antidepressants	2-5 mg/day	5-10 mg/day	15 mg/day

- Abilify MyCite is administered once daily without regard to meals.
- Abilify MyCite should be swallowed whole; not divided, crushed, or chewed.

Dosage Adjustments

- Known CYP2D6 poor metabolizers: Administer half of recommended dose
- Known CYP2D6 poor metabolizers taking concomitant strong CYP3A4 inhibitors: Administer a quarter of recommended dose
- Strong CYP2D6 **or** CYP3A4 inhibitors: Administer half of recommended dose
- Strong CYP2D6 **and** CYP3A4 inhibitors: Administer a quarter of recommended dose
- Strong CYP3A4 inducers: Double recommended dose over 1-2 weeks

Cost

Generic Name	Brand Name	Manufacturer	Dose	Abilify Mycite Cost**	Aripiprazole Oral Tablets Cost**
Aripiprazole tablets with sensor	Abilify MyCite	Otsuka Pharmaceutical	2 to 30 mg/day	$1,650 / 30 days	$250-956 / 30 days

** Wholesale Acquisition Cost

Conclusion

Abilify MyCite is an atypical antipsychotic drug-device that is comprised of aripiprazole tablets embedded with an Ingestible Event Marker sensor intended to track drug ingestion. The safety of Abilify MyCite for the treatment of adults with schizophrenia, treatment of adults with manic and

mixed episodes associated with bipolar I disorder, and adjunctive treatment of adults with MDD has been established and is based on trials of aripiprazole. This includes 13,543 adult patients who participated in multiple-dose, clinical trials in schizophrenia, bipolar disorder, major depressive disorder, and other disorders, and who had approximately 7,619 patient-years of exposure to oral aripiprazole. A total of 3,390 patients were treated with oral aripiprazole for at least 180 days and 1,933 patients treated with oral aripiprazole had at least 1 year of exposure. The conditions and duration of treatment with aripiprazole (monotherapy and adjunctive therapy with antidepressants or mood stabilizers) included (in overlapping categories) double-blind, comparative and noncomparative open-label studies, inpatient and outpatient studies, fixed- and flexible-dose studies, and short- and longer-term exposure. The most common adverse reactions of aripiprazole in adult patients in clinical trials (≥10%) were nausea, vomiting, constipation, headache, dizziness, akathisia, anxiety, insomnia, and restlessness. The most common adverse reactions to Abilify MyCite was pruritus, upper respiratory tract infection, rash, increased appetite, somnolence, dermatitis contact, and erythema. Abilify MyCite was developed to address the medication non-adherence issues that are common in serious mental illnesses and leads to poor outcomes.

Recommendation

The Division recommends adding this drug to the current Antipsychotics, Second Generation (Atypical) reference list edit and the Psychotropic Polyparmacy Clinical Edit.

References

1) National Institute of Mental Health. Schizophrenia. Available at: https://www.nimh.nih.gov/health/statistics/schizophrenia.shtml. Accessed August 28, 2019.
2) National Institute of Mental Health. Bipolar Disorder. Available at: https://www.nimh.nih.gov/health/topics/bipolar-disorder/index.shtml. Accessed August 28, 2019.
3) National Institute of Mental Health. Major Depression. Available at: https://www.nimh.nih.gov/health/statistics/major-depression.shtml. Accessed August 28, 2019.
4) Semahegn A, Torpey K, Manu A, et al. Psychotropic medication non-adherence and associated factors among adult patients with major psychiatric disorders: a protocol for a systematic review. *Syst Rev.* 2018. doi: 10.1186/s13643-018-0676-y.
5) Abilify MyCite [package insert]. Redwood City, CA: Otsuka American Pharmaceutical Inc,; 2017.
6) Lexicomp [database online]. Indianapolis, IN: Wolters Kluwer Health, Inc. http:online.lexi.com. Accessed August 87, 2019.
7) A Multicenter, 8-week, Open-label Study to Assess Usability of the Medical Information Device #1 (MIND1) System in Adult Subjects With Schizophrenia Who Are Treated With Oral Aripiprazole. Available at: clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/study/NCT02219009.

8) Kopelowicz A, Baker R, Zhao C, et al. A multicenter, open-label, pilot study evaluating the functionality of an integrated call center for a digital medicine system to optimize monitoring of adherence to oral aripiprazole in adult patients with serious mental illness. *Neuropsychiatr Dis Treat*. 2017; 13: 2641–2651. doi: 10.2147/NDT.S143091

Prepared by: Brandon Schowengerdt, PharmD
Date: August 30, 2019

