NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	211448
Priority or Standard	Standard
Submit Date(s)	10/18/2019
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PDUFA Goal Date	8/18/2020
Division/Office	Division of Psychiatry / Office of Neuroscience
Review Completion Date	8/18/2020
Established/Proper Name	Aripiprazole
(Proposed) Trade Name	(b) (4)
Pharmacologic Class	Atypical Antipsychotic
Code name	
Applicant	CMG Pharmaceutical Co., Ltd
Dosage form	Soluble film
Applicant proposed Dosing Regimen	Starting dose of 10 mg/day to 15 mg/day, recommended dose of 10 mg/day to 15 mg/day, and maximum dose of 30 mg/day once daily for adults; Starting dose of 2 mg/day and recommended dose of 10 mg/day, and maximum dose of 30 mg/day once daily for pediatric patients (13 to 17 years)
Applicant Proposed Indication(s)/Population(s)	Schizophrenia
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	58214004 |Schizophrenia (disorder)|
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Schizophrenia
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	58214004 |Schizophrenia (disorder)|
Recommended Dosing Regimen	Starting dose of 10 mg/day to 15 mg/day, recommended dose of 10 mg/day to 15 mg/day, and maximum dose of 30 mg/day once daily for adults;

	Starting dose of 2 mg/day and recommended dose of 10 mg/day, and maximum dose of 30 mg/day once daily for pediatric patients (13 to 17 years)

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management
DPV=Divison of Pharmacovigilance
DPMH= Division of Pediatrics and Maternal Health

Glossary

AE	adverse event
AR	adverse reaction
AUC	area under the curve
ALT	aspartate aminotransferase
ANOVA	analysis of variance
AST	alanine aminotransferase
AV	atrioventricular
BA	bioavailability
BE	bioequivalence
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for a Thesaurus of Adverse Reaction Terms
DMEPA	Division of Medication Error Prevention and Analysis
DRESS	drug reaction with eosinophilia and systemic symptoms
ECG	electrocardiogram
eCTD	electronic common technical document
EPS	extrapyramidal symptoms
FDA	Food and Drug Administration
FGA	first-generation antipsychotic
GABA	gamma-amino-butyric acid
HAM-D-7	Hamilton Depression Rating Scale, 7-item version
i.p.	intraperitoneal
iPSP	intitial pediatric study plan
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
LD	listed drug
MDD	major depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities
MG	medication guide
MRHD	maximum recommended human dose
NDA	new drug application
NF	National Formulary
NMDA	N-methyl-D-aspartate
NOAEL	no observed adverse effect level
OAI	official action indicated
OPQ	Office of Pharmaceutical Quality
OSF	oral soluble film
OSI	Office of Scientific Investigation
OTC	over the counter

PK	pharmacokinetics
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PVC	premature ventricular contraction
REMS	risk evaluation and mitigation strategy
SD	standard deviation
SGA	second-generation antipsychotic
TEAE	treatment emergent adverse event
URRA	use-related risk analysis
USP	United States Pharmacopeia

1 Executive Summary

1.1. Product Introduction

CMG Pharmaceutical Co., Ltd has submitted a 505(b)(2) application for aripiprazole oral soluble film (OSF) (proposed proprietary name: (b) (4) for the treatment of schizophrenia in adult and pediatric patients ages 13 years and older. The proposed product, which is designed to dissolve on the tongue within a few seconds and be swallowed, has been developed in 5-mg, 10-mg, and 15-mg dosage strengths. The Applicant anticipates that this product may be useful for patients who are unable to take existing formulations of aripiprazole. The Applicant proposes to rely on the Agency's previous findings of safety and effectiveness for the listed drug (LD), Abilify tablets (NDA 021436).

Aripiprazole is an atypical antipsychotic indicated (as Abilify) for the treatment of schizophrenia (adults and pediatric patients 13 to 17 years); acute treatment of manic or mixed episodes associated with bipolar I disorder (adults and pediatric patients 10 to 17 years); maintenance treatment of bipolar I disorder (adults); adjunctive treatment of major depressive disorder (adults); treatment of irritability associated with autistic disorder (pediatric patients 6 to 17 years); acute treatment of agitation associated with schizophrenia or bipolar I disorder (adults); and for the treatment of Tourette's Disorder. The mechanism of action of aripiprazole is unclear, but it has been proposed that aripiprazole's efficacy is mediated through a combination of partial agonist activity at D_2 and 5-HT_{1A} receptors and antagonist activity at 5-HT_{2A} receptors.

1.2. Conclusions on the Substantial Evidence of Effectiveness

This Application relies on the Agency's findings of safety and effectiveness for Abilify tablets, the LD, as well as two pharmacokinetic studies: a single-dose, crossover, three-treatment, three-sequence bioequivalence/bioavailability (BE/BA) study and a single-dose, crossover, food effect study. The submitted studies demonstrate that aripiprazole oral soluble film is bioequivalent to Abilify.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Aripiprazole OSF is an oral soluble film formulation of aripiprazole. The Applicant has submitted a 505(b)(2) NDA for the treatment of schizophrenia in adults and pediatric patients 13 to 17 years old. In pharmacokinetic trials, the Applicant demonstrated that aripiprazole OSF is bioequivalent to aripiprazole tablets. The Applicant relies on the Agency's previous findings of safety and effectiveness for the LD, Abilify (aripiprazole tablets; NDA 21436) to support the safety and effectiveness of aripiprazole OSF.

An oral soluble film formulation of aripiprazole represents a benefit for patients with schizophrenia. This formulation may benefit patients who are unable to safely swallow a tablet due to dysphagia or other conditions that increase risk of aspiration. This option for individualized treatment may improve medication adherence. Aripiprazole has been approved by the Agency since November 2002; its benefit-risk profile is well-known.

There is no evidence of local toxicity related to the oral film formulation of aripiprazole OSF. There is no evidence from the clinical program that the safety profile for the proposed product differs meaningfully from the LD.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Schizophrenia is a serious mental illness characterized by chronic or recurrent psychosis (e.g., delusions, hallucinations, and thought disorganization). • Schizophrenia is also frequently associated with negative symptoms (e.g., social withdrawal, avolition, blunted affect) and cognitive deficits (e.g., attention, executive function, working memory, and social cognition). • Individuals with schizophrenia experience significant impairments	Schizophrenia is a serious condition, associated with significant disability and a shortened life expectancy.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	in social and occupational functioning and, on average, have a life expectancy around 15 years less than individuals without schizophrenia. • The worldwide prevalence of schizophrenia is approximately 1%. • Schizophrenia is one of the leading causes of years lost due to disability worldwide. • Approximately 50% of individuals with schizophrenia experience a relapse/exacerbation in psychotic symptoms within one year after their last episode; most relapses occur in the context of medication nonadherence. • Medication nonadherence or partial adherence is common, affecting the average patient with schizophrenia.	
Current Treatment Options	• Antipsychotics are the first-line medication therapy for schizophrenia; current practice guidelines recommend that antipsychotics should be initiated as soon as possible in an acute schizophrenia exacerbation and continued to reduce the risk of relapse. • Antipsychotics have been shown to be effective for reducing positive symptoms of schizophrenia (e.g., delusions, hallucinations, disorganized thinking and behavior). Negative symptoms and cognitive deficits of schizophrenia generally show little to no improvement from antipsychotic treatment. • Antipsychotics are broadly categorized as first-generation antipsychotics (e.g., chlorpromazine, fluphenazine, haloperidol) and second-generation antipsychotics (e.g., clozapine, risperidone, olanzapine, quetiapine, and aripiprazole). In general, first-generation antipsychotics have a higher risk for causing extrapyramidal side effects than second-generation antipsychotics.	Antipsychotics reduce the severity of positive symptoms of schizophrenia and the risk of psychosis exacerbations. Nonadherence to daily oral antipsychotics is common in individuals with schizophrenia and can lead to psychiatric hospitalization and other adverse outcomes. Interventions that make antipsychotic medications accessible to individuals who are unable to swallow pills and that improve adherence are critically important to public health.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Adverse reactions from antipsychotics vary between drugs but may include weight gain, extrapyramidal side effects, increased prolactin, sedation, and QT prolongation. • Nonadherence to daily oral antipsychotic treatment is common in individuals with schizophrenia. Potential consequences of medication nonadherence include acute psychosis exacerbation, occupational and social problems, harm to self or others, and psychiatric hospitalization. • Current treatment options for patients who are unable to swallow tablets include oral solutions, oral disintegrating tablets, and sublingual tablets.	
Benefit	• Aripiprazole OSF is designed to dissolve on the tongue within a few seconds and be swallowed. • The effectiveness of aripiprazole OSF is based on the findings of effectiveness for the LD, aripiprazole tablets (Abilify).	Aripiprazole OSF is anticipated to be as effective as the LD, aripiprazole tablets (Abilify). Its oral soluble film formulation may be of benefit to patients who are unable to swallow tablet formulations
Risk and Risk Management	• Analysis of safety data for this product including vital signs, laboratory assessments, and adverse events did not reveal any unexpected safety signals or local toxicity.	The safety profile of this product is expected to be consistent with that of the LD, aripiprazole tablets (Abilify).

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

				Section of review where discussed, if applicable
X	The patient experience data that were submitted as part of the application include:			
	□	Clinical outcome assessment (COA) data, such as		
		□	Patient reported outcome (PRO)	
		□	Observer reported outcome (ObsRO)	
		□	Clinician reported outcome (ClinRO)	
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	X	Other: (Please specify): A usability questionnaire was administered in both Phase 1 studies.		
□	Patient experience data that were not submitted in the application, but were considered in this review:			
	□	Input informed from participation in meetings with patient stakeholders		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Other: (Please specify):		
□	Patient experience data was not submitted as part of this application.			

2 Therapeutic Context

2.1. Analysis of Condition

Schizophrenia is a serious mental illness affecting approximately 1% of the population worldwide. Schizophrenia is a severe, chronic condition with significant morbidity and mortality. The disorder is characterized by a constellation of symptoms that may include delusions, hallucinations, disorganized speech, grossly disorganized behavior, diminished emotional expression, and avolition (American Psychiatric Association 2013). Although cognitive symptoms are not included in the diagnostic criteria of schizophrenia, impairments in processing speed, attention, working memory, and social cognition are frequent and disabling manifestations. Mood and anxiety symptoms are also common in individuals with schizophrenia.

The pathogenesis of schizophrenia is poorly understood. Schizophrenia is a heterogeneous syndrome likely caused by a complex group of diseases resulting from interactions between genes and environment. Rare cases arise from an abnormality in a single genetic locus (e.g., 22q11 deletion syndrome). However,for most people with schizophrenia, multiple genes are involved, each contributing a small amount to the overall condition. Environmental risk factors associated with schizophrenia are equally diverse and include prenatal maternal infections, nutritional deficiencies, obstetrical complications, adverse childhood events, urbanicity, and cannabis use (Padmanaban et al. 2017). Hypothetical neurochemical models of schizophrenia include excessive mesolimbic dopaminergic activity, hypoactivity of N-methyl-D-aspartate (NMDA) glutamate receptors, and dysfunctional gamma-amino-butyric acid (GABA)-mediated modulation of pyramidal neurons (Kantrowitz and Javitt 2010).

The onset of schizophrenia is typically in early adulthood , occurring 5 to 7 years later in women than in men. The course of illness is heterogeneous, with many experiencing multiple acute symptom exacerbations and remissions within a chronic and disabling illness. On average, women tend to have better premorbid functioning and less prominent negative symptoms (e.g., affective flattening, alogia, anhedonia, and avolition) and cognitive impairment (Tandon, Nasrallah et al. 2009).

Schizophrenia is associated with significant impairments in social and occupational functioning and is among the 15 leading causes of disability worldwide (World Health Organization 2016). Individuals with schizophrenia experience premature mortality compared with the general population, with disproportionately high rates of cardiovascular disease, cancer, accidental death, and suicide (Olfson et al. 2015). Schizophrenia is associated with an average of 14.5 years of potential life lost (Hjorthøj, Stürup et al. 2017). The suicide rate among people with schizophrenia spectrum disorders may be more than 100 times higher than in the general population (Zaheer 2020). Overall, schizophrenia is a serious condition, associated with significant disability and a shortened life expectancy.

2.2. Analysis of Current Treatment Options

Antipsychotics constitute the first-line medication treatment for schizophrenia. Most psychiatric practice guidelines recommend that antipsychotics be initiated as soon as possible in an acute schizophrenia exacerbation and continued through the maintenance phase to reduce the risk of relapse (Takeuchi et al. 2012). Antipsychotics are broadly classified as first-generation (FGAs) and second-generation antipsychotics (SGAs). FGAs include those approved prior to clozapine in 1989. Representative medications of this class are chlorpromazine, fluphenazine, and haloperidol. SGAs include clozapine, risperidone, olanzapine, quetiapine, and aripiprazole.

Antipsychotics are effective at treating positive symptoms (e.gs., hallucinations, delusions, and disorganized thinking) in schizophrenia. They have not demonstrated clinically meaningful effects on negative symptoms (e.g., diminished emotional expression and avolition) or cognitive impairment associated with schizophrenia (Davis, Horan, et al. 2014). The mechanism by which antipsychotics improve symptoms is unknown but may involve antagonism of dopamine D2 receptors and serotonin 5-HT2A receptors. The distinction between FGAs and SGAs is somewhat arbitrary. Except for clozapine, which has significant evidence supporting its efficacy in patients who have not responded to other antipsychotics, FGAs and SGAs differ mostly with respect to their safety profiles and not efficacy. In general, FGAs have a higher risk of extrapyramidal symptoms (EPS) such as dystonia, parkinsonism, and tardive dyskinesia. SGAs confer a lower risk of EPS but are associated with significant weight gain and other metabolic side effects.

More than 20 antipsychotics are approved for the treatment of schizophrenia in the United States. Individual patients often require multiple trials of antipsychotics before an optimal treatment is identified. For some patients, an effective treatment cannot be identified despite multiple trials. For these reasons, having additional treatment options in the antipsychotic armamentarium is valuable.

In addition to antipsychotic medications, patients with schizophrenia are frequently treated with adjunctive medications to target depression, anxiety, obsessions and compulsions, and adverse effects of antipsychotics (e.g., dystonia, parkinsonism, tardive dyskinesia, and akathisia). These adjunctive medications may include anticholinergic drugs (e.g., benztropine, diphenhydramine), beta-blockers (e.g., propranolol), benzodiazepines, and antidepressants. Beyond pharmacotherapy, several psychosocial treatments have substantial evidence bases and are recommended for use alongside antipsychotic therapy. Psychosocial treatments may reduce relapse risk, improve coping skills, improve social and vocational functioning, and help individuals with schizophrenia move toward recovery. Recommended psychosocial interventions include cognitive behavioral therapy, assertive community treatment, supported employment, and social skills therapy.

Table 1: FDA-Approved Medications for Schizophrenia

First Generation Antipsychotics	Second Generation Antipsychotics
Chlorpromazine, fluphenazine, haloperidol, loxapine, perphenazine, prochlorperazine, thiothixene, thioridazine, trifluoperazine	aripiprazole, asenapine, brexpiprazole, clozapine, iloperidone, lumateperone, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone

Source: Reviewer-created

Table 2 lists the FDA-approved antipsychotic medications that are available in alternative formulations and that may be prescribed for patients who are unable to swallow pills. FDA-issued Prescribing Information and Medication Guides do not necessarily include guidance about whether oral tablets may be crushed. There are no antipsychotics available in oral soluble film formulation. However, there are a number of antipsychotics available in oral disintegrating tablet formulations. Aripiprazole is currently available as an oral tablet, oral tablet with sensor, oral disintegrating tablet, oral solution, and long-acting intramuscular injection.

Table 2: Summary of Treatment Armamentarium Relevant to Proposed Indication

Product	Relevant Indication	Year of Approval	Route	Important Safety and Tolerability Issues
Saphris	Acute treatment of schizophrenia	2009	Sublingual tablets	Application site reactions, primarily in the sublingual area, including oral ulcers, blisters, peeling, sloughing, and inflammation. Choking has been reported by patients, some of whom may have also experienced oropharyngeal muscular dysfunction or hypoesthesia.
Abilify Discmelt	Schizophrenia	2006	Oral disintegrating tablet	
Fazaclo	For the management of severely ill schizophrenic patients who fail to respond adequately to standard drug treatment for schizophrenia	2004	Oral disintegrating tablet	Higher risk of weight gain. Risk of agranulocytosis; REMS for regular monitoring of absolute neutrophil count (ANC).
Risperdal M-tabs	Schizophrenia	2003	Oral disintegrating tablet	Associated with higher levels of prolactin elevation than other antipsychotic agents.
Zyprexa Zydis	Schizophrenia	2000	Oral disintegrating tablet	Higher risk of weight gain.

Source: Reviewer-created

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Aripiprazole has been marketed in the United States since 2002. Approved aripiprazole formulations include oral tablets, oral solution, oral disintegrating tablets, intramuscular injectable, and multiple formulations of extended-release injectable.

Aripiprazole Indications by Year Granted

2002 Schizophrenia in adults
2004 Acute manic or mixed episodes associated with bipolar I disorder in adults
2004 Bipolar disorder maintenance
2004 Adjunctive treatment of bipolar disorder
2007 Schizophrenia in patients 13 to 17 years of age
2007 Adjunctive treatment of major depressive disorder
2008 Acute manic or mixed episodes associated with bipolar I disorder in patients 10 to 17 years of age
2009 Irritability in children with autism
2009 Agitation associated with bipolar I mania and schizophrenia
2011 Maintenance treatment of bipolar I disorder as an adjunct to lithium or valproate
2014 Tourette's Disorder

3.2. Summary of Presubmission/Submission Regulatory Activity

Aripiprazole oral soluble film was developed for the treatment of schizophrenia under IND 119610, which was allowed to proceed on May 20, 2015. The list below is not exhaustive; rather, it is focused on major pre-submission activities, decisions, and advice.

October 23, 2013: Pre-IND Meeting
This meeting involved discussion of the 505(b)(2) regulatory pathway for this product, dissolution and stability testing, planned studies (including a BA/BE study and a food effect study), a biowaiver for lower strengths of the product, and recommendation of a usability study. The Agency informed the Applicant that the effect of drinking water on bioavailability should also be assessed. The Agency advised that the 10-mg strength could be used in the BE and food effect studies, but that justification was needed for not using the highest strength (15 mg).

May 25, 2017: Initial Pediatric Study Plan submission
The Agency acknowledged the Applicant's plan to request a waiver of the requirement for pediatric assessments for aripiprazole OSF for pediatric patients aged 0 to < 13 years because

studies would be impossible or highly impracticable and the plan to submit an assessment for the treatment of schizophrenia in pediatric patients aged 13 to 17 years based upon bioequivalence to the LD. The Agency also acknowledged that if their product was not bioequivalent to the LD, the Applicant would plan to request deferred studies in pediatric patients aged 13 to 17 years. The Agency notified the Applicant of agreement to the iPSP on September 18, 2017.

February 5, 2018: Pre-NDA meeting
In response to the Applicant's inquiry, the Agency confirmed that the 505(b)(2) regulatory pathway would be appropriate. The Agency agreed with the Applicant that the adverse event data from the two Phase 1 studies should not be pooled, but rather summarized separately in Module 2 of the NDA. The Agency agreed that no integrated summary of effectiveness (ISE) or integrated summary of safety (ISS) would be required. The Agency advised the Applicant that dataset files (.xpt and define.pdf files) for safety data from the two Phase 1 trials would be required in Module 5 of the NDA. The Agency informed the Applicant that a Medication Guide tailored for patients with schizophrenia would be required.

The Agency advised the Applicant to include with the NDA the rationale for a scientific bridging between their product and the LD at dose levels not studied. The Agency also advised the Applicant to justify why different means of administration of two strips (i.e., sequential (b) (4)) are not expected to cause any significant clinical difference. The Agency also advised that, to better inform the review, the Applicant should conduct a use-related risk analysis (URRA).

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

No clinical site inspections were conducted for this application because the clinical sites were inspected in June and July 2019 and the analytical site was inspected in (b) (4) which fell within the surveillance interval. The inspections were conducted under the following submissions: NDAs Non-responsive and ANDAs Non-responsive and Non-responsive The final classification for the inspections was No Action Indicated (NAI).

4.2. Product Quality

Drug Product: Adequate

The to-be-marketed formulation compositions of the proposed drug product contains excipients of USP or NF grade, except for red ink, which is used in trace amount for printing for identifying the product and strength. The Applicant has provided adequate CMC information within the NDA submission to support the use of red ink. The Applicant has performed adequate product development studies to justify the selection of the excipients and to demonstrate/justify their chemical compatibility with the drug substance.

Labeling: Adequate

Minor labelling comments were discussed with DMEPA reviewer and included in the DMEPA review for sending out to the Applicant, along with the other DMEPA comments.

Manufacturing: Inadequate

As of 07/09/2020, the facility status for (b) (4) the drug substance facility, is Official Action Indicated (OAI). Also, Drug product manufacturing facility (Tesa Labtec Company GmbH) review is on-going (704a4 initiated). Satisfactory inspection is necessary for both these facilities before the application is recommended for approval. All other facilities are adequate or required no evaluation (see table below).

Facility name and address	FEI	Responsibilities and profile code(s)	Status
(b) (4)			Withhold - Based on CGMP
Tesa Labtec Company GmbH Heykenaukamp 10 , Hamburg , Hamburg, Germany , 21147	3010375003	(b) (4)	Pending PAI
Tesa Labtec Company GmbH Raiffeisenstrase 4 , Langenfeld, Langenfeld, Germany, 40764	3010969322		Approve - Based on Previous History
		(b) (4)	Approve - Based on Previous History
			No Evaluation Necessary
			No Evaluation Necessary

Source: OPQ review

Biopharmacetucis: Adequate

The Applicant's request for waiver of an in vivo BA/BE study for the proposed aripiprazole OSF, 5 mg and 15 mg, is granted based on the following information and data: (a) the bioequivalence data on the 10 mg strength, (b) same release mechanism and manufacturing process for all strengths, (c) compositional proportionality among all strengths, (d) evidence on linear pharmacokinetics in the dose range of 5 mg to 30 mg, and (e) comparable dissolution profiles among all strengths in multi-pH media (pH 1.2, 4.0, and 6.8). After the Division of Biopharmaceutics recommendation, the Applicant tightened the dissolution acceptance criterion from the originally proposed "Q = (b) (4)% at (b) (4) min" to "Q = (b) (4) at 15 minutes." Both aripiprazole (b) (4) form and (b) (4) form existed in the final drug product [for

example, (b) (4) form API is the predominant form in the biobatch (PV1), while (b) (4) form API is present in PV2 and PV3 batches]. In the response dated 05/29/2020, the Applicant provided comparative aqueous solubility data at 37 ºC for API aripiprazole (b) (4) form and (b) (4) form over pH range of 1.2 – 5 and the solubilities of aripiprazole (b) (4) form and (b) (4) form were not different over this pH range tested.

For more details, refer to OPQ review.

4.3. Clinical Microbiology

No new clinical microbiology data were submitted with this application.

4.4. Devices and Companion Diagnostic Issues

Not applicable.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

As previously agreed by the Division, nonclinical studies were not performed, and therefore, no nonclinical study reports were submitted with this application.

Nonclinical information was proposed by the Applicant to be included in aripiprazole OSF labeling under (b) (4), based on a published article (b) (4) (b) (4) (b) (4) (b) (4) This reviewer's assessment regarding the value of this information was supported by DPMH and it is not included in the drug label.

Another nonclinical issue that arose in the review process was the acceptability of the amount of (b) (4) a leachable component in the finished drug product. Based on review of the published literature on (b) (4) nonclinical toxicology, the amount of (b) (4) in the finished drug product (b) (4) in the 10 mg film, with (b) (4) (b) (4) at the maxim human dose (MRHD) of 30 mg for aripiprazole OSF in the proposed label) is acceptable for the following reasons:

(b) (4)

based on a mg/m^2 body surface area. (b) (4) tested negative in genotoxicity assays in vitro and in vivo and was not clastogenic in (b) (4) carcinogenicity studies in rats and mice. (b) (4) had no reproductive toxicity in a (b) (4) study in rats and was not embryotoxic or teratogenic in embryofetal development toxicity studies in rats and rabbits.

The review of published literature data on (b) (4) nonclinical toxicology is provided in Section 15.3 Appendices, Nonclinical Pharmacology/Toxicology.

6 Clinical Pharmacology

6.1. Executive Summary

In earlier interactions with the Agency (in 2013 and 2018), the Applicant was informed that their development program for this aripiprazole OSF should (i) establish a pharmacokinetic (PK) bridge between aripiprazole OSF and the LD which is aripiprazole immediate release tablets, and (ii) characterize the impact of food on the OSF formulation. In support of the PK bridge, the Applicant has submitted a BA/BE study that compared the pharmacokinetics of aripiprazole OSF with that of the LD. Further, they also submitted a study characterizing the effect of food on the OSF formulation. This review addresses (i) PK bridging for aripiprazole OSF and the LD in healthy subjects and (ii) the effect of food on the OSF formulation.

The main features of the results are that a PK bridge has been established between aripiprazole OSF and the LD. Furthermore, aripiprazole OSF, like the LD, can be administered without regard to meals.

6.1.1. Recommendations

The Office of Clinical Pharmacology (OCP/DNP) finds the PK bridging between aripiprazole OSF and the LD to be acceptable. OCP recommends the approval of aripiprazole oral soluble film.

6.1.2. Post-Marketing Requirements and Commitments

None

6.1.3. Key Clinical Pharmacology Findings

- Aripiprazole OSF in each state of its administration, namely with and without water, is bioequivalent to the LD. Furthermore, aripiprazole OSF administered *with* water is bioequivalent to aripiprazole OSF administered *without* water. The Applicant has successfully completed a pivotal comparative pharmacokinetic study to establish a scientific bridge between aripiprazole OSF and the LD.

- The current labeling for the LD mentions that the drug is to be administered once daily without regard to meals. In this food effect study (Study -51) with the OSF formulation, the extent of absorption of aripiprazole is comparable between the fed and fasted states. C_{max} of aripiprazole is approximately 25% lower while T_{max} is delayed by approximately 3 hours when a 10 mg dose of aripiprazole OSF is administered with food compared to the fasted state. The 25% decrease in C_{max} should not be considered clinically meaningful based on the following evidence: 1) there appears to be no dose-response relationship for effectiveness

in patients with schizophrenia but there appears to be a dose-dependent effect on somnolence and extrapyramidal effect for the dose range of 10 to 30 mg (refer to OCP review for NDA021436, 2/20/2008); 2) the dose of aripiprazole for schizophrenia is titrated to effect. Therefore, a lower C_{max} raises no concerns in terms of effectiveness and safety. Thus, aripiprazole OSF, like the LD, can be given without regard to meals.

6.2. Summary of Clinical Pharmacology Assessment

The Division met with the Applicant regarding their development program in a pre-IND meeting in October 2013. The 505(b)(2) pathway was discussed as well as the types of studies that would be needed to follow this approach, namely a BA/BE study and a food effect study. The Applicant and the Agency agreed that the BA/BE study could be conducted with the aripiprazole OSF 10 mg strength because of tolerability concerns in healthy individuals. Aripiprazole is poorly tolerated by healthy subjects at and above the 15 mg dose level. In several cases there have been high incidences of dropouts due to adverse events like nausea, vomiting and dizziness. Furthermore, the 2019 revision of the product-specific guidance for aripiprazole mentions that the biostudies should be performed with the 10 mg strength. In the pre-NDA meeting with DPP in February 2018 the Applicant informed the Clinical Division that they had performed the two relevant studies (i.e., the BA/BE study using their aripiprazole OSF product and the LD, and the food study on the OSF product).

6.2.1. General Dosing and Therapeutic Individualization

General Dosing

The Applicant is relying on the Agency's findings of safety and efectivenessfor the LD as indicated in the approved labeling, to support the approval of their aripiprazole OSF. The Applicant has completed a pivotal BE study establishing the bridge between aripiprazole OSF and the LD.

Adults: The recommended starting and target dose for aripiprazole OSF is 10 mg/day or 15 mg/day administered on a once-a-day schedule without regard to meals. Aripiprazole has been systematically evaluated and shown to be effective in a dose range of 10 to 30 mg/day, when administered as the tablet formulation; however, doses higher than 10 or 15 mg/day were not more effective than 10 or 15 mg/day. Dosage increases should generally not be made before 2 weeks, the time needed to achieve steady-state.

Maintenance Treatment: Maintenance of efficacy in schizophrenia was demonstrated in a trial involving patients with schizophrenia who had been symptomatically stable on other antipsychotic medications for periods of 3 months or longer. These patients were discontinued from those medications and randomized to either aripiprazole 15 mg/day or placebo, and

observed for relapse. Patients should be periodically reassessed to determine the continued need for maintenance treatment.

Adolescents: The recommended target dose of aripiprazole OSF is 10 mg/day. Aripiprazole was studied in adolescent patients 13 to 17 years of age with schizophrenia at daily dosages of 10 mg and 30 mg. Patients are recommended to start treatment with oral aripiprazole at the 2 mg dose. Then, the daily dosage can be titrated with aripiprazole OSF to 5 mg after 2 days and to the target dose of 10 mg after 2 additional days. Subsequent dose increases should be administered in 5 mg increments. The 30 mg/day dosage was not shown to be more efficacious than the 10 mg/day dosage. Aripiprazole OSF can be administered without regard to meals. Patients should be periodically reassessed to determine the need for maintenance treatment.

Reviewer's Comment: Aripiprazole OSF does *not* have a 2 mg strength. The Applicant is proposing that adolescent patients be started with an immediate release tablet dosage form (2 mg) and subsequently titrated to higher doses of 5 mg and 10 mg with aripiprazole OSF. Regarding the acceptability of the switch, please refer to Clinical section for more information.

Therapeutic Individualization

Dosage adjustments are recommended in patients who are known CYP2D6 poor metabolizers and in patients taking concomitant CYP3A4 inhibitors or CYP2D6 inhibitors or strong CYP3A4 inducers. When the coadministered drug is withdrawn from the combination therapy, aripiprazole OSF dosage should then be adjusted to its original level. When the coadministered CYP3A4 inducer is withdrawn, aripiprazole OSF dosage should be reduced to the original level over 1 to 2 weeks. Patients who may be receiving a combination of strong, moderate, and weak inhibitors of CYP3A4 and CYP2D6 (e.g., a strong CYP3A4 inhibitor and a moderate CYP2D6 inhibitor or a moderate CYP3A4 inhibitor with a moderate CYP2D6 inhibitor), the dosing may be reduced to one-quarter (25%) of the usual dose initially and then adjusted to achieve a favorable clinical response.

Outstanding Issues

None

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of action	The mechanism of action of aripiprazole in schizophrenia or bipolar mania, is unknown. However, the efficacy of aripiprazole could be mediated through a combination of partial agonist activity at D2 and 5-HT1A receptors and antagonist activity at 5-HT2A receptors.

Pharmacokinetics	
Absorption	The absorption of aripiprazole OSF was rapid, typically attaining peak plasma concentrations at approximately 2.0-2.5 hours after administration. Aripiprazole OSF (administered with or without water) was demonstrated to be bioequivalent to aripiprazole tablets at an equal dose in a relative bioavailability study in healthy subjects. The absolute oral bioavailability of the tablet formulation is 87%. The single-dose pharmacokinetics of oral aripiprazole were linear and dose-proportional between the doses of 5 mg to 30 mg. Aripiprazole OSF can be administered with or without food. Administration of a 10 mg aripiprazole OSF with a standard high-fat meal did not affect AUC but lowered C_{max} by 25 % and delayed T_{max} by 3 hours. This is not clinically significant. The pharmacokinetics of the metabolite, dehydroaripiprazole, were not affected by food.
Distribution	The steady-state volume of distribution of aripiprazole following intravenous administration is high (404 L or 4.9 L/kg), indicating extensive extravascular distribution. At therapeutic concentrations, aripiprazole and its major metabolite are greater than 99% bound to serum proteins, primarily to albumin. In healthy human volunteers administered 0.5 to 30 mg/day aripiprazole for 14 days, there was dose-dependent D2 receptor occupancy indicating brain penetration of aripiprazole in humans.
Metabolism	Aripiprazole is metabolized primarily by three biotransformation pathways: dehydrogenation, hydroxylation, and N-dealkylation. Based on *in vitro* studies, CYP3A4 and CYP2D6 enzymes are responsible for dehydrogenation and hydroxylation of aripiprazole, and N-dealkylation is catalyzed by CYP3A4. Aripiprazole is the predominant drug moiety in the systemic circulation. At steady-state, dehydro-aripiprazole, the active metabolite, represents about 40% of aripiprazole AUC in plasma.
Excretion	Following a single oral dose of [14C]-labeled aripiprazole, approximately 25% and 55% of the administered radioactivity was recovered in the urine and feces, respectively. Less than 1% of unchanged aripiprazole was excreted in the urine and approximately 18% of the oral dose was recovered unchanged in the feces.

6.3.2. Clinical Pharmacology Questions

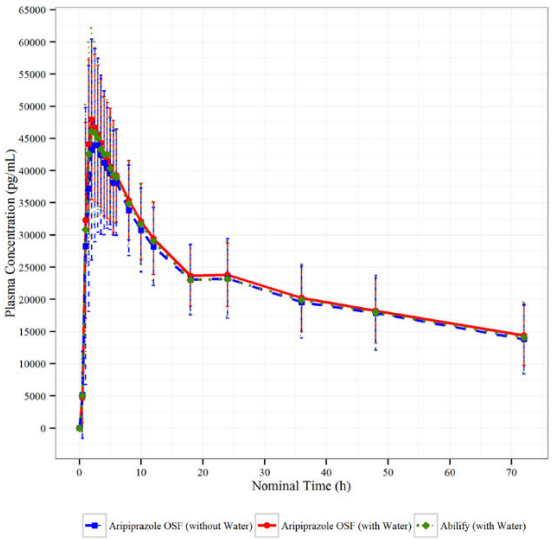
Is there an appropriate PK bridge established for Aripiprazole OSF and Aripiprazole immediate release tablets, the LD? (Study 140052)

A) Aripiprazole: Pharmacokinetics of a single 10 mg dose of aripiprazole OSF administered with or without water (both tests) were each compared to the 10 mg immediate release tablet of aripiprazole, the LD in a BA/BE study in 29 healthy subjects. The results show that:

- For both AUC_{0-72} and C_{max}, aripiprazole OSF *without* water was bioequivalent to aripiprazole OSF *with* water (AUC_{0-72} ratio: 94.8%; 90 % C.I. for AUC_{0-72} 89.1 to 101.0%; C_{max} ratio: 92.9%; 90 % C.I. for C_{max} 85.6 % to 100.8 %)
- For both AUC_{0-72} and C_{max}, aripiprazole OSF *without* water (test) was bioequivalent to the LD (reference) with water (AUC_{0-72} ratio: 97.6%; 90 % C.I. for AUC_{0-72} 91.7% to 103.7%; C_{max} ratio: 91.2%; 90 % C.I. for C_{max} 84.2 % to 98.8 %).
- For both AUC_{0-72} and C_{max}, aripiprazole OSF *with* water (test) was bioequivalent to the LD (reference) with water (AUC_{0-72} ratio: 102.8%; 90 % C.I. for AUC_{0-72} 96.7% to 109.3%; C_{max} ratio: 98.1%; 90 % C.I. for C_{max} 90.6 % to 106.3 %).
- The median T_{max} was comparable between all three treatments and was about 2.5 hours.
- Between subject variability in AUC_{0-72} and C_{max} was similar between the test and reference treatments and was around 23%.

The above results show that in each instance aripiprazole OSF *without* water (test) is comparable in both AUC_{0-72} and C_{max} to the LD (reference), and aripiprazole OSF *with* water (test), is comparable in both AUC_{0-72} and C_{max} to the LD (reference). This establishes the pharmacokinetic bridge for the proposed OSF dosage form of aripiprazole with the LD.

Figure 1: Mean (±SD) concentration-time profile for aripiprazole for each treatment



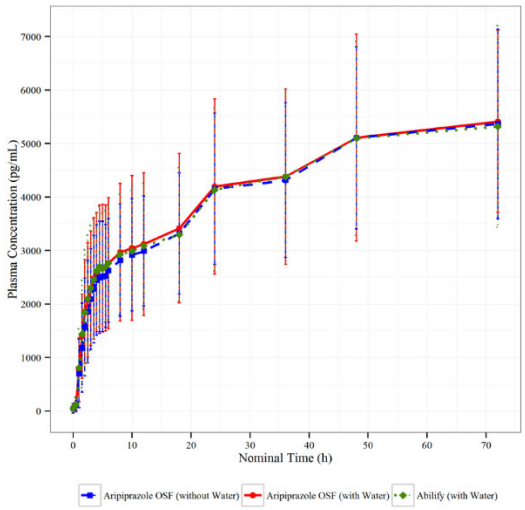
Source: Applicant's study report: 140052, page 45, Figure 11.4.2.3-1

B) Dehydroaripiprazole: (presented as supportive data)
The Applicant also assessed the comparability of dehydroaripiprazole, the major metabolite, for the OSF formulation (test treatment) and the LD (reference treatment). This was supportive data. The results show that:

- For both AUC_{0-72} and Cmax, aripiprazole OSF *without* water was comparable to aripiprazole OSF *with* water (AUC_{0-72} ratio: 96.5%; 90 % C.I. for AUC_{0-72} 89.8 to 103.7.0%; C_{max} ratio: 96.8%; 90 % C.I. for C_{max} 89.9 % to 104.1%)
- For both AUC_{0-72} and C_{max}, aripiprazole OSF *without* water (test) was comparable to the LD (reference) with water (AUC_{0-72} ratio: 96.7%; 90 % C.I. for AUC_{0-72} 90.1% to 103.8%; C_{max} ratio: 97.9%; 90 % C.I. for C_{max} 91.0 % to 105.2 %).
- For both AUC_{0-72} and C_{max}, aripiprazole OSF *with* water (test) was comparable to the LD (reference) with water (AUC_{0-72} ratio: 100.1%; 90 % C.I. for AUC_{0-72} 93.4% to 107.4%; C_{max} ratio: 101.1%; 90 % C.I. for C_{max} 94.1 % to 108.6 %).
- The median T_{max} was comparable between all three treatments and was about 72 hours.
- Between subject variability in AUC_{0-72} and C_{max} was similar between the test and reference treatments and was around 30%.

The figure below shows mean (±SD) concentration-time profile for dehydroaripiprazole for each treatment

Figure 2: Mean (±SD) concentration-time profile for dehydroaripiprazole for each treatment



Source: Applicant's study report: 140052, page 48, Figure 11.4.2.3-2

The Applicant has established the bridge between aripiprazole OSF and the LD at the 10 mg strength/dose level.

Was an inspection of the Relative Bioavailability Study (Study 140052) requested?
The relative BA study (Study 140052) establishes the link between aripiprazole OSF and the LD. This study therefore is not only a pivotal BA/BE study but will also form the basis for the action of this NDA via the 505(b)(2) pathway. Because of the importance of this study in this NDA, OCP formally requested the Office of Study Integrity and Surveillance (OSIS) for the inspection of this study for both its clinical and analytical sites. OSIS replied mentioning that they had determined that an inspection is not warranted at this time for the sites. The reason given by them was that the clinical site was inspected recently in June and July of 2019, and that the analytical site was inspected in (b) (4) They further stated that these dates fall within the surveillance interval of inspection.

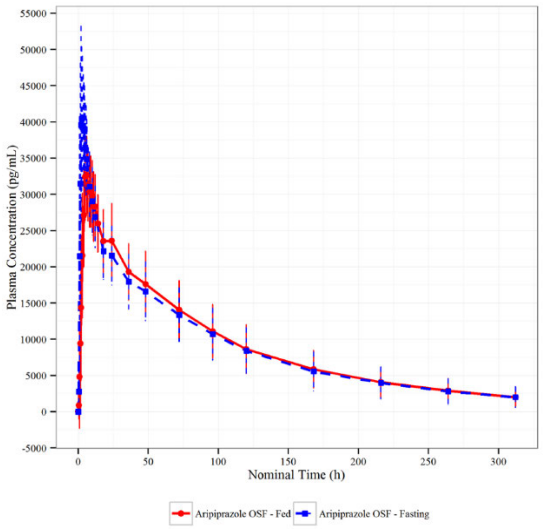
What is the effect of food on the exposure of aripiprazole OSF (Study 140051)?
The effect of food on the pharmacokinetics of the 10 mg strength of aripiprazole OSF was assessed in 25 healthy subjects. For the OSF fed treatment (test) the subjects fasted overnight for 10 hours, and were then served the high-fat, high-calorie FDA breakfast 30 minutes before drug administration. Subjects were administered a single oral dose of one OSF containing 10 mg of aripiprazole. For the reference treatment (OSF fasted) subjects underwent a 10 hour fast and were then administered a single oral dose of one OSF containing 10 mg of aripiprazole.

A) Aripiprazole: Pharmacokinetics of a single 10 mg dose of aripiprazole OSF administered fed (test) and fasted (reference) were compared. The results show that:

- For AUC_{0-t} aripiprazole OSF fed (test) was equivalent to aripiprazole OSF fasted (reference), (AUC0-t ratio: 100.7%; 90 % C.I. for AUC0-t 94.8 to 107.0%); C_{max} ratio was 75.0% with 90 % C.I. of 70.3 % to 80.0 %.
- For AUC_{0-inf} aripiprazole OSF fed (test) was equivalent to aripiprazole OSF fasted (reference), (AUC_{0-inf} ratio: 100.5%; 90 % C.I. for AUC_{0-inf} 94.7% to 106.7%); C_{max} ratio was 75.0% with 90 % C.I. of 70.3 % to 80.0 %.
- The extrapolation of AUC_{0-t} to AUC_{0-inf} was less than 10%.
- Median T_{max} for aripiprazole OSF fed was 6 hours and was 3 hours for aripiprazole OSF in the fasted state. Food delayed T_{max} by 3 hours.

The Figure below shows the Mean (±SD) concentration-time profile for aripiprazole for each treatment.

Figure 3: Mean (±SD) concentration-time profile for aripiprazole for each treatment

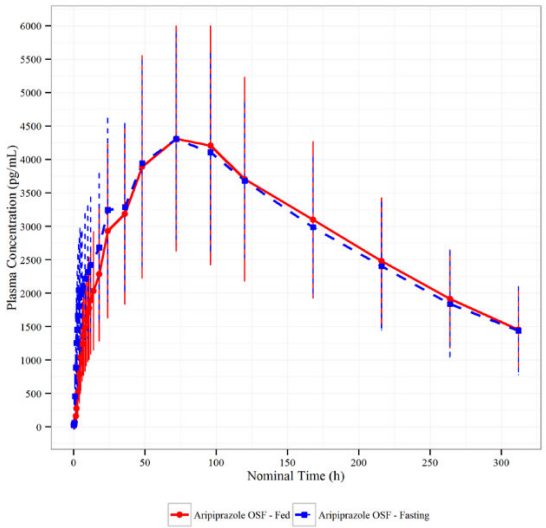


Source: Applicant's study report: 140051, page 50, Figure 11.4.2.3-1

B) Dehydroaripiprazole: Pharmacokinetics of a single 10 mg dose of aripiprazole OSF administered fed (test) and fasted (reference) were compared. The results show that for both AUC_{0-312} and C_{max}, aripiprazole OSF fed (test) was comparable to aripiprazole OSF fasted (reference), (AUC_{0-312} ratio: 100.2%; 90 % C.I. for AUC_{0-312}, 97.2 to 103.2%; C_{max} ratio: 101.9%; 90 % C.I. for C_{max} 97.7 % to 106.3 %). Median Tmax for dehydroaripiprazole was comparable between treatments and was 72 hours.

The figure below shows the mean (±SD) concentration-time profile for dehydroaripiprazole for each treatment.

Figure 4: Mean (±SD) concentration-time profile for dehydroaripiprazole for each treatment



Source: Applicant's study report: 140051, page 53, Figure 11.4.2.3-2

In the current labele for the LD, it mentions that the drug is to be administered once daily without regard to meals. In this food effect study (Study -51) with the OSF formulation, the extent of absorption (AUC) of aripiprazole is comparable between the fed and fasted states. C_{max} of aripiprazole is approximately 25% lower while Tmax is delayed by approximately 3 hours when a 10 mg dose of aripiprazole OSF is administered with food compared to the fasted state.

The 25% decrease in C_{max} should not be considered clinically meaningful based on the following evidence: 1) there appears to be no dose-response relationship for effectiveness in patients with schizophrenia but there appears to be a dose-dependent effect on somnolence and extrapyramidal effect for the dose range of 10 to 30 mg (refer to OCP review for NDA021436, 2/20/2008); 2) the dose of aripiprazole for schizophrenia is titrated to effect. Therefore, a lower C_{max} raises no concerns in terms of effectiveness and safety. Thus, aripiprazole OSF, like the LD, can be given without regard to meals.

Waiver Request for the 5 mg and 15 mg OSF Strengths
As mentioned above, the Applicant, CMG Pharmaceuticals, is relying upon the Agency's findings of safety and effectiveness for the LD (NDA 021436) for the treatment of schizophrenia to support their aripiprazole OSF. In a comparative bioavailability study, the Applicant has established the bridge between their aripiprazole OSF formulation and the LD by demonstrating that 10 mg aripiprazole OSF (administered both with or without water) produces similar rate and extent of absorption of aripiprazole as the 10 mg immediate release tablet of the LD, aripiprazole. The Applicant is requesting a biowaiver for the 5 mg and 15 mg strengths of aripiprazole OSF.

Briefly, the 5-mg, 10-mg, and 15-mg strips consist of identical ingredients and the formulations are compositionally proportional across all strengths; the only difference is the size of the strip. Aripiprazole OSF 5-mg, 10-mg, and 15-mg are the same dosage form (oral soluble film) and have the same release mechanism and the same manufacturing process.

Comparative dissolution studies have been performed to determine similarity between the aripiprazole OSF 5-mg, 10-mg, and 15-mg strengths in media pH 1.2, pH 4.0, pH 6.8, and in water. Similarly, comparative disintegration data for the 10-mg strength and the 5-mg and 15-mg strengths have been presented by the Applicant and it appears that the disintegration time for each of the three strengths of the OSF formulation is less than 1 minute.

The approved labeling for aripiprazole immediate release tablets, the LD, states that the pharmacokinetics of aripiprazole are linear and dose-proportional between the doses of 5 mg to 30 mg. This Applicant notes that, because aripiprazole is also dosed at 20 mg and 30 mg for treatment of schizophrenia, they propose to administer 2×10 mg or 2×15 mg strips as single doses, respectively. The Applicant has demonstrated bioequivalence of aripiprazole OSF (10 mg) to the LD which is the immediate release tablet of aripiprazole (10 mg). The Applicant

states that aripiprazole OSF is predicted to have similar linear pharmacokinetics over the proposed dosage range.

The biowaiver request for the various strengths of aripiprazole OSF has been reviewed by the Division of Biopharmaceutics in the Office of Pharmaceutical Quality.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 3: Table of Clinical Studies

Type of Study	Study Identifier	CTD Location of Study Report	Study Design	Test and Reference Products, Dosage Regimen	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Study Status, Type of Report
Phase 1 Comparative Bioavailability (Bioequivalence)	140052 Bio-analytical report	5.3.1.2 5.3.1.4	Single-dose, randomized, three-period, crossover, comparative study	• Aripiprazole OSF (Test): 10 mg, single oral dose, fasting conditions, without water • Aripiprazole OSF (Test): 10 mg, single oral dose, fasting conditions, with water • Abilify Tablets (Reference):10 mg, single oral dose, fasting conditions, with water	36	Healthy subjects	Complete, final report
Phase 1 Comparative Bioavailability (Fasted-Fed)	140051 Bio-analytical report	5.3.1.2 5.3.1.4	Single-dose, randomized, two-period, crossover, comparability study	• Aripiprazole OSF (Test): 10 mg, single oral dose, fasting conditions • Aripiprazole OSF (Test): 10 mg, single oral dose, fed conditions	32	Healthy subjects	Complete, final report

Source: Applicant, 5.2 Tabular Listing of All Clinical Studies, Table 1, page 2

7.2. Review Strategy

As noted previously, the Applicant relies on the Agency's findings of safety and effectiveness from the LD and did not conduct any efficacy studies. This review focuses on the safety record of the submitted bioequivalence and bioavailability studies 140051 and 140052. The safety review included evaluation of adverse events, vital sign parameters, laboratory assessments, and use of concomitant medications in the BE and BA studies. The major focus of the clinical review was to assess whether there are safety findings associated with this oral soluble film formulation that are different from the safety profile of the LD.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study 140051

Overview and Objectives

Study Title: "A Single-Dose, Randomized, Two-Period, Crossover Comparative Bioavailability Study of a Novel Formulation for Aripiprazole 10 mg Oral Soluble Film, Dosed with and without Food in Healthy Male and Female Volunteers"

Primary Objective:
To evaluate the effect of food on the PKs of aripiprazole OSF 10 mg oral soluble film, administered as 1 x 10 mg oral soluble film under fasting and fed conditions.

Secondary Objectives:
- To evaluate the usability of a new aripiprazole OSF 10 mg oral soluble film formulation
- To evaluate the safety and tolerability of aripiprazole OSF 10 mg oral soluble film

Trial Design

Study 140051 was conducted with a randomized, single-dose, open-label, two-way, crossover design to evaluate the effect of food on the bioavailability of aripiprazole OSF 10 mg. The study was designed to expose all participants to each condition: aripiprazole OSF in the fed condition (Treatment A) and aripiprazole OSF in the fasted condition (Treatment B). Participants were randomly assigned to a treatment. Participants served as their own controls in the study. The aripiprazole OSF dose administered in each treatment condition was 10 mg once daily. Participants remained in the inVentiv Clinical Facility from at least 11 hours prior to drug administration until after the 72-hour post-dose blood draw in each period. Participants were asked to come back to the clinical facility for return visits. The treatment phases were separated by a washout period of 42 days.

Healthy, moderate smokers and non-smokers, ages ≥45 and ≤65 years who had unremarkable screening medical histories, physical examinations, and results on screening parameters were eligible to participate in the study. Participants were required to have a body mass index (BMI) >18.5 and <30.0 kg/m^2 and body weight ≥ 50.0 kg for males and ≥ 45.0 kg for females.

Exclusion criteria included:
- Systolic blood pressure lower than 90 or over 140 mmHg, diastolic blood pressure lower than 50 or over 90 mmHg, or heart rate less than 50 or over 100 bpm

- Decrease in systolic blood pressure of 20 mmHg or higher or decrease in diastolic blood pressure of 10 mmHg or higher within two to three minutes after passing from a supine to a standing position, at screening
- Use of medication other than topical products without significant systemic absorption and hormonal contraceptives:
  a) prescription medication within 14 days prior to the first dosing
  b) over-the-counter products including natural health products (e.g. food supplements and herbal supplements) within seven days prior to the first dosing, with the exception of the occasional use of acetaminophen (up to 2 g daily)
  c) a depot injection or an implant of any drug (other than hormonal contraceptives) within three months prior to the first dosing
- Use of drugs known to induce or inhibit hepatic drug metabolism within 30 days
- Diarrhea, vomiting, or nausea within one week of study enrollment
- 7-item Hamilton Depression Rating Scale (HAM-D-7) total score above 3 at screening

Screening assessments are outlined in Table 4.

Participants could be withdrawn from the study if they experienced vomiting within 14 hours after dosing with Treatment A and within 8 hours after dosing with Treatment B. Study exit procedures were performed for any subjects who did not complete the study. Samples from subjects who did not complete the study due to AEs or vomiting episodes were analyzed and reported but the results were not used for statistical analysis. Subjects who did not complete the study were not replaced.

Reviewer's Comment: *The study eligibility criteria are appropriate for the objectives of this Phase 1 study.*

Study Endpoints

Pharmacokinetic endpoints for aripiprazole included the area under the plasma concentration curve (AUC) from time zero to the last measurable concentration and from time zero to infinity, maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), terminal elimination half-life ($T_{½}$) and first order terminal elimination rate constant (K_{el}). Pharmacokinetic endpoints for dehydroaripiprazole included the AUC_{0-312}, C_{max}, and T_{max}.

Safety assessments included vital signs, medical history, medication history, physical examination, adverse event monitoring, ALT, AST, BUN, creatinine, complete blood count, and UA. A schedule of study assessments is outlined inTable 4.

Table 4: Study 140051 Schedule of Assessments

PROCEDURE	Screening	Periods 1 &2				Study Exit
		D-1	D1	D2-4	*D5-14*	
Demographic Data	X					
Medical and Medication Histories	X					
Review of AEs and Concomitant Medications		X			*X*	
Physical Exam. & Body Measurements	X					
HAM-D-7 scale	X					
Vital Signs	X		X[1]	X[1]		X
Orthostatic Blood Pressure	X		X[2]			
Oral Temperature	X					X
ECG	X		X[3]			X
Biochemistry	X					X
Hematology	X					X
HIV and Hepatitis	X					
Urinalysis	X					X
Urine Drug Screen	X	X				
Alcohol Breath Test		X				
Serum Pregnancy Test		X				
Urine Pregnancy Test	X					X
Confinement		X	X	X		
Drug Administration			X			
Local Tolerability Assessment[4]			X			
Usability Questionnaire[5]			X			
PK Sample[6]			X	X	*X*	
AE Monitoring		X	X	X	*X*	X

1 BP and HR: pre-dose and approximately 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 12, and 24 hours post-dose.

2 Orthostatic blood pressure: pre-dose and approximately 8 hours post-dose.

3 ECG: pre-dose and approximately 3, 5, 8, and 12 hours post-dose.

4 Subjects will undergo a local tolerability assessment prior to and within 15 minutes after dosing. Any alteration of the appearance of the tongue, palate and buccal mucosa space will be recorded.

5 Immediately after dosing.

6 Blood samples:

Treatment A: pre-dose and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, **12, 14**, 18, 24, 36, 48, **72, 96, 120, 168, 216, 264 and 312** hours post-dose.

Treatment B: pre-dose and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 10, 12, 18, 24, 36, 48, **72, 96, 120, 168, 216, 264 and 312** hours post-dose.

Source: 140051-16-1-1 Protocol, Table 2, page 54

Statistical Analysis Plan

To evaluate the pharmacokinetic endpoints, the Applicant conducted an analysis of variance

(ANOVA). No food effect was to be concluded if the 90% geometric confidence interval of the ratio (Fed/Fasting) of least-squares means from the ANOVA of the ln-transformed AUC_{0-t}, AUC_{0-inf}, and C_{max} were within 80% to 125%. No interim analyses were performed on the data. No subgroup analyses were performed. See Section 6 Clinical Pharmacology for discussion of PK methodology.

Protocol Amendments

No protocol amendments were submitted.

Reviewer's Comment: *The study design is appropriate for the study objectives.*

8.1.2. Study Results

Compliance with Good Clinical Practices

The principal investigator has submitted a letter of certification that the clinical study for this application was conducted in compliance with all requirements of good clinical practice.

Financial Disclosure

Please refer to Section Error! Reference source not found.. No disclosable financial interests or arrangements were reported for any of the investigators participating in this study.

Patient Disposition

Fifty-nine subjects were screened, and 36 subjects enrolled in this study. 32 subjects (10 females and 22 males) were randomized and dosed; of these, 25 subjects completed the study. In accordance with the study protocol, data from all subjects who completed the study and for whom the PK profile could be adequately characterized were used for PK and statistical analyses (N=25).

Table 5: Study 140051: Number of Patients Exposed to Aripiprazole OSF per Treatment Period

Treatment Condition	Period I	Period II	Total
Treatment A (OSF fed)	16	13	29
Treatment B (OSF fasted)	16	13	29

Source: Reviewer-created

Protocol Violations/Deviations

In Period 1 (Participants (b) (6) and (b) (6) and in Period 2 (Participant (b) (6), several participants were dosed as late as 31 minutes 50 seconds after beginning to eat, which the Applicant states was due to long medication disintegration time of the previous participant or because the previous participant was dosed late.

Participant (b) (6) drank around 30 mL of coffee between 11 and 13 days (exact time unknown) after study drug administration during Period 1.

Participant (b) (6) drank one glass of wine (exact volume and content of alcohol unknown) approximately five days nine hours 28 minutes after study drug administration in Period 1 and two glasses of red wine (175 mL each; exact content of alcohol unknown) approximately five days nine hours 28 minutes after study drug administration in Period 2.

Participant (b) (6) drank 15 mL of red wine (exact content of alcohol unknown) three days nine hours 16 minutes after study drug administration in Period 1.

Participant (b) (6) only remained at the study center for 24 hours 27 minutes post-dose in Period 2 because he had to leave for a personal reason. However, he returned for 36, 48, and 72-hour post-dose blood draws.

In Period 1, Participant (b) (6) had the 12 hours post-dose electrocardiogram (ECG) taken in semi-reclined position instead of supine position due to nausea.

No study exit respiratory rates were obtained for Participants (b) (6)

Reviewer's Comment: *These violations are not expected to have a clinically significant effect on PK results, given that they occurred at least 5 days after medication administration, long after the C_{max} would be expected to occur (between 3 and 6 hours).*

Table of Demographic Characteristics

The study was conducted at a clinical facility in Quebec, Canada. The study population was comprised of healthy adults ages 45 to 65 years (Table 6). All participants identified their race as "White;" 2 out of 32 participants identified their ethnicity as "Hispanic or Latino." 10 participants identified as female and 22 as male.

Table 6: Study 140051: Demographics

Demographic Parameters	Total (N=32) n (%)
Sex	
Male	22 (69)
Female	10 (31)
Age	
Mean years (SD)	55.7 (5.1)
Median (years)	57.5
Min, max (years)	46, 64
Age Group	
< 65 years	32 (100)
Race	
White	32 (100)
Ethnicity	
Hispanic or Latino	2 (6)
Not Hispanic or Latino	30 (94)
Region (optional)	
Canada	32 (100)

Source: Reviewer-created

Reviewer's Comment: *Although the study was conducted outside of the U.S., pharmacokinetics are expected to be similar between U.S. and Canadian populations. Ideally, women and individuals of other races and ethnicities would have been better represented in the sample to better approximate the target U.S. population. However, aripiprazole's half-life is similar in males and females; gender-based dose adjustments are not recommended for the LD. Therefore, the paucity of female participants is not likely to affect the applicability of these study results. CYP2D6 allele frequency is known to vary among racial and ethnic groups, leading to variations in level of activity of CYP2D6 enzymes. However, guidance on safe dosing in CYP2D6 poor metabolizers is already included in the aripiprazole label. The sample is adequate for assessing PK and safety for this 505(b)(2) application.*

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Prescription medications were prohibited within 14 days of study enrollment. Over-the counter medications, vitamins, and herbal supplements were prohibited within 7 days of study enrollment with the exception of the occasional use of acetaminophen (up to 2 g daily).

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Measurements of treatment compliance were 100%, as subjects were dosed under direct supervision, subject identification was verified and cross-checked with the pre-dispensed medication, and a mouth (using a tongue depressor and a flashlight) and hand check was

performed to ensure subjects had swallowed the study medication. Benztropine mesylate, diphenhydramine, and an antiemetic agent such as dimenhydrinate were available throughout the study as rescue medications but were not used.

Data Quality and Integrity
The application was submitted in the Electronic Common Technical Document (eCTD) format. The datasets for safety data from study 140051 were not included in the NDA submission. AEs were listed in a .pdf document and coded using the dictionary Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART). Although current FDA Data Standards require AEs to be coded in Medical Dictionary for Regulatory Activities (MedDRA), Study 140051 was initiated prior to December 17, 2016. Therefore, the data are considered legacy reports and are not required to be submitted in the formats currently listed in the FDA Data Standards Catalog.

Following a request by the Agency for data files, the Applicant submitted the data tabulations as transport files and define.pdf files for each study. The files were converted, and AEs were recoded in MedDRA by Douglas Warfield, Ph.D., Associate Director of Biomedical Informatics. I compared the original and recoded AEs to verify their accuracy.

8.1.3. Study 140052

Overview and Objectives

Study Title: "A Single-Dose, Randomized, Three-Period, Crossover Comparative Bioavailability Study of a Novel Formulation of Aripiprazole 10 mg Oral Soluble Film, Dosed with and without Water, Versus the Marketed Formulation Abilify 10 mg Tablet (Dosed with Water) in Healthy Male and Female Volunteers in the Fasted State"

Primary Objective:
To compare the rate and extent of absorption of aripiprazole OSF 10 mg with and without water, versus Abilify 10 mg tablet, under fasting conditions.

Secondary Objectives:
- To compare the rate and extent of absorption of aripiprazole OSF 10 mg with water versus without water under fasting conditions
- To evaluate the usability aripiprazole OSF 10 mg
- To evaluate the safety and tolerability of aripiprazole OSF 10 mg
- To compare the rate and extent of absorption of dehydroaripiprazole following administration of aripiprazole OSF 10 mg versus Abilify 10 mg tablet, under fasting conditions

Trial Design

Study 140052 was conducted with a randomized, single-dose, open-label, 3-way crossover design to compare the rate and extent of absorption of a test aripiprazole OSF administered with or without water versus aripiprazole tablets under fasting conditions.

The study was designed to expose all participants to each of the three treatment conditions—aripiprazole OSF without water (Treatment A), aripiprazole OSF with water (Treatment B), and aripiprazole (Abilify) tablets with water (Treatment C). The dose administered in each treatment condition was 10 mg. Participants were admitted to the study site from at least 10 hours prior to drug administration until after the 72.0-hour post-dose blood draw, in each period. The treatment phases were separated by washout periods of 42 days.

Healthy, moderate smoker or non-smoker volunteers, ≥45 and ≤65 years of age were eligible to participate in the study. Participants were required to have a BMI >18.5 and <30.0 kg/m^2 and body weight ≥50.0 kg for males and ≥45.0 kg for females.

Exclusion criteria included:

- Systolic blood pressure lower than 90 or over 140 mmHg, diastolic blood pressure lower than 50 or over 90 mmHg, or heart rate less than 50 or over 100 bpm
- Decrease in systolic blood pressure of 20 mmHg or higher or decrease in diastolic blood pressure of 10 mmHg or higher within two to three minutes after passing from a supine to a standing position, at screening
- Use of any drugs known to induce or inhibit hepatic drug metabolism within 30 days prior to the first study drug administration.
- Use of medication other than topical products without significant systemic absorption and hormonal contraceptives:
  a) prescription medication within 14 days prior to the first dosing;
  b) over the counter (OTC) products including natural health products (e.g., food supplements and herbal supplements) within seven days prior to the first dosing, with the exception of the occasional use of acetaminophen (up to 2 g daily);
  c) a depot injection or an implant of any drug (other than hormonal contraceptives) within three months prior to the first dosing.
- Diarrhea, vomiting, or nausea within one week of study enrollment
- HAM-D-7 scale score above 3 at screening

Screening assessments are outlined in Table 7.

Participants could be withdrawn from the study if they experienced vomiting within eight hours of dosing. Study exit procedures were performed for any participants who did not complete the study. Samples from subjects who did not complete the study due to AEs or vomiting episodes

were analyzed and reported but the results were not used for statistical analysis. Participants who did not complete the study were not replaced.

Study Endpoints

Pharmacokinetic endpoints for aripiprazole included the area under the plasma concentration curve (AUC) from time zero to 72 hours post-dose (AUC_{0-72}), maximum plasma concentration (C_{max}), and time to maximum plasma concentration (T_{max}).

Safety assessments included vital signs, medical history, medication history, physical examination, adverse event monitoring, ALT, AST, BUN, creatinine, complete blood count, and UA. A schedule of study assessments is outlined inTable 7.

Table 7: Schedule of Assessments for Study 140052

PROCEDURE	Screening	Periods 1, 2 & 3			Study Exit
		D-1	D1	D2-4	
Demographic Data	X				
Medical and Medication Histories	X				
Review of AEs and Concomitant Medications		X			
Physical Exam. & Body Measurements	X				
HAM-D-7 scale	X				
Vital Signs	X		X[1]	X[1]	X
Orthostatic Blood Pressure	X		X[2]		
Oral Temperature	X				X
ECG	X		X[3]		X
Biochemistry	X				X
Hematology	X				X
HIV and Hepatitis	X				
Urinalysis	X				X
Urine Drug Screen	X	X			
Alcohol Breath Test		X			
Serum Pregnancy Test		X			
Urine Pregnancy Test	X				X
Confinement		X	X	X	
Drug Administration			X		
Local Tolerability Assessment[4]			X		
Usability Questionnaire[5]			X		
PK Sample[6]			X	X	
AE Monitoring		X	X	X	X

1 BP and HR: pre-dose and approximately 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 12, and 24 hours post-dose.

2 Orthostatic blood pressure: pre-dose and approximately 8 hours post-dose.

3 ECG: pre-dose and approximately 3, 5, 8, and 12 hours post-dose.

4 Subjects will undergo a local tolerability assessment prior to and within 15 minutes after dosing. Any alteration of the appearance of the tongue, palate and buccal mucosa space will be recorded.

5 Immediately after dosing, for Treatments A and B only.

6 Blood samples: pre-dose and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 10, 12, 18, 24, 36, 48, and 72 hours post-dose.

Source: 140052-16-1-1 Protocol, Table 2, page 16

Statistical Analysis Plan

To evaluate the pharmacokinetic endpoints, the Applicant conducted an analysis of variance (ANOVA) using SAS. Bioequivalence was concluded if the 90% geometric confidence interval of the ratio (A/B and B/C) of least-squares means from the ANOVA of the ln-transformed AUC_{0-72} and C_{max} was within 80.00% to 125.00%. No interim analyses were performed on the data. No

subgroup analyses were performed. See Section 6 Clinical Pharmacology for discussion of PK methodology.

Protocol Amendments

No protocol amendments were submitted.

Reviewer's Comment: *The study design is appropriate for the study objectives.*

8.1.4. Study Results

Compliance with Good Clinical Practices

The principal investigator has submitted a letter of certification that the clinical study for this application was conducted in compliance with all requirements of good clinical practice.

Financial Disclosure

See Section Error! Reference source not found.. No disclosable financial interests or arrangements were reported for any of the investigators participating in this study.

Patient Disposition

Sixty-one participants were screened; of these, 41 were enrolled (i.e., participated in Period 1 check-in procedures). 36 participants (6 female and 30 male) were randomized and dosed in this study. 29 participants completed all study periods. Table 8 shows the number of patients who were exposed to each treatment condition during the three treatment periods.

Table 8: Number of Patients Exposed to Aripiprazole OSF per Treatment Period in Study 140052

Treatment Condition	Period I	Period II	Period III	Total
Treatment A (OSF fasted, without water)	12	12	10	34
Treatment B (OSF fasted, with water)	12	10	12	34
Treatment C (Abilify fasted, with water)	12	11	11	34

Source: Reviewer-created

Protocol Violations/Deviations
Participant (b) (6) drank 591 mL of Mountain Dew (86 mg of caffeine) 18 hours 13 minutes before dosing in Period 3. Given that the half-life of caffeine is 5 to 7 hours, more than 2 to 3 half-lives of caffeine elapsed before drug administration, reducing the potential for a significant interaction.

Respiratory rate measurement at study exit was omitted for Participant (b) (6) following his withdrawal for the adverse event of vertigo. His other vital signs were within normal range.

Table of Demographic Characteristics
The studies were conducted at a clinical facility in Quebec, Canada. The study population was comprised of healthy adults ages 45 to 65 years (Table 9). Thirty-five participants identified their race as "White" and one as "Black/African American." One participant identified their ethnicity as "Hispanic." Six participants identified as female and 30 as male.

Table 9: Study 140052 - Demographics

Demographic Parameters	Total (N=) n (%)
Sex	
Male	30
Female	6
Age	
Mean years (SD)	53.5 (6.4)
Median (years)	52.5
Min, max (years)	45, 64
Age Group	
< 65 years	36 (100)
Race	
White	35 (97.2)
Black or African American	1 (2.8)
Ethnicity	
Hispanic or Latino	1 (2.8)
Not Hispanic or Latino	35 (97.2)
Region (optional)	
Canada	36 (100)

Source: Reviewer-created

Reviewer's Comment: *Although the study was conducted outside of the U.S., pharmacokinetics are expected to be similar across U.S. and Canadian populations. Ideally, women and individuals of other races and ethnicities would have been better represented in the sample to reflect the U.S. population. However, aripiprazole's half-life is similar in males and females; gender-based dose adjustments are not recommended for the LD. Therefore, the dearth of female participants is not likely to affect the applicability of these study results. CYP2D6 allele frequency is known to vary among racial and ethnic groups, leading to variations in level of activity of CYP2D6*

enzymes. However, guidance on safe dosing in CYP2D6 poor metabolizers is already included in the aripiprazole label. The sample is adequate for assessing PK and safety for this 505(b)(2) application.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Prescription medication use within 14 days prior to the first dosing was prohibited. OTC products including supplements were prohibited within seven days prior to the first dosing, with the exception of the occasional use of acetaminophen (up to 2 g daily).

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance was 100%, as subjects were dosed under direct supervision, subject identification was verified and cross-checked with the pre-dispensed medication, and a mouth (using a tongue depressor and a flashlight) and hand check was performed to ensure subjects had swallowed the study medication. Benztropine mesylate, diphenhydramine, and an antiemetic agent such as dimenhydrinate were available throughout the study as rescue medications but were not used.

Data Quality and Integrity
The application was submitted in eCTD format. The dataset files for safety data for study 140052 were not included in the NDA submission. AEs were listed in a .pdf document and coded using the dictionary COSTART. Although current FDA Data Standards require AEs to be coded in MedDRA, study 140052 was initiated prior to December 17, 2016. Therefore, the data are considered legacy report and are not required to be submitted in the formats currently listed in the FDA Data Standards Catalog.

Following a request by the Agency for data files, the Applicant submitted the data tabulations as transport files and define.pdf files for each study. The files were converted, and AEs were recoded in MedDRA by Douglas Warfield, PhD, Associate Director of Biomedical Informatics. I compared the original and recoded AEs to verify their accuracy.

8.1.5. Assessment of Efficacy Across Trials

The two clinical studies submitted with this NDA were intended to establish bioequivalence between aripiprazole OSF and Abilify tablets (Study 140052) and compare bioavailability of aripiprazole OSF between fasted and fed states (Study 140051). There were no efficacy endpoints for Studies 140051 and 140052. The primary endpoints were pharmacokinetic to establish a bridge to the LD. Aripiprazole OSF relies on the Agency's finding of effectiveness for Abilify tablets.

8.1.6. Integrated Assessment of Effectiveness

Not applicable; the submitted studies were not designed to assess the effectiveness of

aripiprazole OSF. Aripiprazole OSF relies on the findings of effectiveness of aripiprazole tablets (Abilify).

8.2. Review of Safety

8.2.1. Safety Review Approach

The safety review included evaluation of adverse events occurring under all treatment conditions as well as an assessment of changes in vital sign parameters and laboratory assessments following exposure to the drug. The review also referred to safety information contained in the label for the LD.

8.2.2. Review of the Safety Database

Overall Exposure

In these two crossover studies, all participants who completed the studies were exposed to all the treatment conditions. The safety population (all who received at least one dose of the study medication) included 36 and 32 healthy volunteers in Studies 140052 and 140051, respectively. Only 35 volunteers received aripiprazole OSF in Study 140052, because one participant withdrew after administration of the LD. Therefore, the total number of individuals exposed to aripiprazole OSF in the two Phase 1 studies was 67.

Adequacy of the safety database:

The safety population included all participants who received a dose of study medication. As noted above, the demographic characteristics of enrolled participants do not reflect the general U.S. population. However, this application relies on the established safety of the LD, aripiprazole tablets, which is well-characterized. The dose and duration of exposure to aripiprazole OSF are considered adequate to obtain accurate assessment of bioequivalence and comparative bioavailability and to assess safety issues specific to this new administration route. The sample size for BA/BE studies are acceptable for assessing product-specific safety issues.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The application was submitted in eCTD format. The dataset files for safety data from the two Phase 1 trials were not included in the original NDA submission. AEs were listed in .pdf documents and coded using the dictionary COSTART. Although current FDA Data Standards require AEs to be coded in MedDRA, Studies 140051 and 140052 were initiated prior to December 17, 2016. Therefore, the data are considered legacy and are not required to be submitted in the formats specified in the FDA Data Standards Catalog. Following a request by

the Agency for data files, the Applicant submitted the data tabulations as transport files and define.pdf files for each study.

Categorization of Adverse Events

The Applicant categorized adverse events using COSTART. The files were converted to .JMP by the Associate Director of Bioinformatics, Dr. Douglas Warfield, to facilitate the safety review. Dr. Warfield recoded the adverse events using MedDRA 23.0, and the accuracy of the recoding was confirmed by this clinical reviewer. Adverse events were examined by system organ class (SOC) as well as by preferred terms.

Routine Clinical Tests

Routine clinical tests were performed as per the schedule of study assessments described in Table 4 and Table 7.

Reviewer's Comment: *The Applicant's selection and schedule of safety assessments are reasonable.*

8.2.4. Safety Results

Deaths

No deaths occurred during the clinical studies.

Serious Adverse Events

No serious adverse events occurred during the clinical studies.

Dropouts and/or Discontinuations Due to Adverse Effects

Table 10 summarizes the withdrawals and discontinuations during the studies.

Table 10: Withdrawals or Discontinuations

Study	Subject	Discontinuation Reason
140051	(b) (6)	Withdrawn for vomiting in Period 1 only
		Withdrawn for vomiting in Period 1 only
		Withdrawn for vomiting in Period 1 only
		Discontinued due to failed ECG pre-dose
		Subject elected to withdraw for personal reason in Period 1
		Withdrawn for vomiting in Period 2 only
		Subject elected to withdraw for personal reason in Period 1
140052		Withdrawn for vomiting in Period 1 only
		Withdrawn for vomiting in Period 1 only
		Discontinued for non-compliance (positive drug screen)
		Withdrawn for vomiting in Period 1 only
		Discontinued due to adverse event (vertigo)
		Discontinued due to adverse event (syncope)
		Withdrawn for vomiting in Period 1 only

Source: Reviewer-created

Significant Adverse Events

No significant AEs were reported during study 140051. In Study 140052, Subject (b) (6) experienced the significant AE "Vertigo," and Subject No. (b) (6) experienced the significant AE "Syncope."

Treatment Emergent Adverse Events (TEAEs) and Adverse Reactions

A total of 103 TEAEs involving 28 subjects were recorded during Study 140051. 144 TEAEs were recorded by 35 subjects during Study 140052.

In adult patients in clinical trials of Abilify, the most common adverse reactions (≥10%) were nausea, vomiting, constipation, headache, dizziness, akathisia, anxiety, insomnia, and restlessness. In pediatric clinical trials, the most common adverse reactions (≥10%) were somnolence, headache, vomiting, extrapyramidal disorder, fatigue, increased appetite, insomnia, nausea, nasopharyngitis, and weight increased.

The most commonly reported TEAE in Studies 140051 and 140052 was somnolence. The incidence of somnolence was similar under fasting or fed conditions in Study 140051 (59% and 48%) and between the OSF formulation without water, OSF with water, and aripiprazole tablets with water in Study 140052 (53%, 47%, and 62%).

In both studies, several participants experienced vomiting. In Study 140051, one participant experienced vomiting in the fed condition and four in the fasting condition. In this study, aripiprazole OSF appeared to be better tolerated in the fed state. However, the rate of vomiting reported in the fasting condition (14%) is similar to what is described in the label of the LD. In

short-term, placebo-controlled trials in adult patients, 11% of patients reported vomiting with oral Abilify compared to 6% with placebo.

In Study 140052, 12% of participants reported vomiting following administration of aripiprazole OSF without water compared with 6% in the OSF with water condition and none in the aripiprazole tablets with water condition. In this study, aripiprazole OSF appeared to be better tolerated with water than without. However, the rate of vomiting reported without water (12%) is comparable to the rate describe in the label of the LD (11%). The absence of vomiting following dosing with aripiprazole tablets in Study 140052 differs from the rates in studies that supported approval of the LD. Aripiprazole has been poorly tolerated by healthy volunteers in some bioequivalence studies, particularly at doses greater than 10 mg (FDA Guidance on Aripiprazole, revised February 2019). In several cases, AEs have resulted in a high incidence of dropouts.

Local tolerability of aripiprazole OSF was assessed by oral examination, local tolerability severity grading, and AE analyses. No clinically significant pattern of dysphagia, dysgeusia, burning, stinging, tingling, erythema, swelling, or ulceration of the mucosa was observed. There were no cases of stomatitis, gingivitis, xerostomia, or staining of the mucosa. Local tolerability severity was assessed as Grade 0 (normal mucosa) at each time point for each subject.

In summary, the adverse events that occurred in studies 140051 and 140052 are consistent with the known safety profile of aripiprazole tablets (Table 11 and Table 12).

Reviewer's Comment: *Because only 29 participants were exposed to each condition in Study 140051 and 34 in Study 140052, these trials were not powered to detect whether safety differences between treatment conditions were statistically significant. It is also difficult to make meaningful comparisons between rates of AEs in these PK studies and rates in the studies that supported the approval of the LD, given the differences in size, population, and treatment conditions. Overall, the safety findings from Studies 140051 and 140052 are consistent with the safety profile of the LD.*

Table 11: Study 140051 Selected Adverse Events by Treatment Condition

Adverse Event (Preferred Term)	Treatment A (OSF Fed) N = 29	Treatment B (OSF Fasted) N = 29
Somnolence	17 (59%)	14 (48%)
Nausea	2 (7%)	11 (40%)
Headache	4 (14%)	4 (14%)
Hot flush	1 (3%)	6 (21%)
Vomiting	1 (3%)	4 (14%)
Dyspepsia/Reflux	1 (3%)	1 (3%)
Nasal congestion/Rhinorrhea/ Nasopharyngitis	2 (7%)	5 (17%)
Dysgeusia	1 (3%)	1 (3%)
Eructation	0	1 (3%)
Hiccups	0	1 (3%)

Source: Reviewer-created

Table 12: Study 140052 Selected Adverse Events by Treatment Condition

Adverse Event	Treatment A (OSF without water) N = 34	Treatment B (OSF with water) N = 34	Treatment C (LD with water) N = 34
Somnolence	18 (53%)	16 (47%)	21 (62%)
Hot flush	5 (15%)	5 (15%)	2 (6%)
Nausea	6 (18%)	3 (9%)	1 (3%)
Orthostatic heart rate	3 (9%)	4 (12%)	0
Vomiting	4 (12%)	2 (6%)	0
Hiccups	0	3 (9%)	1 (3%)
Decreased appetite	0	1 (3%)	0
Dyspepsia	0	0	1 (3%)
Hypoesthesia oral	0	0	1 (3%)

Source: Reviewer-created

Laboratory Findings

As per the schedules of assessments above, laboratory assessments were conducted at screening and exit for both studies. Post-study assessments included BUN, creatinine, complete blood count, urinalysis, and liver enzyme tests. The laboratory values

were examined for clinical significance. No pattern of laboratory changes that represented a new safety signal was found.

In Study 140051, the lowest exit hemoglobin value was 116 g/L. The lowest exit leukocyte value was 3.5 x 10^9 cells/L and the highest value was 11.3 x 10^9 cells/L. No platelet abnormalities were observed. In Study 140052, hemoglobin, leukocyte, and platelet values were all in normal range at the time of study exit.

Twenty participants experienced elevations in liver function enzymes above the upper limit of normal at either the Screening or Study Exit tests. However, liver function enzyme values greater than 3 times the upper limit of normal were not observed.

Reviewer's Comment: *The elevations in liver-related tests were reviewed for each patient in both studies were not considered to be clinically significant.*

Vital Signs

For the majority of participants in Studies 140051 and 140052, vital signs fell within the normal range. However, among several participants in both studies, there was a pattern of elevation in heart rate and decrease in systolic and diastolic blood pressure following administration of aripiprazole oral soluble film and tablets. This effect was most pronounced in the fasting condition (Treatment B) in study 140051. Overall, mean blood pressures were similar across treatment conditions; however, there were a number of outliers who experienced clinically significant vital sign changes. All of the participants who experienced vomiting in Study 140051 (subjects (b) (6) and (b) (6) also experienced significant vital sign changes. Three of four participants who experienced vomiting in Study 140052 (subjects (b) (6) experienced significant vital sign changes, as did the participants who experienced vertigo and syncope (subjects (b) (6) and (b) (6). For participants who experienced vomiting, decreased blood pressure and increased heart rate may have been, in part, the result of hypovolemia. In addition, aripiprazole is associated with orthostatic hypotension, which may be due to its α1- adrenergic receptor antagonism.

Table 13: Study 140051: Participants Experiencing Significant Vital Sign Change from Baseline At Any Time Point After Treatment

	Test Drug Fed N = 29	Test Drug Fasted N = 29
HR Elevation ≥ 20 BPM	5 (17%)	10 (34%)
HR Decrease ≥ 20 BPM	2 (7%)	5 (17%)
SBP Elevation ≥ 20 mmHg	7 (24%)	4 (14%)
SBP Decrease ≥ 20 mmHg	4 (14%)	12 (41%)
DBP Elevation ≥ 20 mmHg	1 (3%)	3 (10%)
DBP Decrease ≥ 20 mmHg	2 (7%)	10 (34%)

Source: Reviewer-created from Applicant-submitted datasets

Table 14: Study 140052: Participants Experiencing Significant Vital Sign Change from Baseline At Any Time Point After Treatment

	Test without water N = 34	Test with water N =34	Reference with water N =34
HR Elevation ≥ 20 BPM	14 (41%)	12 (35%)	6 (18%)
HR Decrease ≥ 20 BPM	3 (9%)	2 (6%)	2 (6%)
SBP Elevation ≥ 20 mmHg	8 (24%)	3 (9%)	9 (26%)
SBP Decrease ≥ 20 mmHg	10 (29%)	10 (29%)	6 (18%)
DBP Elevation ≥ 20 mmHg	2 (6%)	1 (3%)	0
DBP Decrease ≥ 20 mmHg	7 (21%)	8 (24%)	6 (18%)

Source: Reviewer-created from Applicant-submitted datasets

Electrocardiograms (ECGs)

Several participants in Studies 140051 and 140052 experienced sinus bradycardia and first degree atrioventricular (AV) block during study ECGs. Most participants displayed these findings at screening and throughout the studies. However, a few subjects with normal baseline ECGs developed ECG abnormalities after receiving study drug.

In Study 140051, Subject (b) (6) experienced sinus bradycardia in the first period, 3 hours after dosing in the fasted state, which resolved by 5-hours post-dose. Subject (b) (6) experienced first degree AV block in period 1 beginning at 5-hours post-dose in the fasted state, which normalized by 12 hours post-dose. Subject (b) (6) developed non-specific intraventricular conduction delay post-dosing in both periods, which resolved by 12-hours post-dose. Subject (b) (6) experienced two premature ventricular contractions (PVCs) in period 1, 5-hours after dosing in the fasted state. The same subject demonstrated a non-specific T wave anomaly in V2 at 8 hours post-dose in the second period (fed state), which subsequently resolved.

In Study 140052, Subject (b) (6) had a normal ECG at screening and in the first two periods. In the third period, this participant had PR interval of 200 ms pre-dose, which was prolonged to 206 ms (first degree AV block) at 3 hours post-dosing with aripiprazole OSF and subsequently resolved. Subject (b) (6) had a normal ECG at screening but developed first degree AV block (PR interval 233 ms) at 3 hours post-dosing with aripiprazole OSF in the first period, which subsequently resolved.

According to the label for Abilify, bradycardia was a frequent adverse event (defined as occurring in at least 1/100 patients) in premarket trials. AV block was an infrequent adverse event (defined as occurring in 1/100 to 1/1000 patients).

Reviewer's comment: *In most cases, prolonged PR interval or low heart rate was present prior to dosing, suggesting that this was not simply a treatment effect. The prevalence of first degree AV block is known to increase with age, affecting up to 6% of individuals over the age of 60. Sinus bradycardia is also more common in older populations. Studies 140051 and 140052 excluded subjects under the age of 45; median ages were 52.5 and 57.5 years. This demographic may account in part for the incidence of first degree AV block and sinus bradycardia seen in both studies. The ECG abnormalities were mild and not clinically significant.*

QT

Several participants experienced prolonged QTcF interval during the course of Studies 140051 and 140052.

In Study 140051, Subject (b) (6) experienced prolonged QTcF (458 ms) prior to dosing in the fasted state, which persisted at three hours post-dose (454 ms) and subsequently normalized. Subjects (b) (6) and (b) (6) experienced prolonged QTcF (both to 456 ms) at follow up visits several weeks after dosing in the second period. Subject (b) (6) displayed prolonged QTcF (451 ms) during screening and pre-dose in the second period, along with nonspecific intraventricular conduction delay. As a result, he was withdrawn from Period 2. Subject (b) (6) who experienced sinus bradycardia throughout the study (41 to 67 bpm), briefly developed prolonged QTcF (460 ms) at 5-hours post-dose in the fasted state, which resolved and then recurred at follow-up several weeks later (456 ms).

In Study 140052, Subject (b) (6) exhibited a normal QTcF in the first two periods of the study and pre-dose in the third period (441 ms). Following dosing with aripiprazole OSF in the third period, the QTcF became prolonged to 450 ms at 3 hours and 452 ms at 5 hours post-dose, normalizing by the 12-hour time point (432 ms).

As described in the label, the LD also increased the risk of QT prolongation in clinical trials.

Reviewer's comment: *The degree of QTcF prolongation in Studies 140051 and 140052 was mild and not clinically significant.*

Immunogenicity

Not applicable.

8.2.5. Analysis of Submission-Specific Safety Issues

The primary submission-specific safety issue was local toxicity. Local tolerability of the OSF formulation was assessed by oral examination, local tolerability severity grading, and AE analyses. No clinically significant pattern of dysphagia, dysgeusia, burning, stinging, tingling, erythema, swelling, or ulceration of the mucosa was observed. There were no cases of stomatitis, gingivitis, xerostomia, or staining of the mucosa. Local tolerability severity was assessed as Grade 0 (normal mucosa) at each time point, for each participant. There was no indication of AEs related to the route of administration.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Not applicable.

8.2.7. Safety Analyses by Demographic Subgroups

There was no apparent association between the major safety findings (i.e., somnolence and vomiting) and the age or sex of participants.

8.2.8. Specific Safety Studies/Clinical Trials

Not applicable.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No new information about human carcinogenicity or tumor development was submitted in this application.

Human Reproduction and Pregnancy

No new information about human reproduction and pregnancy was submitted in this application. No participants became pregnant during the course of the studies.

Pediatrics and Assessment of Effects on Growth

No pediatric data was submitted with this application.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No analyses or assessments regarding overdose, drug abuse potential, withdrawal, or rebound

were conducted in these studies. Our understanding of these areas are informed by the LD.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The following adverse reactions have been identified and added to product labeling since the initial approval of Abilify in 2002: occurrences of allergic reaction (anaphylactic reaction, angioedema, laryngospasm, pruritus/urticaria, or oropharyngeal spasm), pathological gambling, hiccups, blood glucose fluctuation, oculogyric crisis, and drug reaction with eosinophilia and systemic symptoms (DRESS).

Expectations on Safety in the Postmarket Setting

The Applicant has demonstrated that aripiprazole oral soluble films are bioequivalent to the LD, Abilify (aripiprazole tablets). The postmarket safety profile is anticipated to be similar to that of the LD. Studies 140051 and 140052 were conducted in healthy volunteers with no experience taking antipsychotics. With regard to nausea, vomiting, and hypotension, a more favorable profile would be expected in individuals with previous experience taking antipsychotic medication. Because the Applicant intentionally limited the population to adults 45 years and older to reduce the risk of dystonia, higher rates of dystonia would be expected in the postmarket setting.

8.2.11. Integrated Assessment of Safety

The determination of safety for this product relies almost entirely on investigations conducted with aripiprazole tablets (Abilify). A smaller amount of safety data was derived from bioequivalence/bioavailability studies for this product. These data were analyzed for potential safety issues specific to the OSF formulation that might differ from the LD. There were no apparent issues with local tolerability. There were high rates of vomiting in both studies; however, these rates were similar to what is described in the label of the LD. Overall, this safety review has not identified any safety issues related to the OSF formulation that would preclude the approval of this NDA.

8.3. Statistical Issues

This development program did not include efficacy studies that would be subject to statistical review. Please refer to section 6 for discussion of statistical issues related to PK comparison.

8.4. Conclusions and Recommendations

Results of the submitted studies indicate that aripiprazole oral soluble film is bioequivalent to

the LD, aripiprazole tablets. The safety profile of aripiprazole oral soluble film is also consistent with that of aripiprazole tablets. Therefore, we recommend approval of this application.

9 Advisory Committee Meeting and Other External Consultations

This 505(b)(2) application relies on the findings of safety and efficacy of the LD. There were no questions for an Advisory Committee. No external consultations were needed for review of this application.

10 Pediatrics

No new pediatric data was submitted with this application; this application relies on the Agency's findings of safety and effectiveness for the LD, aripiprazole tablets. This application triggered PREA because of the proposed new route of administration (oral soluble film) proposed. The Applicant's iPSP was reviewed by the Pediatric Review Committee in September 2017. No additional pediatric trials will be required for this formulation. Pediatric labeling for the treatment of schizophrenia will be consistent with Abilify. The Applicant is not pursuing the other pediatric indications found in the Abilify label.

The recommended initial dose of Abilify and aripiprazole OSF for the treatment of schizophrenia in pediatric patients 13 to 17 years of age is 2 mg/day. The lowest available dose of aripiprazole OSF is 5 mg. Therefore, the label will specify that patients will need to use another formulation of aripiprazole prior to initiating treatment with aripiprazole OSF 5 mg/day. We are proposing a postmarketing study commitment to the Applicant to develop a 2-mg dosage strength of the oral soluble film so pediatric patients will not need to initiate treatment with another formulation.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Labeling for aripiprazole oral soluble film is generally consistent with that of Abilify. Dosage and administration guidelines have been expanded to account for new modes of administration, current class language has been included to describe warnings and precautions when appropriate, and references to the indications other than schizophrenia have been removed. Pertinent differences between the aripiprazole oral soluble film and Abilify labels are described below.

HIGHLIGHTS
The Boxed Warning has been updated to align with the more recent Increased Mortality In Elderly Patients with Dementia-Related Psychosis and Suicidal Thoughts and Behaviors warnings. The first boxed warning indicates that elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. The second boxed warning indicates that there is increased risk of suicidal thinking and behavior in pediatric and young adult patients taking antidepressants and advises healthcare professionals to closely monitor all antidepressant-treated patients for clinical worsening and emergence of suicidal thoughts and behaviors. This boxed warning was included in the label for Abilify because of the adjunctive treatment of major depressive disorder (MDD) indication. Although the Applicant is not pursuing that indication for aripiprazole OSF, the review team decided to include the boxed warning to avoid implying a different risk for suicidal ideation and behavior than the LD.

1 INDICATIONS AND USAGE
Aripiprazole OSF is indicated for the treatment of schizophrenia in adults and pediatric patients 13 to 17 years old. The Applicant did not seek indications for acute treatment of manic and mixed episodes associated with bipolar I, adjunctive treatment of major depressive disorder, irritability associated with autistic disorder, or treatment of Tourette's disorder.

2 DOSAGE AND ADMINISTRATION
Dosage and administration guidelines have been updated for clarity and concision. Dosage and administration guidelines also differ from guidelines in Abilify labeling because they instruct the prescriber to refer patients and caregivers to the "Instruction for Use." The guidelines provide general instructions for use of the film, including a reminder that the film should not be cut.

The recommended starting dose of 2 mg for pediatric patients 13 to 17 years old is not available in the film formulation. As a result, this section has been updated to note that use of another formulation will be required for initial dosing.

3 DOSAGE FORMS AND STRENGTHS
This section differs from the Abilify label because it includes descriptions of the appearance of

each strength of film.

5 WARNINGS AND PRECAUTIONS
Warnings and precautions regarding neuroleptic malignant syndrome; tardive dyskinesia; metabolic changes; leukopenia, neutropenia, and agranulocytosis; and seizures have been revised to include the most recent class language. References to unapproved indications have been replaced with the term "another indication." Information from studies of aripiprazole for management of acute treatment of manic and mixed episodes associated with bipolar I, adjunctive treatment of major depressive disorder, irritability associated with autistic disorder, or treatment of Tourette's disorder that were not pooled with schizophrenia studies have been removed from labeling. Data on pediatric metabolic changes from trials of aripiprazole for the treatment of Tourette's disorder have been removed due to orphan exclusivity limitations.

6 ADVERSE REACTIONS
The beginning of this section was updated to note that because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse event data presented in Section 6 are generally unchanged from those presented in the Abilify label. However, several changes were made as a result of the Applicant pursuing only the schizophrenia indication. References to unapproved indications have been replaced with the term "another indication." Unpooled data on adverse effects from trials of oral aripiprazole for the treatment of Tourette's disorder have been removed. Tourette's disorder data was also removed from pooled data due to orphan exclusivity limitations.

A sentence was added to explain that the safety of aripiprazole OSF for the treatment of schizophrenia in adults and pediatric patients 13 to 17 years is based on clinical trials of oral aripiprazole.

8 USE IN SPECIFIC POPULATIONS
Section 8 (Use in Specific Populations) has been revised to replace references to unapproved indications with "another condition." Data from trials of oral aripiprazole for the treatment of Tourette's disorder have been removed due to orphan product exclusivity limitations.

11 DESCRIPTION
This section has been updated to include physical description of the film and information about solubility and physical properties of the drug substance.

14 CLINICAL STUDIES
Clinical studies that evaluated the efficacy of aripiprazole for management of acute treatment of manic and mixed episodes associated with bipolar I, adjunctive treatment of major

depressive disorder, irritability associated with autistic disorder, or treatment of Tourette's disorder have been removed from labeling.

Other Prescription Drug Labeling

Labeling for the LD Abilify includes a Medication Guide (MG). A MG was considered for aripiprazole OSF; however, the decision was made not to include one. The reason for inclusion of a MG with Abilify was because it is indicated for the adjunctive treatment of MDD. Much of the information provided in Abilify's MG concerns its use in the MDD population. Aripiprazole OSF is only approved for schizophrenia. The review team concluded that a MG focused on depression and depression-related adverse reactions could be confusing to individuals with schizophrenia and would not be relevant to their treatment.

Labeling for the LD Abilify includes a Medication Guide (MG). A MG was considered for aripiprazole OSF; however, the decision was made not to include one. The reason for inclusion of a MG with Abilify was because it is indicated for the adjunctive treatment of MDD. Much of the information provided in Abilify's MG concerns its use in the MDD population. Aripiprazole OSF is only approved for schizophrenia. The review team concluded that a MG focused on depression and depression-related adverse reactions could be confusing to individuals with schizophrenia and would not be relevant to their treatment.

12 Risk Evaluation and Mitigation Strategies (REMS)

Not applicable. There were no findings in the clinical review of this application that suggested the need for REMS.

13 Postmarketing Requirements and Commitment

Aripiprazole OSF has been developed in 5-, 10-, and 15-mg formulations. The label for the LD, Abilify tablets, specifies that for the treatment of schizophrenia in pediatric patients 13 to 17 years of age, the starting dose should be 2 mg. It is anticipated that there will be a significant number of patients who would benefit from an aripiprazole OSF dose of 2 mg/day. We have added language to product labeling indicating another formulation of aripiprazole will need to be used prior to initiating treatment with aripiprazole OSF 5 mg. The label also specifies that the OSF should not be cut.

We are proposing that the Applicant develop a 2-mg soluble film formulation of their product as a postmarketing requirement. Development of a 2-mg soluble film for use in adolescents with schizophrenia will include formulation development, associated pharmaceutical testing, generation of adequate stability data, and collection of adequate data supporting a biowaiver for this strength.

14 Division Director (Clinical) Comments

I have reviewed and edited the above document and modified as needed. I agree with the conclusions of the review team.

15 Appendices

15.1. References

American Psychiatric Association (2013). Diagnostic and Statistical Manual of Mental Disorders (DSM-5), American Psychiatric Publishing.

Davis, M. C., W. P. Horan and S. R. Marder (2014). "Psychopharmacology of the negative symptoms: current status and prospects for progress." European Neuropsychopharmacology 24(5): 788-799.

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Kantrowitz, J. and D. Javitt (2010). "Thinking glutamatergically: changing concepts of schizophrenia based upon changing neurochemical models." Clinical Schizophrenia & Related Psychoses 4(3): 189-200.

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Tandon, R., H. A. Nasrallah and M. S. Keshavan (2009). "Schizophrenia, "just the Facts" 4. Clinical features and conceptualization." Schizophrenia Research 110(1): 1-23.

Takeuchi, H., Suzuki, T., Uchida, H., Watanabe, K., & Mimura, M. (2012). Antipsychotic treatment for schizophrenia in the maintenance phase: a systematic review of the guidelines and algorithms. Schizophrenia Research 134(2-3): 219-225.

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Zaheer, J., Olfson, M., Mallia, E., Lam, J. S., de Oliveira, C., Rudoler, D., .and Kurdyak, P. (2020). Predictors of suicide at time of diagnosis in schizophrenia spectrum disorder: A 20-year total population study in Ontario, Canada. Schizophrenia Research. S0920-9964(20): 30232-2.

15.2. Financial Disclosure

Covered Clinical Studies: 140051, 140052

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 14		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: NA Significant payments of other sorts: NA Proprietary interest in the product tested held by investigator: NA Significant equity interest held by investigator in sponsor of covered study: NA		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

15.3. Nonclinical Pharmacology/Toxicology

Review of published literature data on (b) (4) nonclinical toxicology
Repeat-dose Oral Toxicity: Sub-chronic and chronic oral toxicity of (b) (4) have been studied in several animal species (rats, mice, dogs and rabbits).

(b) (4)

(b) (4)

Genetic Toxicity: No evidence for genotoxic potential of (b) (4) was found in vitro (b) (4)

(b) (4)

(b) (4)

Summary: Based on the review of the published literature data on (b) (4) nonclinical toxicology, (b) (4) based on a mg/m2 body surface area. (b) (4) was negative in genotoxicity assays in vitro and in vivo and was not carcinogenic in (b) (4) carcinogenicity studies in rats and mice. (b) (4) had no reproductive toxicity in a (b) (4) fertility study in rats and was no embryotoxic or teratogenic in embryofetal developmental toxicity studies in rats and rabbits.

Conclusion: The amount of (b) (4) in the aripiprazole OSF finished drug product (b) (4) (b) (4) in the 10 mg film, with maximum (b) (4) exposure around (b) (4) at the MRHD of 30 mg for aripiprazole OSF in the proposed label) is acceptable.

References:

(b) (4)

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15.4. OCP Appendices (Technical documents supporting OCP recommendations)

This section includes information on the bioanalytical method validation and performance supporting the pharmacokinetic studies.

15.4.1. Summary of Bioanalytical Method Validation and Performance

For both studies (-52, the BA/BE study, and -51, the food study) plasma concentrations of aripiprazole and dehydroaripiprazole were ascertained using a validated High Performance Liquid Chromatographic Method using Tandem Mass Spectrometry Detection with an automated extraction system for the determination of aripiprazole (500 to 100000 pg/mL) and dehydroaripiprazole (50 to 10000 pg/mL) in human EDTA plasma. The assay was LC/MS/MS. The assay was specific for aripiprazole with a retention time of 1.8 minutes and for dehydroaripiprazole with a retention time of 1.52 minutes, with no interfering peaks. The internal standard used was aripiprazole-d8. The samples were extracted automatically with liquid-liquid extraction using a mixture of methyl tert-butyl ether and ethyl acetate.

For study -52 (relative BA/BE study), aripiprazole: the accuracy is 96.7 % to 102.5 % and the variation in precision is low at 3 %. For dehydroaripiprazole the accuracy is 94.3 % to 103.7 % and the precision is low at 3%.
For study -51 (the food study), aripiprazole: the accuracy is 98.5 % to 101.9 % and the variation in precision is low at 2 %. For dehydroaripiprazole accuracy is 97.1 % to 104.5 % with a low variation in precision of 3%.
Linearity of the assay calibration had a correlation coefficient, r, of 0.999 for both moieties.
Stability: First date of analysis to the last date of analysis was 12 days which was within the validated stability period of 700 days. Freeze and thaw stability was 4 cycles at -20°C.
The method for the determination of aripiprazole and dehydroaripiprazole in human EDTA K2 plasma was precise, accurate, sensitive and selective over the validated ranges. The method is reliable and reproducible, and the analytes and the internal standards are stable under the conditions tested. From these results, the method is considered suitable for the analyses of aripiprazole and dehydroaripiprazole in human EDTA K2 plasma over the ranges of 500 to 100000 pg/mL for aripiprazole and 50 to 10000 pg/mL for dehydroaripiprazole.

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