Aripiprazole tablets with sensor (Abilify Mycite®)
FDA approved November 2017

Indication: Aripiprazole tablets with an Ingestible Event Marker (IEM) sensor is indicated for the treatment of adults with schizophrenia, bipolar I disorder, or as an adjunctive treatment of patients with major depressive disorder (MDD)

Limitations of Use: The ability of aripiprazole drug-device combination product

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

Mechanism of Action: Unclear, thought to 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

Aripiprazole drug-device combination system: consists of four components

1. Aripiprazole tablet embedded with an IEM sensor
2. Mycite® patch, a wearable sensor detects signal from the IEM sensor after ingestion & transmits information to a smartphone
3. Mycite App, an application used with a compatible smartphone to display information for the patient
4. Web-based portal for healthcare providers (HCPs) & caregivers

- Educate clients how to use the medication, patch, app, and portal prior to initial use
- Ensure clt is capable and willing to use smartphones/apps
- Instruct clts to download the app & follow instructions. Ensure the app is compatible with clt's smartphone
- It may take 30 minutes to two hours for the smartphone app and web portal to detect the ingestion
- If the ingestion of the tablet is not detected, do not repeat the dose
- The status of the patch is indicated by a status icon in the app. Instruct clts to ensure that the app is paired with the patch
- The patch sends the date and time of pill ingestion and the clt's activity level via Bluetooth to a cellphone app. The app lets clts to add their mood, the hours they have rested, and transmits the information to a database that prescribers/caregivers who have clts' permission can access

Dosage & Administration

Dosage	**Initial**	**Recommended**	**Maximum**
Schizophrenia	10-15 mg/d	10-15 mg/d	30 mg/d
Bipolar mania - monotherapy	15 mg/d	15 mg/d	30 mg/d
Bipolar mania - adjunct to lithium or valproate	10-15 mg/d	15 mg/d	30 mg/d
MDD – Adjunct to antidepressants	2-5 mg/d	5-10 mg/d	15 mg/d
Hepatic or renal impairment	No dosage adjustment needed		

Administration	• Administer once daily without regard to meals • Swallow tablet whole; do not divide, crush, or chew

	Patch • Apply patch only when instructed by the app to the left side of the body just above the lower edge of the rib cage • Do not place the patch on irritated skin or a location that overlaps the area of the most recently removed patch • Keep patch on when showering, swimming, or exercising • Change patch weekly or sooner as needed (app reminds clt to change the patch & directs to apply/remove patch correctly) • Remove patch in case of skin irritation
Dosage forms & strengths	Tablets with sensor: 2, 5, 10, 15, 20, and 30 mg
How Supplied	The Abilify Mycite kit contains aripiprazole tablets embedded with an IEM sensor co-packaged with 7 Mycite patches

DDIs

• Known CYP2D6 poor metabolizers • Strong CYP2D6 **or** CYP3A4 inhibitors	Administer half of usual dose
• Known CYP2D6 Poor Metabolizers and strong CYP3A4 inhibitors • Strong CYP2D6 and CYP3A4 inhibitors	Administer quarter of recommended dose
• Strong CYP3A4 inducers	Double recommended dose over 1 to 2 weeks

Warnings & precautions

- Cerebrovascular adverse reactions in elderly patients with dementia-related psychosis
- Neuroleptic Malignant Syndrome
- Tardive Dyskinesia
- Metabolic change (hyperglycemia/DM, dyslipidemia, & weight gain)
- Pathological gambling and other compulsive behaviors
- Orthostatic hypotension
- Leukopenia, neutropenia, & agranulocytosis
- Seizures
- Potential for cognitive & motor impairment
- Boxed warning
    - Increased mortality in elderly patients with dementia-related psychosis
    - Increased risk of suicidal thoughts & behaviors in pediatric and young adult patients taking antidepressants
    - Safety and effectiveness of Abilify Mycite® have not been established in pediatric patients

Pharmacokinetics

Onset	Initial: 1 to 3 weeks
Tmax	3 to 5 hours
Bioavailability	87 %
Metabolism	Hepatic via CYP2D6, CYP3A4
Half-life	aripiprazole: 75 hours, dehydro-aripiprazole: 94 hours

Safety

AEs ≥ 10%	Nausea, vomiting, constipation, headache, dizziness, akathisia, anxiety, insomnia, and restlessness

Most frequently reported AE (≥5% & twice the rate of placebo)	
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
MDD (adjunctive treatment to antidepressants)	Akathisia, restlessness, insomnia, constipation, fatigue, and blurred vision

Skin Irritation (patch)	12.4% (61 pts) experienced localized skin rashes

Role in Therapy

Abilify Mycite®, the first FDA approved sensor-embedded medication, is a collaboration between aripiprazole's manufacturer Otsuka and Proteus Digital Health

- The aripiprazole drug-device combination product may improve adherence (reduced ED visits/inpatient stays) and help monitor whether clients are taking medication as prescribed
    - will enable earlier detection, monitoring/intervention of noncompliance; however, no data to support that the digital pill improves compliance (anticipated to be studied after sales begin)
- FDA recommends Human Factors (HF) testing for drug-device combinations to assess/mitigate use-related hazards
    - HF studies indicate "acceptable safety and good usability" of the Digital Medicine System
- Challenges/concerns
    - a non-compliant clt would need to remember to take the medication and to wear the patch appropriately
    - clt experiencing delusions of being watched may feel scrutinized
    - efficacy – does ingestible sensor technology affect pharmaceutical properties of the medication?
    - added expense of the technology
    - Responsibility of managing the data
        - Prescribers, pharmacists, or medical assistants
        - Would they be responsible for the negative outcomes due to non-adherence
    - 12% of pts experienced application site rash
        - how do patients obtain additional patches
    - Ethical concerns - could close monitoring may eventually
        - cause medication coverage loss due to non-compliance

        - require digital medications as a condition for parole or releasing clts from psychiatric facilities
    - Privacy concerns
        - Concern that an individual's privacy is being violated (HCPs & insurance companies gaining more access into pts' personal lives)
            - Safeguards to address privacy concerns – pts can stop HCPs & others from seeing some/all of their data (app allows blocking recipients)
- Need for careful consent procedures
- Clts who agree to be monitored can decide who monitors them, and if there are rewards for being monitored. Insurers might eventually offer incentives such as copayment discounts
- Potential candidates for the drug-device combination product
    - clts at risk of stopping medication after feeling better
    - clts at high risk of re-hospitalization due to non-compliance
    - clts who refuse long-acting injections (clinic visits, painful/other concerns)
    - clts who want to prove compliance or feel paranoid about being accused of non- compliance?
- The goal of the digital pill is to improve compliance and to inform caregivers and healthcare providers about clt's medication adherence in a timely manner. However, reasons for non-compliance include side effects, pts' belief that they don't have an illness, or paranoid thoughts about HCPs. A system that will monitor behavior and notify HCPs might not be acceptable to many psychiatric clts. "Abilify Mycite does not help with the challenge of daily use; just the monitoring of it"
- Abilify went off patent, but now Otsuka has exclusive rights to embed aripiprazole with IEM sensor
- Other options to help improve medication compliance
    - pillboxes, watch alarms, pill stations (filled weekly/monthly, remotely monitored), prescription bottles with caps that change color when clts are late to take meds, sensor implanted medication bottle caps that transmit bottle openings to apps/remote dashboards for monitoring
- Future implications
    - expanded use of digital pills for high risk clts for whom non-adherence could have a significant clinical/economic impact
    - elderly population who want help remembering to take pills
    - monitoring of a clinical trial medication
    - individuals taking medication for a specific duration such as tuberculosis (nurses often need to observe pts taking medication)
    - controlled substance monitoring
    - may include more medications when the technology becomes less expensive
- Long term experience in routine clinical patients, the price, and whether digital pills improve medication compliance, will define the role of digital medicine system

Price comparison:

Drug	Dose	Monthly Cost
Aripiprazole generic	30mg/day	$51
Abilify brand	30mg/day	$1260
Abilify Maintena	400mg/month	$2275
Abilify MyCite	30mg/day	$1650

Prerequisite to use:

Completion of Healthcare provider preregistration and Patient enrollment form

Smart phone with internet access to download MyCite APP and access MyCite Dashboard

Formulary Considerations:

BHRS P&T raised following concerns regarding Abilify Mycite:
*Patient selection and cooperation in paranoid schizophrenic population
*HIPAA compliance and protected patient information with digital tracking and online sharing
*Patient information residing with 3rd party vendor
*Technology and secured network requirements for patient and provider
*Need for Informed Consent prior to therapy
*Unclear advantage and its role in current management of schizophrenia
*Limited roll-out of Abilify MyCite via Magellan does not include California at this time.

Recommend: Nonformulary for all lines of business