CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207202Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	October 20, 2017
From	
Subject	Cross-Discipline Team Leader Review
NDA #	207202
Applicant	Otsuka Pharmaceutical Company Ltd.
Date of Submission	April 21, 2017
PDUFA Goal Date	October 21, 2017
Proprietary Name / Established (USAN) names	Abilify MyCite (aripiprazole tablets with sensor)
Dosage forms / Strength	Tablets with Sensor/ 2, 5, 10, 15, 20 and 30 mg
Proposed Indication(s)	The system is intended to track ingestion of aripiprazole tablets as indicated for schizophrenia, acute treatment of manic and mixed episodes associated with bipolar I disorder, and adjunctive treatment of major depressive disorder in adult patients.
Recommended:	*Approval*

1. Introduction and Background

Aripiprazole is an atypical antipsychotic originally approved on November 15, 2002 (tradename Abilify; NDA 021436). It is indicated in adults for the treatment of schizophrenia, acute treatment of manic and mixed episodes associated with bipolar I disorder, and adjunctive treatment of major depressive disorder. With this Class 2 resubmission, the Applicant (Otsuka) is seeking approval of Abilify MyCite (aripiprazole tablets with sensor), a system intended (b) (4) for the above indications in adult patients. The Applicant is not pursuing approval for aripiprazole's pediatric indications (i.e., irritability associated with autistic disorder or for the treatment of Tourette's disorder).

The proposed product is a drug-device combination in which the Applicant's product, aripiprazole (Abilify tablets), is combined with a 510(k)-cleared device manufactured by Proteus Digital Health (hereafter, "Proteus"). The Proteus device, cleared in February, 2014, includes an ingestible sensor or ingestible event marker (IEM) and a wearable patch to detect when the IEM has been ingested. The product under review includes the IEM embedded within aripiprazole tablets, the wearable patch, a medical device data system (MDDS) that runs on the patient's smartphone, a smartphone application (app), and a web portal for use by the prescriber if permission is granted by the patient. When used together, the Applicant claims that this system (known as "MIND1" during development) will allow patients in the currently-indicated populations listed above (b) (4); if the patient chooses, he or she can also allow others (e.g., physician, caregivers, etc.) to review the information recorded.

This resubmission is a response to the complete response (CR) action taken on April 26, 2016. A CR action was taken mainly due to the risk to the patient [redacted] (b) (4) Another related problem noted in the initial review was the relatively high number of ingested tablets the system failed to detect and the high variability in latency times for data transmission within the system. The CR letter also stated that the Human Factors (HF) study did not provide sufficient data to conclude that the app's user interface supported safe and effective use of this product. The Agency requested improvements to the user interface to mitigate the risk for medication errors and to ensure that the product could be used safely by intended users for intended uses and environments. In the CR letter, the Agency also agreed that the removal of the [redacted] (b) (4) of the app was an acceptable risk-mitigating step to address these concerns.

In response to the CR action, the Applicant:

- Updated the app and removed the [redacted] (b) (4). Because the [redacted] (b) (4) was removed, the Agency agreed in the June 28, 2016, Type A Meeting Preliminary Comments that the additional clinical trial requested in the CR letter was no longer necessary.
- Resubmitted all software documentation after incorporating the changes to address the human factors deficiencies.
- Updated the proposed comparability protocol for postmarketing system updates and routine revisions, following completion of the human factors studies.
- Provided the full commercial drug product manufacturing batch records for each dose strength.
- Conducted another HF validation study to test the app.

2. CMC/Device

The Office of Pharmaceutical Quality (OPQ) and Center for Devices and Radiological Health (CDRH) reviews were conducted by the following team of reviewers:

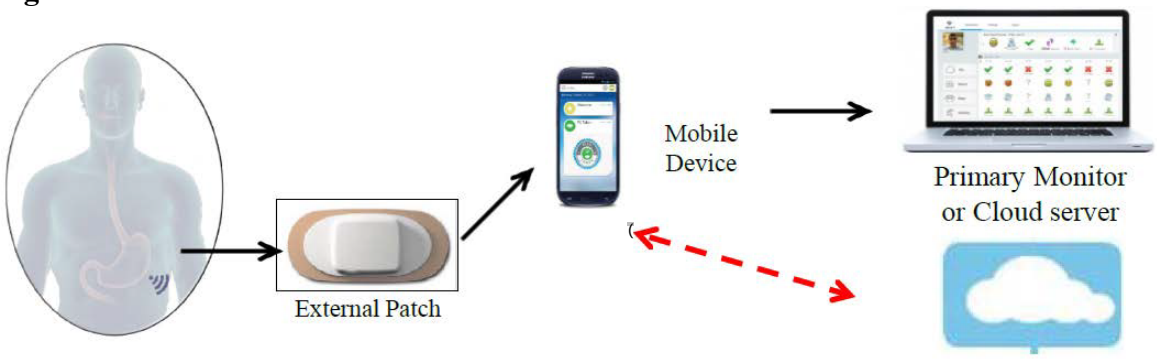
DISCIPLINE	PIMARY/SECONDARY REVIEWER
Drug Substance & Drug Product	Mariappan Chelliah/Wendy Wilson
Process and Microbiology	Hang Guo/Akm Khairuzzaman
Facility	Steven Hertz/Peter Qiu
CDRH Lead Reviewer	Luke Ralston/Shawn Forrest
CDRH Software Reviewer	Natalie Yarkony
CDRH OC reviewer	Katelyn Bittleman/Nazia Rahman
RBPM	Teshara Bouie
Application Technical Lead	David Claffey

All members of the OPQ and CDRH review team and their consultants recommend approval for this resubmission.

In summary, the proposed drug-device combination product is composed of the following main components (see Figure 1):

1. Aripiprazole immediate-release tablets imbedded with an IEM sensor in the same strengths as the approved Abilify tablets (2, 5, 10, 15, 20 and 30 mg). The composition of the proposed tablets is qualitatively and quantitatively identical to Abilify tablets, except for the addition of the IEM sensor and the use of different amounts of colorants to distinguish them from Abilify tablets.
2. MyCite Patch: This is a wearable sensor which adheres to the torso; it picks up the signal from the IEM [redacted] (b) (4) and transmits it to the patient's smartphone (via Bluetooth).
3. Smartphone software (app): Receives data from the patch and displays data about the ingestion event for the patient. The app can also transmit the data to the Otsuka Cloud-based server. This allows the designated healthcare professional (HCP) or caregiver to review the data if the patient grants the necessary permissions.

Figure 1: Product Overview



The OPQ Office of Policy for Pharmaceutical Quality (OPPQ), in consultation with US Pharmacopeia (USP), determined that the nonproprietary name will be "(aripiprazole) tablets with sensor". The term 'with sensor' will be added to an upcoming USP General Chapter to describe products of this type.

In the previous review cycle, the Applicant adequately demonstrated their capability to manufacture the proposed combination product with defined and consistent quality, as demonstrated by the results of in vitro manufacturing controls and bench performance testing. The April, 2016, CR letter included deficiencies related to an Otsuka manufacturing site (FEI:3003808559). The Applicant has resolved these issues.

Luke Ralston from CDRH reviewed the hardware for the original application and for this resubmission. In his latest review, he concludes that "the data support use of the TRADEMARK system for tracking and trending now that the [redacted] (b) (4) has been removed from the mobile app".

It should be noted that the app software [redacted] (b) (4) processes this information for display on the phone. The Otsuka component also transmits the data to the Otsuka Cloud-based server for sharing with designated parties. Nathalie Yarkony and Linda Ricci from CDRH evaluated the app in this review cycle.

Note that the proposed use of the patient's mobile device to perform data analytics changes its classification in the 510(k)-cleared Proteus device as an accessory (under the Mobile Medical Application paradigm) to the primary monitor – a Class II medical device not subject to enforcement discretion.

3. Nonclinical Pharmacology/Toxicology

No new nonclinical data were provided with this resubmission.

4. Clinical Pharmacology/Biopharmaceutics

No new clinical pharmacology information was provided with this resubmission.

5. Clinical Microbiology

No clinical microbiology information was submitted with this application.

6. Clinical/Statistical- Efficacy

No new clinical efficacy data were submitted with this application.

7. Safety

The Applicant successfully demonstrated bioequivalence between the approved oral aripiprazole tablets and the proposed product during the original NDA submission. The Applicant relies on the Agency's previous efficacy and safety findings for aripiprazole oral tablets for the proposed product for the intended indications. No new clinical data were submitted in this review cycle.

Daniel Lee, MD, was the clinical reviewer for this resubmission; he recommends approval. As previously discussed, a major concern during the initial review cycle was the potential for patients to take additional tablets, [redacted] (b) (4) if the system failed to register an ingestion. Dr. Lee agrees with other review team members that the removal of this function sufficiently mitigates this risk. In reviewing the entire safety data provided by the Applicant during the first review cycle, Dr. Lee notes frequent but mild and self-limited rashes at patch application site in trials extending up to 12 weeks. However, he believes the risks for skin irritation can be mitigated with labeling.

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