EXHIBIT

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology

Pharmacovigilance Review

Date:	March 10, 2016
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Product Name(s):	Abilify (aripiprazole); Abilify Maintena (aripiprazole); Aristada (aripiprazole lauroxil)
Subject:	Impulse-Control Disorders
Application Type/Number:	NDA 021436, 021729, 021866, 202971, 207533 ANDA 078583, 078607, 078608, 078612, 078613, (b) (4) 078708, (b) (4) 201519, 202102, 203906, 203908, 204094, 204171, 205064
Applicant/Sponsor:	Otsuka American Pharmaceutical, Inc.; Alkermes, Inc.
OSE RCM #:	2015-2507

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EXECUTIVE SUMMARY

This review evaluates cases identified in the FDA Adverse Event Reporting System (FAERS) database and the published medical literature for an association between aripiprazole and impulse-control disorders and related disorders (ICD-RDs). The purpose of this review is to determine if this safety issue warrants any regulatory action.

DPV identified an association between aripiprazole and ICDs. This association is based on the temporal relationship and positive dechallenge reported in 184 case reports (167 FAERS case reports and 17 literature case reports), of which four also contained positive rechallenge information. Aripiprazole's dopamine partial agonist activity could theoretically stimulate dopamine transmission in the mesolimbic pathway, a core component of the brain reward circuitry, providing biological plausibility for treatment-emergent ICDs. The specific ICDs reported in FAERS and in the literature include: pathological gambling (n=164); compulsive sexual behaviors (n=9); compulsive buying (n=4); compulsive eating (n=3); and multiple ICDs (n=4).

Based on the data analyzed in this review, DPV recommends the following:

1. Addition of the following statement to Section 5, Warnings and Precautions, of the label for Abilify, Abilify Maintena, and Aristada:

   Pathological Gambling and Impulse-Control Disorders
   Case reports suggest that patients can experience intense urges, particularly for gambling, and the inability to control these urges while taking aripiprazole. Other urges, reported less frequently than gambling, include: sexual urges, uncontrolled spending, binge or compulsive eating, and other urges with impulsive and compulsive features. These urges were reported to have stopped when the dose was reduced or the medication was discontinued. Because patients may not recognize these behaviors as abnormal, it is important for prescribers to specifically ask patients or their caregivers about the development of new or increased gambling urges, sexual urges, uncontrolled spending, binge or compulsive eating, or other urges while being treated with aripiprazole. If left unrecognized, these urges may result in harm to the patient and to others. Consider dose reduction or stopping the medication if a patient develops such urges while taking aripiprazole.

2. Addition of the above warning information to Section 17 – Patient Counseling Information, and the Medication Guide.

3. Issuance of a Drug Safety Communication containing the above warning information.

1 INTRODUCTION

This review evaluates cases identified in the FDA Adverse Event Reporting System (FAERS) database and the published medical literature for an association between aripiprazole and impulse-control disorders and related disorders (ICD-RDs). The purpose of this review is to determine if this safety issue warrants any regulatory action.

1.1 BACKGROUND

On November 2, 2015, Health Canada issued a product label update for Abilify (aripiprazole) and Abilify Maintena (aripiprazole), adding a new warning statement for pathological gambling, and adding hypersexuality to the post-market adverse drug reaction section of the Canadian product monograph.[1] The Canadian product monograph revisions were a result of a Health Canada safety review that found an association between pathological gambling and hypersexuality with the use of aripiprazole.[1] Health Canada's decision to prioritize this safety issue was partially due to the European Medicines Agency's (EMA) decision in 2012 to include a warning for pathological gambling in aripiprazole's product label. Health Canada's review and subsequent product label update prompted the Division of Pharmacovigilance I (DPV-I) to further evaluate the safety issue of pathological gambling and hypersexuality, as well as other ICD-RDs, in association with aripiprazole use.

Impulse-Control Disorders and Related Disorders

Defining Impulse-Control Disorders: A Moving Target

Broadly defined, impulse-control disorders (ICDs) are a group of psychiatric disorders that involve problems with behavioral self-control resulting in harm to oneself or to others.[2] Core characteristics of ICDs include: (1) a behavior that is repetitive or compulsive, despite adverse consequences; (2) an inability to stop the harmful behavior; (3) an urge or craving to engage in the harmful behavior; and (4) a pleasurable ("hedonic") quality to the harmful behavior.[3] ICDs are also termed behavior addictions, due to increasing recognition of similarities between ICDs and alcohol and drug addiction in terms of clinical features, cognitive changes, treatment, and underlying neurobiological processes.[4,5,6] For example, people with a gambling disorder exhibit cravings, tolerance through a need to increase betting, euphoric "highs," and even withdrawal symptoms similar to what people with a drug addiction experience.[5]

Examples of specific ICDs include, but are not limited to, pathological gambling (PG; also known as gambling disorder or compulsive gambling), compulsive sexual behavior (i.e. hypersexuality or sexual addiction), compulsive buying/shopping (i.e. shopping addiction), and compulsive eating (i.e. binge eating).[3,7] Many psychiatric conditions feature impulsive-compulsive behaviors, such as attention-deficit/hyperactivity disorder, mania, and substance use disorders, although they are not formally labeled as an ICD.[2,8,9] The classification of a specific disorder as an ICD, and the very definition of an ICD, is an evolving field of psychiatry, as evidenced by changes in the latest edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). What was known as the *Impulse-Control Disorders Not Elsewhere Classified (NEC)* section in the previous edition of the DSM (DSM-IV-TR) was overhauled and renamed *Disruptive, Impulse-Control, and Conduct Disorders*. Additionally, "Pathological

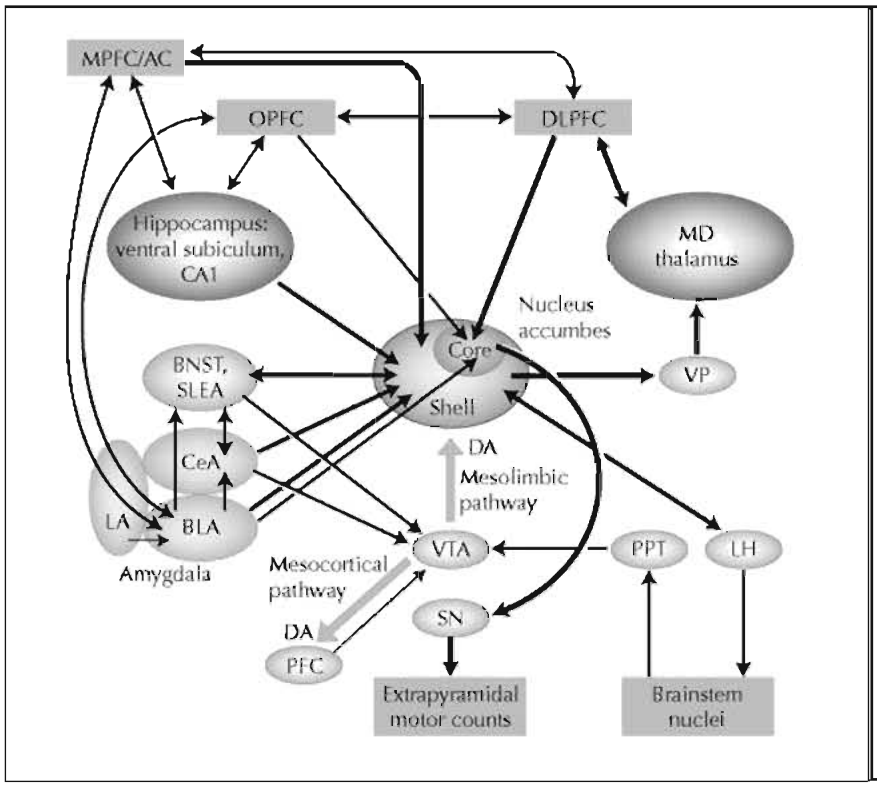
Gambling," which was categorized under the *Impulse-Control Disorders NEC* section in the DSM-IV-TR, was renamed "Gambling Disorder" and moved to the *Substance-Related and Addictive Disorders* section in the DSM-5.[2,10]

Pathophysiology of ICDs: The Role of Dopamine

Underlying all ICDs is a dysfunction in reward processing – a complex process involving several psychological and physiological components.[11] One of the key pathways in reward processing is the mesolimbic dopamine pathway, in which dopamine neurons from the ventral tegmental area project to the nucleus accumbens (NA; also known as the ventral striatum) (Figure 1).[11] Activation of dopamine neurons in the mesolimbic pathway, which can occur from behaviors such as eating food, having sex, or consuming drugs of abuse, serves to provide positive reinforcement of behaviors.[11]

Impulsivity - the inability to stop the initiation of actions – involves a brain circuit centered on the NA, and linked to the thalamus, the medial prefrontal cortex (MPFC), and to the anterior cingulate (AC).9 In simplified terms, impulsivity can be thought of as imbalanced input between the NA and the MPFC, resulting in the NA inappropriately sending information to the prefrontal cortex that leads to impulsive behavior. Compulsivity - the inability to terminate ongoing actions – involves a different brain circuit centered on the dorsal striatum, and linked to the thalamus and orbital prefrontal cortex (OPFC).9 Impulsive acts such as drug use and gambling can eventually become compulsive due to neuroplastic changes that engage the dorsal striatum.9,12 Impulses, initially motivated by positive reinforcement, shift towards compulsions that are motivated by negative reinforcement (relief from stress and anxiety) and automaticity.[12]

Figure 1: Brain reward circuitry[11]



Legend
AC–anterior cingulate
BLA–basal lateral amygdala
BNST–bed nucleus of stria terminalis
CeA–central nucleus of amygdala
DA–dopamine
DLPFC–dorsolateral prefrontal cortex
LA–lateral amygdala
LH–lateral hypothalamus
MD–mediodorsal
MPFC–medial prefrontal cortex
OPFC–orbital prefrontal cortex
PPT–pedunculopontine tegmental nucleus
SLEA–sublenticular extended amygdala
SN–substansia nigra
VP–ventral pallidum
VTA–ventral tegmental area.

Brain reward circuity is complex and widespread, involving several different structures, including the prefrontal-temporal limbic regions, thalamus, and hypothalamic and basal forebrain nuclei.[11] At the center of this process lies the NA, which serves as a gateway for limbic information to access motor pathways. DA plays a key role in this process, as information through the NA is gated by DA. Thick arrows indicate limbic cortical-striatal-thalamic pathways providing limbic-to-motor interface.

The observation of ICDs in Parkinson's Disease (PD) patients treated with dopaminergic agents provides additional evidence of the role of dopaminergic pathways in the pathogenesis of ICDs. Since pathological gambling in PD patients was first described in case reports published in 2000,[13,14] an association between ICDs and dopamine replacement therapy (DRT) in PD patients has become well established.[15,16] The four major ICDs seen in PD patients are pathological gambling, compulsive buying, compulsive sexual behaviors, and compulsive eating.[16] The prevalence of ICDs in PD patients treated with DRT varies from 3.5% to 13.6%.[17] There are no large studies of the life-time prevalence of most ICDs in the general population to compare with the prevalence rates of ICDs in the PD population, except pathological gambling. The estimated lifetime prevalence of pathological gambling in the general population varies between 0.5% to 1.0%.[17] Within the PD population, the lifetime prevalence of pathological gambling ranges between 1.7% to 6.1% (median 5%). PD patients receiving treatment with a dopamine agonist have an even higher pathological gambling prevalence of 8%.[17] Several case-control studies have supported the finding that PD patients treated with DRT have a higher prevalence of ICDs than PD controls.[17]

Following is the proposed mechanism for the association between ICDs and dopaminergic medications:[15]

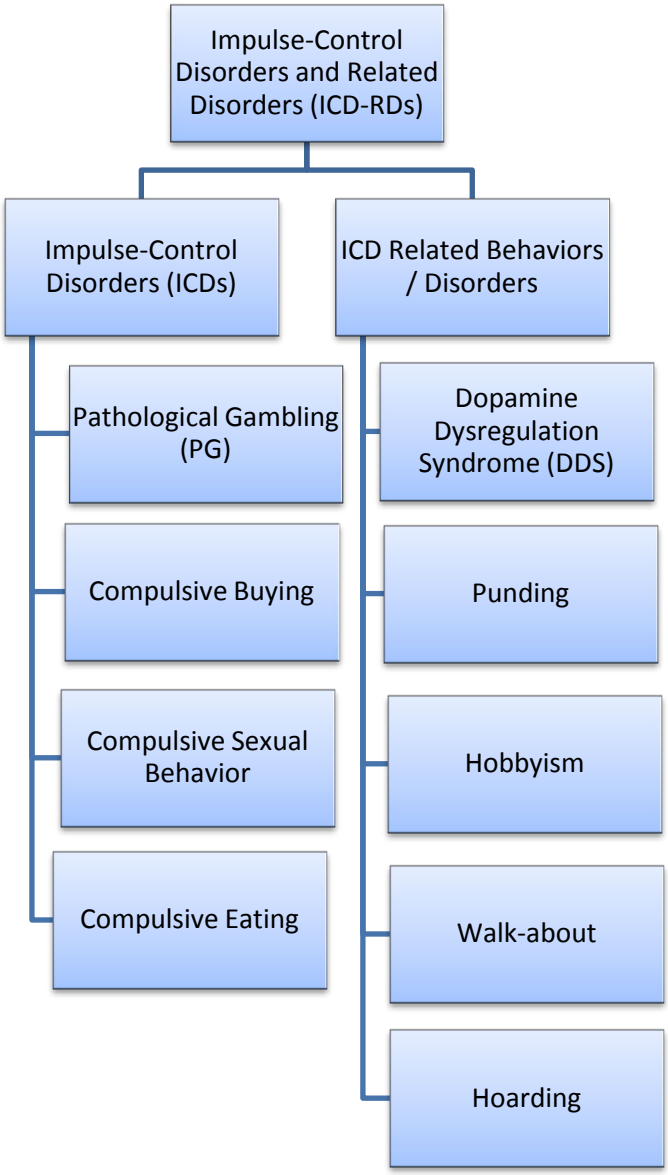
1. Changes in dopamine release patterns disrupt its normal physiological roles: dopamine is released from the VTA to the NA in certain phasic and tonic patterns in response to anticipating a reward and when receiving an unanticipated reward. The magnitude of dopamine release varies with the magnitude of the reward. Phasic suppression of dopamine release occurs when reward is expected but not received. Excessive doses of a dopaminergic drug, appropriate doses in the context of impaired dopamine receptor density or function, or postsynaptic dopamine receptor stimulation by dopamine agonists may result in disruption of normal physiological patterns of dopamine activity leading to behavioral problems.
2. Stimulation of dopamine receptors, particularly in the mesolimbic pathway, result in impulsive behaviors: the D_3 dopamine receptor subtype is found predominantly in the limbic regions of the brain, and has been implicated in addiction. Additionally, dopamine agonists such as pramipexole or ropinirole, which have a higher specific affinity for the D_3 receptor compared to levodopa, are more strongly associated with ICDs.[18]
3. Initial dopamine stimulation shifts from impulsive behaviors to compulsive behaviors via habit formation.
4. Chronic dopamine stimulation results in neuroplastic changes – specifically neuronal sensitization of the ventral or dorsal striatum – leading to increased susceptibility to compulsive behaviors.

Other impulse-control behaviors (ICBs) observed in PD patients include:[16]

- Dopamine dysregulation syndrome (DDS): a compulsion to overmedicate with dopaminergic treatment, taking increasingly high doses despite adverse events or well-controlled PD symptoms.
- Punding: repetitive, purposeless behaviors involving a specific item or activity, such as collecting, arranging, or taking apart objects.
- Hobbyism: similar to punding, but involves more complex behaviors, such as excessive exercising or internet use.
- Walk-about: excessive, aimless wandering.
- Hoarding: acquiring large amounts of items with little or no objective value.

ICBs are related to ICDs but are not as well-defined. Limited information is known about ICBs in terms of neurobiological processes and in what ways they are similar or different to ICDs. The above ICBs are referred to as "ICD related behaviors"[19] or "ICD related disorders"[20] in the literature. For the purposes of this review, the ICDs pathological gambling, compulsive buying, compulsive sexual behaviors, and compulsive eating, along with the ICBs DDS, punding, hobbyism, walk-about, and hoarding, are collectively referred to as ICD-RDs. (Figure 2)

Figure 2: Breakdown of conditions grouped together as ICD-RDs



Assessment of ICD-RDs

DSM-5 criteria exist for PG (i.e. gambling disorder), compulsive eating (i.e. binge eating disorder), and hoarding disorder.[2] No formal DSM-5 criteria exist for compulsive sexual behavior, compulsive buying, or any of the other ICD-RDs. Several screening tools exist for assessing ICD symptoms in PD.[16] The Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP) is one of the more comprehensive screening tools, and is validated to assess all four of the above mentioned ICDs, hobbyism, and punding in PD patients.[7] A rating scale version of the QUIP, known as the QUIP-RS, is also a validated tool to assess severity of ICD-RDs.[20] The Minnesota Impulsive Disorders Interview (MIDI) is another instrument

commonly used in research and clinical practice, although it only includes questions for three ICDs: compulsive gambling, buying, and sexual behavior.[20]

1.2 REGULATORY HISTORY

Aripiprazole, an atypical antipsychotic, received FDA approval on November 15, 2002 under the trade name Abilify. Aripiprazole lauroxil, an aripiprazole prodrug, received FDA approval on October 5, 2015 under the trade name Aristada. The mechanism of action of aripiprazole is unknown; however, it has been proposed that the efficacy of aripiprazole is mediated through a combination of partial agonist activity at the D_2 and 5-HT_{1A} receptors and antagonist activity at 5-HT_{2A} receptors. Of note, aripiprazole's D_2 receptor partial agonist activity is unique compared to other atypical antipsychotics, which exhibit full D_2 receptor antagonist activity (with the exception of recently approved brexpiprazole [FDA approval date July 13, 2015] and cariprazine [FDA approval date: September 17, 2015]).[21,22] Table 1 below summarizes aripiprazole's FDA approved indications.[23,24,25]

Table 1. Aripiprazole Formulations and Approved Indications

Product and Formulation	Indications
Aripiprazole (Abilify) – oral (tablets, orally disintegrating tablets, oral solution)	1. Schizophrenia 2. Acute treatment of manic and mixed episodes associated with bipolar I disorder 3. Maintenance treatment of bipolar I disorder 4. Adjunctive treatment of major depressive disorder 5. Irritability associated with autistic disorder 6. Treatment of Tourette's disorder
Aripiprazole (Abilify) –injection, intramuscular	Agitation associated with schizophrenia or bipolar mania
Aripiprazole (Abilify Maintena) – extended-release injectable suspension, intramuscular	Treatment of schizophrenia
Aripiprazole lauroxil (Aristada) – extended-release injectable suspension, intramuscular	Treatment of schizophrenia

1.3 PRODUCT LABELING

Abilify

Under Section 6.2 Postmarketing Experience (PME) of the Abilify label, "pathological gambling" is listed. "Pathological gambling" was added to the PME section of the label on January 15th, 2016, as a result of a Changes Being Effected supplement submitted by the Market Authorization Holder (Otsuka) on January 8th, 2016.[26]

The Abilify product label lists *impulsivity* under the Warnings and Precautions, Section 5.3 Suicidal Thoughts and Behaviours in Children, Adolescents, and Young Adults:

> "The following symptoms,[*sic*] anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for MDD as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality."[23]

The warning only mentions impulsivity in the context of "emerging suicidality." There is no mention of ICDs more generally, or of specific ICD-RDs as defined in this review.

Under Section 6.1 Clinical Trials Experience, the Abilify label lists "libido increased":[23]

> "Other Adverse Reactions Observed During the Premarketing Evaluation of Abilify Adults – Oral Administration
> *Psychiatric Disorders: infrequent* – aggression, loss of libido, delirium; *rare* – libido increased, anorgasmia, tic, homicidal ideation, catatonia, sleep walking"

Abilify Maintena

"Pathological gambling" was added to the PME section of the Abilify Maintena label on January 15th, 2016.

Since Abilify Maintena is not indicated for adjunctive treatment of major depressive disorder, its label does not contain the "Suicidal Thoughts and Behaviors in Children, Adolescents, and Young Adults" warning. Therefore, the Abilify Maintena label does not have any language regarding impulsivity.

Under Section 6.1 Clinical Trials Experience, the Abilify Maintena label lists "hypersexuality":[24]

> "Other Adverse Reactions Observed During the Clinical Trial Evaluation of Abilify Maintena
> *Psychiatric Disorders: frequent* - anxiety, insomnia restlessness, *infrequent*- agitation, bruxism, depression, psychotic disorder, suicidal ideation, *rare* - aggression, hypersexuality, panic attack"

Aristada

The Aristada label does not include any language regarding pathological gambling, hypersexuality, or any other ICDs. Except, the label does mention that "libido increased" was observed in clinical trials with oral aripiprazole, under Section 6.1 Clinical Trials Experience:[25]

> "Adverse Reactions Reported in Clinical Trials with Oral Aripiprazole
> *Psychiatric Disorders*: aggression, loss of libido, delirium, libido increased, anorgasmia, tic, homicidal ideation, catatonia, sleep walking"

1.4 FOREIGN PRODUCT LABELING

Health Canada[27,28]

The Health Canada Abilify and Abilify Maintena product labels have the following statement under the "Warning and Precautions" Section:

> **Pathological Gambling**
> Post-marketing reports of pathological gambling have been reported in patients treated with ABILIFY. In relation to pathological gambling, patients with a prior history of gambling disorder may be at increased risk and should be monitored carefully.

Additionally, hypersexuality and pathological gambling are listed under the "Adverse Events" section, "Post-Market Adverse Drug Reactions" subsection of the label.

European Medicines Agency (EMA)[29,30]

The EMA Abilify and Abilify Maintena product labels have the following statement under Section "4.4 Special warnings and precautions for use":

> **Pathological gambling**
> Post-marketing reports of pathological gambling have been reported among patients prescribed oral aripiprazole, regardless of whether these patients had a prior history of gambling. Patients with a prior history of pathological gambling may be at increased risk and should be monitored carefully (see Section 4.8).

Under Section "4.8 Undesirable Effects," the following is listed under the "Post-Marketing" subsection:

> Psychiatric disorders: agitation, nervousness, pathological gambling, aggression; suicide attempt, suicidal ideation, and completed suicide (see Section 4.4)

Hypersexuality is listed under Section "4.8 Undesirable Effects," subsection "Tabulated list of adverse events," as an adverse reaction observed more often than placebo during clinical trials (i.e. pre-marketing adverse event).

2 METHODS AND MATERIALS

2.1 CASE DEFINITION

Cases meeting the following inclusion criteria were included in the case series:

Inclusion criteria

- Domestic (US) case.
- The ICD was reported within one year or less after initial or increased exposure to aripiprazole.
- A positive dechallenge after dose reduction or discontinuation of aripiprazole.

AND

- Diagnosis by a healthcare professional (HCP) of an ICD-RD, including PG, compulsive sexual behavior, compulsive buying, compulsive eating, dopamine dysregulation syndrome, punding, hobbyism, walk-about, and hoarding.

OR

- Symptoms consistent with ICD-RDs, such as any of the following symptoms (adapted from the QUIP-RS):[20]
    - The patient is unable to stop thinking of or stop feeling guilty about gambling, sex, buying, eating, performing tasks or hobbies, repeating simple activities, wandering, or taking aripiprazole
    - The patient has urges or desires for the following behaviors that the patient feels are excessive or cause distress (including becoming restless or irritable when unable to participate in them): gambling, sex, buying, eating, performing tasks or hobbies, repeating simple activities, wandering, or taking aripiprazole
    - The patient has difficulty controlling the following behaviors (such as increasing them over time, or having trouble cutting down or stopping them): gambling, sex, buying, eating, performing tasks or hobbies, repeating simple activities, wandering, or taking aripiprazole
    - The patient engages in activities specifically to continue the following behaviors (such as hiding what they're doing, lying, hoarding things, borrowing from others, accumulating debt, stealing, or being involved in illegal acts): gambling, sex, buying, eating, performing tasks or hobbies, repeating simple activities, wandering, or taking aripiprazole

Exclusion Criteria

- Concomitant use of a medication labeled for ICDs (e.g., dopamine agonists).
- Concomitant use of recreational drugs (e.g., cocaine, methamphetamine, marijuana).
- Concurrent substance use disorder, including alcohol use disorder.

- History of ICD-RDs of interest (PG, compulsive buying, sex, eating, DDS, punding, hobbyism, walk-about).
- ICD-RD is better accounted for by mania (e.g. concurrent reports of manic symptoms).
- A negative rechallenge after re-initiation of aripiprazole.

2.2 FAERS SEARCH STRATEGY

DPV searched the FAERS database using two different strategies; each strategy is described separately in Table 2 (Search Strategy 1) and Table 3 (Search Strategy 2). Please note, although two separate search strategies were utilized, case counts will be reported as one consolidated result.

Table 2. FAERS Search Strategy 1[*]	
Date of search	January 13, 2016
Time period of search	Through January 13, 2016
Search type	FAERS Business Intelligence Solution (FBIS) Quick Query
Product Terms	Product Active Ingredient: Aripiprazole; Aripiprazole lauroxil
MedDRA Search Terms (Version 18.1)	Preferred Terms (PTs) – Binge eating; Compulsions; Compulsive hoarding; Compulsive shopping; Dopamine dysregulation syndrome; Excessive exercise; Excessive masturbation; Excessive sexual fantasies; Gambling; Hyperphagia; Hypersexuality; Impulse-control disorder; Libido increased; Obsessive-compulsive disorder; Obsessive-compulsive personality disorder; Pathological gambling; Promiscuity; Sexual activity increased; Stereotypy
Country (Derived)[†]	USA
[*] See Appendix A for a description of the FAERS database. [†] In an effort to limit the heterogeneity inherent in the case material, as societal norms differ between countries and as an adequate number of domestic reports were observed, the FAERS search was limited to reports derived from the USA	

Table 3. FAERS Search Strategy 2*	
Date of search	January 13, 2016
Time period of search	Through January 13, 2016
Search type	FAERS Business Intelligence Solution (FBIS) Quick Query
Product Terms	Product Active Ingredient: Aripiprazole; Aripiprazole lauroxil
Reporter Narrative†	Shop; Buying; Wandering; Walk-about; Walkabout; Punding; Compulsive hobby; Compulsive grooming; Compulsive driving; Hoarding
Country (Derived) ‡	USA

* See Appendix A for a description of the FAERS database.

† "Reporter Narrative" refers to a narrative text search within the report's Reporter Narrative field. Using the FBIS Reporter Narrative prompt allows searching for a keyword. A separate query must be run for each keyword. The purpose of searching the Reporter Narrative field is to find cases that report events of interest, but do not have an appropriate MedDRA preferred term (PT) to capture that event (e.g. walk-about). FBIS Quick Query search was run for each individual "Reporter Narrative" keyword, for a total of 10 individual queries.

‡ In an effort to limit the heterogeneity inherent in the case material, as societal norms differ between countries and as an adequate number of domestic reports were observed, the FAERS search was limited to reports derived from the USA

2.3 LITERATURE SEARCH

DPV searched the medical literature with the strategies described in Tables 4-7. (Note: asterisks present in Tables 4-7 refer to a wildcard character used in the search terms, and are not in reference to a footnote.)

Table 4. Literature Search Strategy 1	
Date of search	December 14th, 2015
Database	PubMed@FDA
Search Terms	(aripiprazole OR abilify) AND (risk OR risks OR ratio OR probability OR adverse) AND (impulsive control disorder* OR impulsive behavior OR impulsive behaviors OR impulsive behaviour OR impulsive behaviours OR impulsivity OR impulsivities OR pathological gambling OR pathological gamblings OR hypersexuality OR hypersexual OR binge eating OR compulsive shopping OR compulsive behavior OR compulsive behaviors OR compulsive behaviour OR compulsive behaviours OR impulsive OR compulsion OR compulsive*)
Years included in search	Through December 14, 2015

Table 5. Literature Search Strategy 2	
Date of search	December 14th, 2015
Database	Embase
Search Terms	'aripiprazole'/exp/mj/dd_ae OR 'aripiprazole'/exp AND ('risk'/exp OR ratio OR 'probability'/exp) AND ('impulsive control disorder' OR 'impulsive control disorders' OR 'impulsive behavior'/exp OR 'impulsive behaviors' OR 'impulsive behaviour'/exp OR 'impulsive behaviours' OR 'impulsivity'/exp OR impulsivities OR 'pathological gambling'/exp OR 'pathological gamblings' OR 'hypersexuality'/exp OR hypersexual OR 'binge eating' OR 'compulsive shopping' OR 'compulsive behavior'/exp OR 'compulsive behaviors' OR 'compulsive behaviour'/exp OR 'compulsive behaviours' OR compulsiveness OR compulsive OR impulsive) AND [humans]/lim AND [english]/lim
Years included in search	Through December 14, 2015

Table 6. Literature Search Strategy 3	
Date of search	December 14th, 2015
Database	Ebsco
Search Terms	SU (aripiprazole OR abilify AND adverse) AND (risk OR risks OR ratio OR probabilit*) AND (impulsive control disorder* OR impulsive behavior OR impulsive behaviors OR impulsive behaviour OR impulsive behaviours OR impulsivity OR impulsivities OR pathological gambling OR pathological gamblings OR hypersexuality OR hypersexual OR binge eating OR compulsive shopping OR compulsive behavior OR compulsive behaviors OR compulsive behaviour OR compulsive behaviours OR impulsive OR compulsion OR compulsive*)
Years included in search	Through December 14, 2015

Table 7. Literature Search Strategy 4	
Date of search	December 14th, 2015
Database	Web of Science
Search Terms	TS=(aripiprazole OR abilify AND adverse) AND TS=(risk OR risks OR ratio OR probability) AND TS=(impulsive control disorder* OR impulsive behavior OR impulsive behaviors OR impulsive behaviour OR impulsive behaviours OR impulsivity OR impulsivities OR pathological gambling OR pathological gambling OR hypersexuality OR hypersexual OR binge eating OR compulsive shopping OR compulsive behavior OR compulsive behaviors OR compulsive behaviour OR compulsive behaviours OR impulsive OR compulsion OR compulsive*)
Years included in search	Through December 14, 2015

2.4 EMPIRICA SIGNAL SEARCH

The Empirica Signal database was searched with the strategy described in Table 8. The purpose of the search was to compare EB05 scores among atypical antipsychotics for the PT *Pathological gambling*, in order to gain further insight on whether the safety issue may be a class effect. We used an algorithm in Empirica to remove reports that may have potentially been driven by litigation. Removal of these reports enabled the calculation of EB05 and EBGM scores of the data without the inclusion of potentially litigation-driven reports.

Table 8. Data Mining Search Strategy*	
Data Refresh Date	September 20, 2015[†]
Product Terms[‡]	Aripiprazole, Asenapine, Brexpiprazole, Clozapine, Iloperidone, Lurasidone, Olanzapine, Paliperidone, Quetiapine, Risperidone, Ziprasidone
Empirica Signal Run Name	Generic (S) – litigation excluded[§]
MedDRA Search Strategy	PT: Pathological gambling

* See Appendix A for a description of Data Mining of FAERS using Empirica Signal.
[†] Due to a lapse in service, as of the date of this review, the Empirica Signal database has not refreshed since September 20, 2015.
[‡]Aripiprazole lauroxil and cariprazine are not included in the search because they were both approved before being added to the Empirica Signal drug database.
[§] The Litigation Excluded Run excludes from the results cases where the reporter occupation equals lawyer, or one of the following litigation-related terms are found in the narrative of the report: litigation, attorney, plaintiff, legal, lawsuit, civil action, defendant, summons, law, and counsel.

2.5 SPONSOR'S SUBMISSION

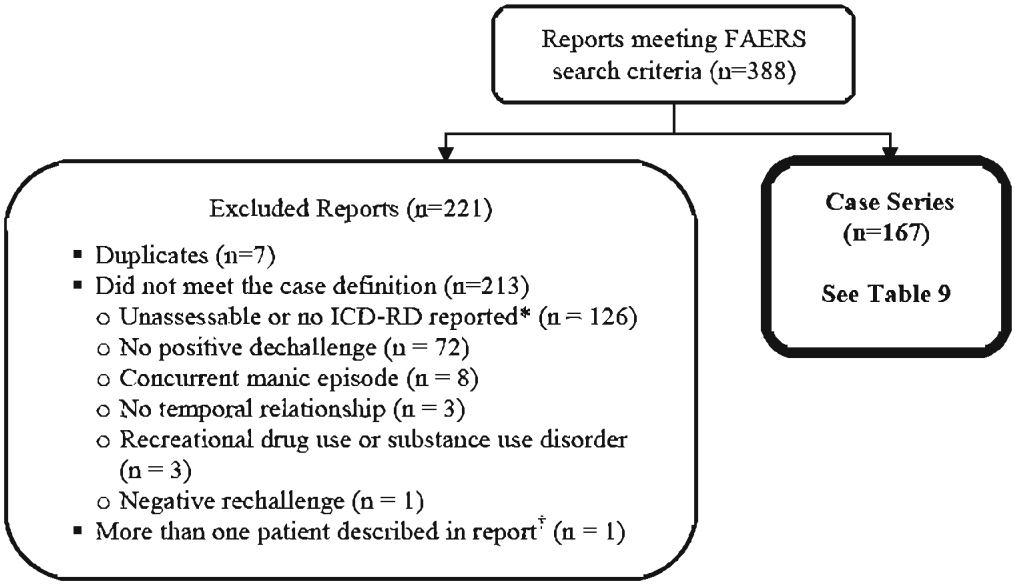
Information from supporting documents the Sponsor submitted with the Changes Being Effected supplement (NDA 21436/S-40), specifically the document titled, "Clinical Overview – CBE-0 Jan2016 – Pathological Gambling" were considered in this review.[26]

3 RESULTS

3.1 FAERS CASE SELECTION

The FAERS searches retrieved 388 reports. After applying the case definition in Section 2.1 and accounting for duplicate reports, 167 cases were included in the case series of ICD-RDs reported with aripiprazole use (see Figure 3). Reports were then assessed for both a qualifying ICD-RD diagnosis and confounding condition(s) simultaneously.

Figure 3. FAERS Case Selection



* The case either did not include a diagnosis of an ICD-RD by an HCP, enough information for reviewer to determine whether the adverse event was an ICD-RD per the case definition, or did not describe an event of interest

† One report contained information for more than one patient. A physician reported that he had started aripiprazole treatment with "about 15 patients," but had to discontinue treatment in all except two patients. The physician reported that aripiprazole was "too activating" and the patients became sexually aggressive after they were initiated on treatment with aripiprazole.

Table 9 summarizes the 167 FAERS cases of ICD-RDs reported with aripiprazole for this case series.

Appendix B lists all the FAERS case numbers, FAERS version numbers, and Manufacturer Control numbers (MCN), and select individual case characteristics, for the 167 cases in this case series.

Table 9. Descriptive characteristics of ICD-RDs reported in FAERS with aripiprazole use, received by FDA through January 13th, 2016 (N=167)

Age (years) (n=37)*	Mean = 42 Median = 42 Range = 5-65
Sex (n=42)*	Female = 25 Male = 17
Serious outcome† (n=14)	Hospitalization = 3 Life-threatening = 1 Other = 8 Required intervention = 2
Initial FDA received year	2004 = 2 2005 = 3 2007 = 2 2008 = 1 2009 = 3 2010 = 1 2011 = 4 2012 = 2 2013 = 4 2014 = 6 2015 = 138‡ 2016 = 1
Case type	Non-expedited = 151 Direct = 10 Expedited = 6
Type of ICD-RD	Gambling = 153 Sexual behavior = 4 Buying = 4 Eating = 3 Multiple ICDs§ = 3
Reporter	Consumer = 19 Health professional = 4 Lawyer = 134‖ Medical doctor = 10

* The majority of cases that did not report an age or sex were submitted by a lawyer with limited patient information (n=125).

† Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events.

‡ The increase in reports seen in 2015 is accounted for by 133 cases submitted by a lawyer, likely in relation to a class-action lawsuit.

§ One case described compulsive gambling and eating; one case described compulsive buying and eating; one case described compulsive buying, eating and sexual behavior.

‖ Four cases were coded as "Consumer" but the cases narratives specify an attorney as the reporter, and were therefore categorized under "Lawyer" in this table.

The one case that reported a life-threatening outcome (FAERS #9774393) was a direct report from a consumer. The case did not report an obvious life-threatening outcome, but presumably, the consumer indicated that the event was life-threatening because she experienced suicidal thoughts. The consumer did not report a suicide attempt. A total of seven cases reported suicidal ideation or suicide attempts (including the previously mentioned life-threatening case). Only in three cases was the suicide attempt (n = 1) or suicidal ideation (n = 2) specifically attributed to

distress from an ICD (pathological gambling in all three cases). No fatal cases were included in the case series.

Other noteworthy sequelae associated with the development of ICDs were reported, but were not captured as serious outcomes per regulatory definition. This included, but was not limited to, reports of dysfunction in family relationships, such as taking money from family members to support gambling activities (FAERS #10275269), or unspecified stress on marriage and family life due to PG (FAERS #9321989 and FAERS #10854248). Financial problems were commonly reported – one case reported over $100,000 in gambling losses (FAERS #9321989). There were three cases in which bankruptcy was reported as a result of either gambling (FAERS #9774393) or compulsive buying (FAERS #8015166 and FAERS #6212455). See Table 10 for a summary of the number of cases that reported a sequela, and Appendix B for additional descriptions of sequelae for each case in the case series.

Table 10. Number of cases reporting ICD-related sequelae[*] (n = 152)[†]

Financial	149
Mental health	135
Relationships	5
Weight gain	3
Work performance	2
Legal	1

[*] Sequelae refer to negative consequences related to the ICD as reported in the case narrative. Sequelae were categorized by the reviewer into six main types: (1) financial (e.g. monetary loses); (2) mental health (e.g. suicidal ideation, emotional distress); (3) relationships (e.g. stress on marriage; sexually inappropriate behavior towards family member); (4) weight gain (self-explanatory); (5) work performance (e.g. missed days at work, decreased work performance); (6) legal (e.g. stealing money).
[†]Some cases reported more than one type of sequela.

One hundred thirty-four cases were received from an attorney, the majority of which contained limited medical information. The narratives for 125 of the attorney cases simply had language along the lines of the following:

> *"A patient developed compulsive gambling behaviors and other compulsive behaviors while on therapy with aripiprazole.*
>
> *The patient began taking aripiprazole and began compulsively gambling shortly thereafter, and stopped compulsively gambling soon after ceased taking aripiprazole. However, the patient had suffered and would continue to suffer, neuropsychiatric and physical injury, emotional distress, harm, and economic loss."*

Even with limited information, the above mentioned attorney cases met all case definition criteria, including the report of a positive dechallenge, and were therefore included in the case series.

No cases of intramuscular (IM) aripiprazole formulations or aripiprazole lauroxil were identified. In all cases in which a dosage form or route was specified (n=139), the dosage form was always tablet and the route was always oral.

No cases of ICBs (DDS, punding, hobbyism, walk-about, and hoarding) were included in the case series.

Summary of Representative Cases:

FAERS Case #11913338, USA, 2016
Direct Report; Other serious outcome; Positive dechallenge

The following is a case reported by a 43 year old female consumer concerning herself. The consumer reported taking aripiprazole at a starting dose of 2.5 mg once daily by mouth for depression, increased to 5 mg once daily "a few months" later. Concomitant medications reported include, "Cymbalta, Ocella, Topamax, Aderral [sic], Vesicare" (routes, dose, frequency, indication not reported). No other past medical history reported. "Shortly thereafter" the aripiprazole dose increase, the consumer developed an impulse to gamble with scratcher tickets. The consumer never had an issue with gambling prior to using aripiprazole. The consumer describes the gambling problem as an obsession, "where I would spend my mornings prior to work, my lunch hours, my breaks and my evenings scratching lottery tickets. It didn't make sense to me why I was doing it…why I was compelled to waste my money…I knew in my head that I was just going to lose money that I couldn't afford to lose. I just couldn't stop. It was a full-fledged compulsion. I couldn't help myself." The consumer reports attending Gamblers Anonymous, which did not help. Approximately two years after starting aripiprazole, and three weeks prior to this report, the consumer saw a television advertisement about a link between aripiprazole and compulsive gambling. The consumer had never heard about this before, and reports, "Something clicked in my head. Everything made sense to me. The timing of the increase in my dosage and the onset of the gambling problem." As a result, the consumer immediately stopped taking aripiprazole. After two days from discontinuing aripiprazole, the consumer's urges to gamble went away, and she has not gambled since discontinuing aripiprazole. The consumer goes on to report she has suffered during the past two years, believing she was "weak in character" and "morally flawed" due to the inability to stop herself from buying scratcher tickets. The consumer reported having thoughts of suicide, "There were several times within the past two years that I had gambled so much money away that I was to the point of attempting suicide. I believe it is because I was not fully aware of the side effects of Abilify that I had become desperate to the point of suicide."

Reviewer's comments: This case describes a temporal relationship between aripiprazole treatment and new onset of PG in a patient who had no history of gambling prior to aripiprazole treatment. The consumer also reports that her urges to gamble, which were ongoing for approximately two years, resolved within two days of aripiprazole discontinuation, indicating a positive dechallenge. The consumer also makes a compelling point that if she knew sooner about a possible association between aripiprazole and compulsive gambling, she could have saved herself from suffering, financial loss, and despair to the point of suicidal ideation.

FAERS Case #9774393, USA, 2013
Direct Report; Life-threatening; Positive dechallenge

The following is a case reported by a 37 year old female consumer concerning herself. The consumer reported taking an unknown dose of oral aripiprazole daily for 5 months, as "add on for depression." Past medical history was reported as depression, anxiety, high blood pressure, and diabetes. The consumer specifically denied ever having "manic symptoms" in the past. The consumer reported multiple compulsive behaviors, including eating, buying, and sexual behavior, which she began experiencing when she started aripiprazole therapy and were ongoing until she discontinued aripiprazole. Compulsive eating was described as, "While taking [aripiprazole] I only wanted to eat one thing…chocolate milkshakes. It was like there was a food monster on my shoulder that constantly tapped me to get a milkshake several times a day." The consumer reported her "sugar went up" and she gained 10 pounds as a result of her consumption of milkshakes. The consumer also described spending money on jewelry and "lots of cloths," which was out of character for her. As a result, she "was racking up tons of debt" and "now [has] to file bankruptcy for spending close to $15000 which [she] cannot repay." The consumer also mentioned "sudden promiscuity" which she reports never having a problem with in the past. Lastly, the consumer experienced suicidal thoughts, which resulted in discontinuation of aripiprazole therapy. The consumer reported that "within days" of discontinuing aripiprazole, she stopped experiencing all of the above reported symptoms.

Reviewer's comments: This case describes a temporal relationship between aripiprazole treatment and the onset of ICD behaviors that were reportedly "out of character" for the patient. An additional strength of this case was the lack of obvious confounders for the development of ICD behaviors, such as history of bipolar mood disorder or substance use disorder. The ICD behaviors resulted in significant negative consequences, such as having to file for bankruptcy. Suicidal ideation was also reported, but was confounded by underlying depression.

FAERS Case #10869881 (MCN JP-BRISTOL-MYERS SQUIBB COMPANY-BMS-2015-010384), USA, 2015
Expedited 15-day; Hospitalization; Positive Dechallenge

The following is a case reported by a physician concerning himself. The physician/consumer, a 36 year old male, reported he attempted suicide following gambling loss while on therapy with aripiprazole. The consumer's past medical history was significant for, "bipolar schizoaffective disorder, major depressive disorder with psychosis and anxiety." He was initiated on aripiprazole, titrated to a dose of 30 mg (frequency and route not reported), during a hospital stay. He started gambling "soon after" he was discharged from the hospital. The report notes, "he did not gamble at all for several years prior to starting aripiprazole...he began gambling heavily during aripiprazole therapy." Approximately 17 months after his discharge from the hospital, "he began frequenting the casinos several times a week." He had difficulties limiting his gambling, and would drink energy drinks to stay awake through the night and continue gambling. The consumer reported at least two occasions where he continued gambling for three days straight without sleeping. He "drained his savings accounts and took cash advances from his credit cards to support his gambling compulsions. His credit was ruined." Approximately 2.5 years from initiation of aripiprazole treatment, the consumer "lost more money," felt hopeless, and

attempted suicide by ingesting an unspecified number of unspecified medications. He was admitted to the emergency room in a "drowsy but arousable" state, received supportive care, and was discharged the following day. The consumer reported "the primary contributor to his suicide attempt was his gambling losses." Aripiprazole was discontinued approximately 6 months after his suicide attempt and replaced with ziprasidone (dose, route, frequency, indication, start date not reported). The consumer reported that since he stopped aripiprazole therapy "he had no desire to gamble even though there was a casino ten minutes away from his home."

Reviewer's comments: This case describes a temporal relationship between the initiation of aripiprazole treatment and new onset of PG. PG was associated with significant financial loss, as well as feelings of hopelessness and a suicide attempt.

FAERS Case #6770511, USA, 2008
Direct; Required Intervention; Positive Dechallenge

The following is a case reported by a physician regarding a 40 year old female patient. The patient was prescribed aripiprazole 2 mg daily by mouth for bipolar I. The patient was concurrently taking Depakote ER 1500 mg daily, sertraline 200 mg daily, bupropion XL 300 mg daily, alprazolam 1 mg at bedtime as needed for sleep, and Lovaza fish oil. The patient was switched from lithium to aripiprazole due to the development of diabetes insipidus, which was attributed to lithium by the physician. On day 49 of treatment the patient reported to the physician she had been "gambling compulsively" since two weeks after initiating aripiprazole treatment. The patient stated she was "writing checks that would bounce; she spent her entire paycheck." She would go to the casino "like there is no tomorrow." The physician specified the patient "had no other evidence of mania - no pressured speech, other risky behavior, elevated or irritable mood, increased distractibility…she was not getting by on less than usual amount of sleep." The physician decided to stop treatment with aripiprazole because the gambling behavior was "uncharacteristic" for the patient, as well as the physician hypothesized aripiprazole's "dopamine partial agonism" could increase the risk for compulsive activity. The patient was switched to risperidone. The patient stopped compulsively gambling approximately two weeks after discontinuing aripiprazole. The physician reported the patient's obsessive thinking about gambling was "abating" and that the patient had "turned her finances over to [the patient's] daughter."

Reviewer's comments: this case describes a close temporal relationship between the initiation of aripiprazole treatment and the onset of compulsive gambling behavior. Strengths of the case include a sudden onset of gambling behavior that was uncharacteristic for the patient and medical confirmation of compulsive gambling that was not better accounted for by mania.

3.2 LITERATURE SEARCH

DPV performed a literature search of the PubMed, Embase, Ebsco, and Web of Science databases. The search identified 23 case reports of ICDs associated with aripiprazole use.[31-39] Of the 23 cases identified, 17 met the case definition outlined under Section 2.1; 12 cases of PG (including one case of concurrent compulsive eating), and five cases of compulsive sexual behavior. Four cases were excluded due to no positive dechallenge, two cases due to a history of

an ICD prior to aripiprazole treatment. None of the literature case reports were included in the FAERS case series because all of the literature case reports were derived from foreign countries. Table 11, adapted from Grall-Bronnec et al.,[40] summarizes the characteristics of the 12 cases of PG. Table 12 summarizes the characteristics of the five compulsive sexual behavior cases.

Table 11. Characteristics of Literature cases of Pathological Gambling Reported with Aripiprazole[40]

Article	Sex (M/ F)	Age (yrs)	Psych Dx	History of SUD	ARI Dose (mg/day)	Hx of gambling prior to ARI	Time to PG onset after ARI prescription	Time to PG resolution after ARI D/C
Roxanas, 2010*	F	64	S	No	15	Yes	Few months after ARI dosage increase	1 month
Gavaudan et al., 2010 Case 1	M	46	S	No	15	Yes	Few days	1 week
Gavaudan et al., 2010 Case 2	M	19	S	THC	10	NS	Few months	Few weeks
Cohen et al., 2011 Case 1	M	30	SAD	NS	15	No	Few months. Gambling onset 1 month after ARI	Few weeks
Cohen et al., 2011 Case 2	M	20	S	NS	15	No	Few weeks. Gambling onset 1 week after ARI	1 week
Cohen et al., 2011 Case 3	M	19	S	NS	10	NS	1 month	Few weeks
Smith et al., 2011 Case 1	M	29	S	NS	5, then 15	Yes	NS	NS †
Smith et al., 2011 Case 2	M	28	SAD	NS	15	Yes	Few months	Few months
Smith et al., 2011 Case 3	M	26	S	NS	15	No	1 year	1 month
Gaboriau et al., 2014 Case 5‡	M	38	BD	alcohol	20	Yes	Few weeks after ARI dosage increase	Few weeks
Gaboriau et al., 2014 Case 7‡	M	29	S	alcohol, THC	10	Yes	Few days	Few weeks)
Gaboriau et al., 2014 Case 8‡	M	32	SAD	alcohol, THC, other illicit substances	10, then 20, then 15	Yes	Few days after ARI dosage increase	PG resolved with ARI dosage decrease

ARI: aripiprazole; BD: bipolar disorder; D/C: discontinuation; Dx: diagnosis; Hx: history; NS: not specified; PG: pathological gambling; S: schizophrenia; SAD: schizoaffective disorder; SUD: substance use disorder; THC: tetrahydrocannabinol (cannabis)

* Roxanas' case was a report of multiple ICDs: PG and compulsive eating.

† Smith et al. reported a positive dechallenge with aripiprazole.

‡Gaboriau et al. published a case series of eight cases, of which Case 5, Case 7, and Case 8 met our case definition and are included in this table.

Table 12. Characteristics of Literature Cases of Compulsive Sexual Behaviors Reported with Aripiprazole

Article	Sex (M/ F)	Age (yrs)	Psych Dx	History of SUD	ARI Dose (mg/day)	Time to CSB onset after ARI prescription	Time to CSB resolution after ARI D/C
Schlachetzki et al., 2008	F	24	SAD	NS	30	Few days	NS*
Kodama et al., 2010 Case 1	M	57	BD	NS	3, then 6	1 week	1week*
Cheon et al., 2013 Case 1	F	37	S	NS	20	1 month	NS
Cheon et al., 2013 Case 2	F	36	S	NS	20	NS	NS – "rapidly"
Vrignaud et al., 2014	M	35	S	NS	30	6 months	Few weeks*

ARI: aripiprazole; BD: bipolar disorder; D/C: discontinuation; Dx: diagnosis; Hx: history; NS: not specified; PG: pathological gambling; S: schizophrenia; SAD: schizoaffective disorder; SUD: substance use disorder; THC: tetrahydrocannabinol (cannabis)
* Vrignaud et al., Kodama et al., and Schlachetzki et al., reported a positive rechallenge with aripiprazole.

There were four literature case reports that included a positive rechallenge. These four cases are summarized below. A summary of each of the remaining literature case reports can be found in Appendix C.

Schlachetzki et al.[32] published a case of hypersexuality in a 24 year old female after initiating aripiprazole. The patient was diagnosed with schizoaffective disorder depressive type when she was 21 years old, and was treated with several different medication regimens over the course of three years, including a trial of aripiprazole during which she was "relatively stable" but was discontinued after one year and switched to quetiapine. Nine months since she was switched off of aripiprazole, she was admitted to a general acute psychiatric ward and was restarted on aripiprazole. Concomitant medications included citalopram and chlorprothixene. A few days after re-initiating aripiprazole 30 mg daily, she experienced increased sexual desire and an uncontrollable urge to masturbate. She had no other signs of a manic episode, and her aripiprazole plasma level was "within normal limits" (lab value unspecified). The patient reported that she had the same experience of hypersexuality when she first received aripiprazole over a year ago. Prior to taking aripiprazole, the patient reported a low sexual drive and interest. At a three month follow-up visit, the patient was still experiencing an "elevated libido and an unstoppable sexual desire around 2 to 3 times a week."

Reviewer's comments: This case describes a close temporal relationship (within days) from initiating aripiprazole and the onset of compulsive sexual behaviors such as an uncontrollable urge to masturbate. This case also describes a positive rechallenge – the patient had a similar experience of hypersexuality when she first started aripiprazole, hypersexuality resolved after discontinuing aripiprazole, and then reappeared after restarting aripiprazole.

Kodama et al.[34] published two case reports of ICDs and aripiprazole – one case of hypersexuality and one case of compulsive shopping. The case of compulsive shopping did not meet the case definition as outlined in Section 2.1 due to the patient's history of compulsive shopping prior to aripiprazole exposure. The case of hypersexuality involves a 57 year old male with bipolar I disorder. He was started on aripiprazole 3 mg daily to target symptoms of loss of energy, poor concentration, and social withdrawal. He was concurrently taking lithium carbonate 1000 mg daily and carbamazepine 600 mg daily. One week after starting aripiprazole he reported "unusual sexual desire and a strong urge to masturbate, although he was still in a depressive state and showed no other manic symptom." Aripiprazole was discontinued, and one week later hypersexuality (as termed by the authors) disappeared. The patient's overall mood improved without further treatment. A year later, the patient again began to experience symptoms of loss of energy and diminished interest and pleasure. Aripiprazole was restarted at 3 mg daily and titrated to 6 mg daily one week later. The patient again experienced hypersexuality 2 weeks after restarting aripiprazole. Aripiprazole was discontinued, and hypersexuality diminished within an unspecified time frame. The patient did not have any other manic symptoms.

Reviewer's comments: This case describes a positive rechallenge, in which hypersexuality reappeared shortly after restarting aripiprazole.

Vrignaud et al.[31] published a case on hypersexuality and aripiprazole in a 35 year old male with schizophrenia. Six months after starting treatment with aripiprazole 30 mg, diazepam, loxapine, and lithium, the patient felt "more easily sexually aroused." One month later (seven months since starting aripiprazole), "he experienced hypersexual behaviour, including daily masturbation, involvement with prostitutes and sexual impulses." Aripiprazole dose was titrated down to 10 mg daily over the course of a month without significant improvement in symptoms of hypersexuality. Aripiprazole was discontinued and within 20 days, hypersexual behavior "disappeared completely." Resolution of hypersexuality was maintained until 5 months later, when aripiprazole was restarted at 5 mg daily. Hypersexuality and "exhibitionist impulses" reappeared within a month of restarting aripiprazole. Aripiprazole treatment was discontinued again, and 3 weeks later the symptoms resolved. The authors note that no other medications were discontinued, and the patient did not receive any specific treatment for hypersexuality.

Reviewer's comments: This case describes a positive rechallenge, in which the symptoms of hypersexuality reappeared within a month of restarting aripiprazole.

Smith et al.[37] published three cases of PG and aripiprazole. In Case 1, a 29 year old with a history of paranoid schizophrenia experienced an escalation in gambling after starting treatment with aripiprazole 5 mg (route and frequency not specified). After discontinuing aripiprazole he was able to significantly reduce his gambling, but six weeks later, was restarted on aripiprazole 15 mg (route and frequency not specified) due to a relapse of psychotic symptoms. After restarting aripiprazole he reported the return of strong urges to gamble, had difficulty resisting gambling, became preoccupied with thoughts of gambling, and his gambling became impulsive. He committed unspecified crimes to obtain funds for gambling. As a result, he was switched off of aripiprazole to first quetiapine 400 mg, and then to sulpiride 600 mg. After aripiprazole discontinuation, he reported no longer having thoughts and plans to gamble, and was able to remain abstinent from gambling at 6 months follow-up.

Reviewer's comments: Although the patient (Case 1) had a history of gambling prior to starting aripiprazole, the case does not indicate that he had a gambling problem or a history of PG. His gambling became pathological only after initiating treatment with aripiprazole. There was also a positive dechallenge within weeks of discontinuing aripiprazole, as well as the patient was rechallenged with aripiprazole and PG reappeared, indicating a positive rechallenge. The authors offer the following text to describe their cases:

> "It should be noted that in the three cases reported, prescription of aripiprazole is not immediately followed by the onset of pathological gambling. In two cases there was also evidence of problem gambling behavior prior to the medication being started. The observations do, however, indicate an association between aripiprazole and a reduction in the impulse control relating to their behaviour."

The case series of 8 cases (of which 3 are include in Table 11) by Gaboriau et al[38] was derived from a cohort of 166 individuals with a history of PG attending a clinic in France. The authors describe their experience with the 8 individuals who received treatment with aripiprazole for: bipolar disorder (n=4), schizophrenia (n=2), major depression (n=1), or schizoaffective disorder (n=1). In review of these 8 cases that reported an increase in gambling following initiation of aripiprazole, the authors score 7 cases as "possibly" linked to aripiprazole and 1 case as "doubtful." [As noted above, only 3 of these cases met the case definition applied for the review.] The authors noticed that, when information on a substance use disorder was available, substance use disorders were frequent among their cases. They address this point – both in etiology and risk mitigation - in their conclusion:

> *"A subgroup of pathological gamblers display high levels of psychopathology, in particular depression, anxiety and alcohol dependence. In these individuals, called "emotionally disturbed," psychiatric or addictive comorbid disorders are primary conditions and constitute an important risk factor for the development of pathological gambling. These primary conditions would precisely justify the prescription of aripiprazole, in some cases.*
>
> *Therefore the causal part of aripiprazole should be confirmed by a case–control study conducted on a psychiatric population treated by aripiprazole. In the meantime, prescribers should be careful concerning aripiprazole prescription in patients presenting a SUD history or a regular gambling."*

In support of their recommendation to limit the use of aripiprazole in patients with a history of a substance use disorder or history of gambling, these authors describe the specific use (or channeling) of aripiprazole in the treatment of individuals with selected "psychiatric or addictive comorbid disorder," which they propose, might actually increase their risk of *PG*.

Additionally, DPV is aware of literature reports of new onset or exacerbation of obsessive-compulsive disorder (OCD) symptoms in patients treated with atypical antipsychotics, including clozapine, risperidone, quetiapine, and aripiprazole.[41,42] It is hypothesized that dopamine disinhibition via 5-HT_{2A} receptor blockade is the underlying mechanism for this adverse effect.[43]

Although there are some overlapping symptoms among OCD and ICDs, the disorders have marked differences in clinical presentation (e.g. gender distribution, age at onset, and clinical course), underlying neurocircuitry, and treatment response.[44,45] Regarding treatment response, there are studies showing that atypical antipsychotics, including aripiprazole, may be effective in treating OCD (as augmentation to antidepressant/serotonin reuptake inhibitor therapy).[46] DPV was unable to find studies exploring the efficacy of aripiprazole for treating specific ICDs of interest (i.e. PG, compulsive sexual behavior, buying, and eating). Due to the controversial relationship between ICDs and OCD,[42,44,47] this review is not inclusive of studies regarding aripiprazole and treatment of OCD.

3.3 EMPIRICA SIGNAL SEARCH

Table 13 shows the data mining scores by generic name for atypical antipsychotics. The search results exclude any potential litigation-related cases. These scores, denoted as Empirical Bayes Geometric Mean (EBGM) values, provide an estimate of the relative reporting of an event for a particular drug relative to all other drugs and events in FAERS. The lower and upper 90% confidence limits for EBGM values are denoted EB05 and EB95, respectively. An EB05 >2 is commonly used as a signaling threshold. The data mining scores in Table 13 indicate that PG is disproportionally reported with aripiprazole relative to all other atypical antipsychotics. These data do not, by themselves, demonstrate causal associations; they may serve as a signal for further investigation.

Table 13. Data mining results using Empirica Signal for MedDRA PT *Pathological gambling* reported with atypical antipsychotics, sorted by descending EB05 score

	Drug*	N	EB05†	EBGM	EB95
1	Aripiprazole	46	6.304	8.185	10.637
2	Olanzapine	4	0.362	0.834	1.702
3	Quetiapine	5	0.319	0.677	1.297
4	Risperidone	2	0.132	0.414	1.049

* Drugs that were included in the search strategy but do not appear in this table had zero cases for the PT *Pathological gambling*. This included asenapine, brexpiprazole, clozapine, iloperidone, lurasidone, paliperidone, and ziprasidone.
† A score (EB05) of ≥ 2 indicates 95% confidence that a drug-event combination appears at least twice the expected rate when considering all other drugs and events in the database.

3.4 SPONSOR'S SUBMISSION

The sponsor's clinical review included a safety and clinical database search of the PT *Pathological gambling* in the Otsuka clinical trial database, the Otsuka post-marketing database, and the BMS AWARE database.[26] The review also included a medical literature search of Medline, Embase, BIOSIS Previews, and SciSearch.

In total, the sponsor identified 238 PG cases (236 post-marketing cases and one clinical trial case report with oral aripiprazole, and one post-marketing case with Abilify Maintena). Of the 236 oral aripiprazole post-marketing cases, PG resolved in 154 cases and was recovering in 10 cases

after aripiprazole was discontinued. The sponsor also identified 18 literature case reports of PG temporally associated with aripiprazole use. All 18 literature case reports were captured in our review.

The sponsor concluded the data shows a possible causal association between aripiprazole use and PG, and added "pathological gambling" to the Company Core Datasheet (CCDS) as an "expected adverse drug reaction."

4 DISCUSSION

DPV identified an association between aripiprazole and ICDs, based on the temporal relationship and positive dechallenge information reported in 184 case reports (167 FAERS case reports and 17 literature reports), of which four also reported positive rechallenge information. This association confirms the sponsor's conclusions that there is a possible causal association between aripiprazole use and PG. The association between aripiprazole and ICDs is further strengthened by the biological plausibility that aripiprazole's partial DA agonist actions could theoretically stimulate DA release in the mesolimbic pathway. DPV did not identify any cases of ICD Related Disorders – DDS, punding, hobbyism, walk-about, or hoarding. The rest of the discussion will focus on the association between aripiprazole and the following specific ICDs: PG, compulsive sexual behavior, compulsive buying, and compulsive eating.

Aripiprazole has a high receptor affinity for the D_2 and D_3 dopamine receptor subtypes, as well as for the 5-HT_{2A} and 5-HT_{1A} receptors.[48] At the D_2 receptor, aripiprazole acts as a partial agonist, activating dopamine receptors in a less effective manner than dopamine itself.[9] Up until the approval of brexpiprazole and cariprazine in 2015, aripiprazole was the only antipsychotic in the US market with D_2 receptor partial agonist activity. As a D_2 partial agonist, aripiprazole is hypothesized to have "dopamine system stabilization" or "normalization" actions that supposedly normalize both hypoactive and hyperactive dopaminergic transmission in patients with psychiatric disorders (e.g. schizophrenia, bipolar mood disorder).[49] Some clinicians consider aripiprazole as too much of an agonist and not enough of an antagonist, based on observations that it can be activating in some patients, causing mild agitation, and nausea and vomiting.[9]

Of particular interest to our review is aripiprazole's action at the D_3 receptor. Activation of D_3 receptors, which are primarily found in the limbic region, is implicated in addiction (including behavioral addiction), and is associated with treatment-emergent ICDs in patients with PD receiving dopamine agonist therapy.[15,18] Although aripiprazole has a high affinity to the D_3 receptor, its action at the D_3 receptor is not well defined in the literature. Roxanas suggested that aripiprazole may have D_3 agonist activity, which could explain the biological mechanism of the appearance of ICDs after aripiprazole exposure.[35] Additionally, it is theorized that potential D_3 agonist/partial agonist activity may be exaggerated in patients who were previously treated with full dopamine antagonists (e.g. other typical or atypical antipsychotics), due to up-regulation and sensitization of dopamine receptors.[39] More research on the subject is needed before any conclusive statements can be made.

A possible confounding variable in all of our cases is the underlying psychiatric conditions for which aripiprazole is indicated for. We attempted to minimize this by only including cases that documented a positive dechallenge, as well as by excluding cases in which concurrent mania or

symptoms of mania, and active substance abuse disorder were reported. A case-control study would help clarify the association between ICDs and aripiprazole, and further minimize underlying disease as a confounder. Nonetheless, until such a study is conducted, it would be prudent to warn HCPs and the public of the potential for new onset of ICDs associated with aripiprazole treatment. Especially in the context of a plethora of well-documented case reports in the literature, which include reports of positive rechallenge; multiple FAERS cases showing a temporal relationship and positive dechallenge; and the risk of devastating consequences if the ICD is left unrecognized and unmanaged, such as unemployment, marital problems, financial ruin, worsening anxiety and depression, and even increased risk of suicide.[16]

Lastly, it is noteworthy that DPV and the Division of Neurology Products (DNP) struggled with similar data limitations when they reviewed the safety issue of ICDs and dopaminergic antiparkinson drugs in 2006. The following is an excerpt from the Discussion section of Dr. Gerard Boehm's review on the matter:[50]

"Given the lack of quantitative risk information and our inability to obtain such information in the near future, one is left to decide if the evidence in the reports sufficiently supports the hypothesis of a relationship between these drugs [pramipexole, ropinirole, apomorphine, pergolide, bromocriptine, levodopa] and uncontrollable urges and warrants that these events be described in labeling…These reports could reflect events that one would see regardless of treatment with these medications (background events) or it could be that the reports reflect an increased risk compared to the general population but that the increased risk is associated with PD [Parkinson's Disease] itself rather than an effect of the medications. Unfortunately, evaluation of these potential explanations requires background risk information as well as accurate risk estimates in the treated populations and as explained above, neither of these risk estimates is available at this time. Reports occurring in patients treated for RLS [Restless Legs Syndrome] could be considered evidence against a Parkinson's disease/effect relationship but again, further information is needed to support such a conclusion.

…The AERS database and medical literature include a number of de-challenge cases but not re-challenge cases and therefore we lack strong case-based evidence of a drug adverse event relationship…Despite the lack of conclusive evidence of a drug/effect relationship, I believe that the labeling should describe these events. While investigation continues, prescribers should be aware of and monitor patients for these events. The reports suggest that these urges may cease or diminish with dose reduction or stopping drug, potentially important information for prescribers and patients. One could argue that mention in the medical literature is sufficient at this stage but I believe that patients should be aware that these events may occur. Patients are far more likely to have access to this information in labeling than they would to the medical literature."

Even with the limited evidence at the time, and arguably weaker evidence than what we present in our review of aripiprazole currently, DNP recognized the importance of raising awareness on the possible relationship between DRT and ICDs, and moved forward with adding a warning for gambling, hypersexuality, and other uncontrollable urges to the labels of dopaminergic antiparkinson drugs. We suggest that there is a similar need to move forward with a warning for aripiprazole based on currently available evidence.

5 CONCLUSION

DPV identified an association between aripiprazole and ICDs, based on the FAERS and medical literature data, and biological plausibility offered by aripiprazole's partial dopamine agonist activity. The association between aripiprazole and ICDs warrants inclusion in the aripiprazole label.

6 RECOMMENDATIONS

Based on the data analyzed in this review, DPV recommends the following:

1. Addition of the following statement to Section 5, Warnings and Precautions, of the label for Abilify, Abilify Maintena, and Aristada:

   Pathological Gambling and Impulse-Control Disorders
   Case reports suggest that patients can experience intense urges, particularly for gambling, and the inability to control these urges while taking aripiprazole. Other urges, reported less frequently than gambling, include: sexual urges, uncontrolled spending, binge or compulsive eating, and other urges with impulsive and compulsive features. These urges were reported to have stopped when the dose was reduced or the medication was discontinued. Because patients may not recognize these behaviors as abnormal, it is important for prescribers to specifically ask patients or their caregivers about the development of new or increased gambling urges, sexual urges, uncontrolled spending, binge or compulsive eating, or other urges while being treated with aripiprazole. If left unrecognized, these urges may result in harm to the patient and to others. Consider dose reduction or stopping the medication if a patient develops such urges while taking aripiprazole.

2. Addition of the above warning information to Section 17 – Patient Counseling Information, as well as the Medication Guide.

3. Issuance of a Drug Safety Communication containing the above warning information.

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8 APPENDICES

8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

Data Mining of FAERS using Empirica Signal

Empirica Signal refers to the software that OSE uses to perform data mining analyses while using the Multi-item Gamma Poisson Shrinker (MGPS) data mining algorithm. "Data mining" refers to the use of computer algorithms to identify patterns of associations or unexpected occurrences (i.e., "potential signals") in large databases. These potential signals can then be evaluated for intervention as appropriate. In OSE, the FDA Adverse Event Reporting System (FAERS) database is utilized for data mining. MGPS analyzes the records in FAERS and then quantifies reported drug-event associations by producing a set of values or scores that indicate varying strengths of reporting relationships between drugs and events. These scores, denoted as Empirical Bayes Geometric Mean (EBGM) values, provide a stable estimate of the relative reporting of an event for a particular drug relative to all other drugs and events in FAERS. MGPS also calculates lower and upper 90% confidence limits for EBGM values, denoted EB05 and EB95, respectively. Because EBGM scores are based on FAERS data, limitations relating to FAERS data also apply to data mining-derived data. Further, drug and event causality cannot be inferred from EBGM scores.

8.2 APPENDIX B. FAERS CASE NUMBERS, FAERS VERSION NUMBERS, MANUFACTURER CONTROL NUMBERS, AND SELECT INDIVIDUAL CASE CHARACTERISTICS

FAERS Case #	Version	Manufacturer Control #	Age in Years	Sex	ICD type	Sequelae type*	Sequelae narrative description*
11913338	1		43	F	PG	Financial, mental health	"There were several times within the past two years that I had gambled so much money away that I was to the point of attempting suicide."
11689718	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2015-075330	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
11689714	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2015-075334	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
11689712	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2015-075327	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
11689702	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2015-075332	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
11644779	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2015-069054	NS	M	PG	NS	NS
11242925	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2015-043269	NS	F	PG	NS	NS
11220271	1		37	M	PG	NS	NS
10998088	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007806	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10998087	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007807	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10998085	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007805	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10998084	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007808	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""

FAERS Case #	Version	Manufacturer Control #	Age in Years	Sex	ICD type	Sequelae type*	Sequelae narrative description*
10998082	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007803	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10998081	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007804	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10998060	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007799	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10998058	2	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007798	42	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10998057	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007797	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10998056	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007801	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10998055	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007802	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10998054	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007800	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10998053	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007796	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10998034	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007793	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10998033	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007794	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10998031	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007795	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""

FAERS Case #	Version	Manufacturer Control #	Age in Years	Sex	ICD type	Sequelae type*	Sequelae narrative description*
10998004	2	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007792	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10997948	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007791	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10997856	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007788	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10997854	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007789	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10997853	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007790	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10997852	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007786	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10997847	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007787	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10997764	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007837	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10997763	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007835	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10997761	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007836	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10997731	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007783	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10997729	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007782	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""

FAERS Case #	Version	Manufacturer Control #	Age in Years	Sex	ICD type	Sequelae type*	Sequelae narrative description*
10997728	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007785	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10997727	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007784	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10997631	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007833	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10997630	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007834	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10997570	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007832	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10997569	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007831	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10997567	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007780	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10997566	2	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007779	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10997565	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007778	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10997564	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007781	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10997496	2	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007774	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10997495	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007830	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""

FAERS Case #	Version	Manufacturer Control #	Age in Years	Sex	ICD type	Sequelae type*	Sequelae narrative description*
10997494	2	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007771	53	M	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10997493	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007777	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10997492	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007775	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10997491	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007776	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10997490	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007772	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10997489	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007773	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10997154	3	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007829	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10997146	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007828	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10997126	2	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007826	NS	F	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10997120	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007827	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10997091	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007768	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10997087	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007825	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""

FAERS Case #	Version	Manufacturer Control #	Age in Years	Sex	ICD type	Sequelae type*	Sequelae narrative description*
10997084	2	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007770	60	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10997082	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007769	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10997059	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007762	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10997057	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007763	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10997056	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007758	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10997055	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007760	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10997052	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007765	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10997051	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007766	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10997050	2	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007767	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10997047	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007761	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10997046	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007764	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10997045	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007759	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""

FAERS Case #	Version	Manufacturer Control #	Age in Years	Sex	ICD type	Sequelae type*	Sequelae narrative description*
10997020	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007756	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10997019	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007757	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10997018	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007754	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10997017	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007753	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10997015	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007755	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10997014	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007752	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10996982	2	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007751	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10996980	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007750	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10996864	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007749	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10996834	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007748	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10996833	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007746	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10996831	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007744	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""

FAERS Case #	Version	Manufacturer Control #	Age in Years	Sex	ICD type	Sequelae type*	Sequelae narrative description*
10996830	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007747	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10996829	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007745	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10996785	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007739	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10996780	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007741	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10996779	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007740	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10996777	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007743	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10996776	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007742	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10996751	2	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007738	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10996594	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007734	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10996593	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007737	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10996592	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007736	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10996591	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007735	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""

FAERS Case #	Version	Manufacturer Control #	Age in Years	Sex	ICD type	Sequelae type*	Sequelae narrative description*
10996570	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007728	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10996563	2	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007731	33	M	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10996562	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007729	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10996560	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007733	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10996559	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007730	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10996557	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007732	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10995536	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007727	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10995520	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007723	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10995519	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007726	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10995517	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007724	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10995516	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007725	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10995515	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007722	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""

FAERS Case #	Version	Manufacturer Control #	Age in Years	Sex	ICD type	Sequelae type*	Sequelae narrative description*
10995491	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007822	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10995487	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007718	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10995486	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007721	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10995485	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007719	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10995484	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007720	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10995483	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007823	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10995482	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007824	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10995461	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007714	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10995460	2	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007717	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10995459	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007715	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10995456	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007713	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10995455	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007821	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""

FAERS Case #	Version	Manufacturer Control #	Age in Years	Sex	ICD type	Sequelae type*	Sequelae narrative description*
10995454	2	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007716	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10995410	2	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007820	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10995409	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007819	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10995347	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007818	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10995346	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007817	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10995345	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007816	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10995302	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007814	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10995301	2	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007815	42	M	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10995263	2	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007813	NS	F	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10995262	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007812	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10995261	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007811	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10995260	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007810	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""

FAERS Case #	Version	Manufacturer Control #	Age in Years	Sex	ICD type	Sequelae type*	Sequelae narrative description*
10995214	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-007809	NS	NS	PG	Financial, mental health	""…neuropsychiatric and physical injury, emotional distress, harm, and economic loss.""
10869881	3	JP-BRISTOL-MYERS SQUIBB COMPANY-BMS-2015-010384	36	M	PG	Financial, mental health	"He drained his savings accounts and took cash advances from his credit cards to support his gambling compulsions. His credit was ruined.. he lost more money. At that time, he felt hopeless and attempted suicide...He informed his doctor that a primary contributor to his suicide attempt was his gambling losses."
10854779	3	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2015-010382	29	M	PG	Mental health, work performance	"He would become extremely and intolerably anxious until he satisfied the urge to gamble…Gambling took up so much of his time and his energy that his job performance suffered."
10854248	2	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2015-010381	45	F	PG	Financial, relationships	"She lost the financial security that she had worked for years to create and preserve. Her marriage suffered during her aripiprazole use as gambling was all she thought about. Her obsession with gambling consumed her life."
10825789	2	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2015-010380	32	F	PG	Financial	"…her savings were depleted and her previously strong credit was destroyed. The consumer was financially secure prior to aripiprazole therapy...The consumer incurred financial hardship and debt as a result of her compulsion to gamble on aripiprazole."
10825779	3	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2015-010379	38	M	PG	Financial, relationships, work performance	"…became overwhelmed with stress, guilt, and remorse every time he gambled not only because of the financial devastation his gambling was causing, but also because he was lying to people about his uncontrollable gambling behavior and missing work to gamble. His compulsive gambling on aripiprazole left him cash poor at times and without the means to pay his bills."
10784525	1		44	F	PG	Financial	"I spent roughly 125,000.00 in four years."
10655252	2	US-BRISTOL-MYERS SQUIBB COMPANY-21680103	NS	F	PG	Financial, mental health	".. neuropsychiatric and physical injury, emotional distress, harm, and economic loss."
10438411	1	US-BRISTOL-MYERS SQUIBB COMPANY-20561585	65	M	PG	Financial	"…lost lots of money."
10437008	1	US-BRISTOL-MYERS SQUIBB COMPANY-20836789	NS	M	PG	NS	NS
10436880	1	US-BRISTOL-MYERS	46	F	PG	Financial	"…would bounce checks."

FAERS Case #	Version	Manufacturer Control #	Age in Years	Sex	ICD type	Sequelae type*	Sequelae narrative description*
		SQUIBB COMPANY-20805206					
10275269	1	US-BRISTOL-MYERS SQUIBB COMPANY-21087721	42	F	PG	Relationship, financial	"…had to take money from boyfriend."
10200760	1		40	F	PG	Financial	"…lost all my retirement and most of my possessions."
9774393	1		37	F	CE, CB, CSB	Mental health, financial, weight gain	".. my sugar went up and I gained 10 lbs..I spent most of my time thinking about what jewelry I was going to buy and was racking up tons of debt...One side effect which I can never erase is my sudden promiscuity which has NEVER been a problem in the past...and eventually having suicidal thoughts...I now have to file bankruptcy for spending close to $15000 which I cannot repay."
9458667	1		28	F	CB, CE	Financial, weight gain	"…I spent about $15,000 within about two months and gained 10 pounds within a few weeks."
9448901	1	US-BRISTOL-MYERS SQUIBB COMPANY-18966259	57	F	CB	NS	NS
9321989	1		55	F	PG	Financial, relationships	"…This is a devastating reaction causing me over $100,000 in gambling debts, untold stress on my marriage and family life, and financial destruction during a time when we were financially stable."
8973301	1	US-BRISTOL-MYERS SQUIBB COMPANY-16436453	53	M	CSB	NS	NS
8521436	1	US-BRISTOL-MYERS SQUIBB COMPANY-16514762	53	F	CE	Weight gain	"…she started to compulsively eat carbohydrates and she started gaining weight…[within approximately a one year period] she had gained 60 pounds. Due to the weight gain, she was taken off aripiprazole...She then had a manic episode...She was then placed back on aripiprazole and she gained 10 more pounds."
8295769	1	US-BRISTOL-MYERS SQUIBB COMPANY-15985351	58	M	PG	NS	NS
8295613	2	US-BRISTOL-MYERS SQUIBB COMPANY-15921448	49	F	CB	NS	NS
8015166	3	US-BRISTOL-MYERS SQUIBB COMPANY-	40	M	CB	Financial	"…he felt like he had no control over his spending and spent half of their retirement and maxed out all of their credit cards.. he was going to

FAERS Case #	Version	Manufacturer Control #	Age in Years	Sex	ICD type	Sequelae type*	Sequelae narrative description*
		15853963					have to file bankruptcy because of the increase in spending."
7909835	1		36	M	CE, PG	Financial	"…He reported $5000 loss."
7573519	2	US-BRISTOL-MYERS SQUIBB COMPANY-15266943	NS	F	PG	Financial, legal	"…she was also having a problem with compulsive behavior (stealing money)."
7216691	1	US-BRISTOL-MYERS SQUIBB COMPANY-14756183	28	M	CSB	NS	NS
7214697	1	US-BRISTOL-MYERS SQUIBB COMPANY-14408934	49	F	PG	NS	NS
6883176	1	US-BRISTOL-MYERS SQUIBB COMPANY-13945951	47	F	PG	NS	NS
6770511	1		40.65	F	PG	Financial	"…She was writing checks that would bounce; she spent her entire paycheck."
6212455	1	US-BRISTOL-MYERS SQUIBB COMPANY-13427794	32.33	F	PG	Financial	"…developed a new behavior of compulsive gambling to the point that she went bankrupt."
6211790	1	US-BRISTOL-MYERS SQUIBB COMPANY-13165816	23	M	CSB	Relationships	"…sexually inappropriate with his mother."
5931934	1	US-BRISTOL-MYERS SQUIBB COMPANY-13063094	25	M	CSB	NS	NS
5885930	1		50	F	PG	Financial, mental health	"…Days without showering, combing my hair, my car was full of garbage as I lived in it from casino to casino...I was writing bad checks to support my gambling. Taking money out of my 401K to pay for bad checks. "
5746818	1	US-BRISTOL-MYERS SQUIBB COMPANY-12764288	NS	F	CB	NS	NS
4096101	1	US-BRISTOL-MYERS SQUIBB COMPANY-12435301	62	F	CE	NS	NS

FAERS Case #	Version	Manufacturer Control #	Age in Years	Sex	ICD type	Sequelae type*	Sequelae narrative description*
4096100	1	US-BRISTOL-MYERS SQUIBB COMPANY-12435228	5	F	CE	NS	NS

* Sequelae refer to negative consequences related to the ICD as reported in the case narrative. Sequelae were categorized by the reviewer into six main types: (1) financial (e.g. monetary loses); (2) mental health (e.g. suicidal ideation, emotional distress); (3) weight gain; (4) relationships (e.g. stress on marriage; sexually inappropriate behavior towards family member); (5) work performance (e.g. missed days at work, decreased work performance); (6) legal (e.g. stealing money).

Definitions: CB – Compulsive buying; CE – Compulsive eating; CSB – Compulsive sexual behavior; FAERS – FDA Adverse Event Reporting System; F – Female; ICD – Impulse-control disorder; M – Male; NS – Not specified; PG – Pathological gambling.

8.3 APPENDIX C. LITERATURE CASE REPORT NARRATIVES

Gaboriau et al.[39] published a case series of eight patients enrolled in a specialty PG treatment clinic that were identified as being on aripiprazole at the time they first initiated care with the clinic. Only three of the eight cases reported in this case series met the case definition outlined under Section 2.1 (three cases were excluded due to no positive dechallenge, one case due to history of pathological gambling prior to aripiprazole treatment, and one case due to history of pathological gambling prior to aripiprazole treatment and no positive dechallenge). The following is a summary of the three cases that met the case definition:

Case 1 (Gaboriau et al.):[39]
This case involves a 38 year old male with a history of bipolar (type not specified), which he has received treatment for since he was 28 years old. The patient gambled regularly (horse races) since he was 24 years old. He first started aripiprazole 10 mg daily (route unspecified) when he was 37 years old. "About a year later" aripiprazole was increased to 20 mg daily (route unspecified). Within weeks after his aripiprazole dose was increased, the patient "start[ed] feeling an irresistible urge to gamble," and reported "several negative consequences" including marital breakdown, financial problems, and worsening depression. At an unspecified date ("age 38"), the patient sought care for PG, discontinued aripiprazole (on an unspecified date), received psychotherapy, and recovered from PG (on an unspecified date).

Reviewer's Comments: This case describes a close temporal relationship (within weeks) of increased exposure to aripiprazole and new onset of PG. The PG resolved after discontinuation of aripiprazole. The positive dechallenge is confounded by the (presumably) concomitant introduction of psychotherapy. Although not provided in the report, it is reasonable to assume that the reason the patient's aripiprazole dose was increased an entire year after it was first initiated was due to worsening of the patient's underlying condition. New onset of PG is confounded by disease progression in this case.

Case 2 (Gaboriau et al):[39]
This case involves a 30 year old male with a history of paranoid schizophrenia. The case also mentioned a history of substance use disorder (nicotine, alcohol and cannabis) but did not specify whether the SUD was in remission or active. The patient had gambling experiences in his early teens, but he did not have a history of PG prior to starting aripiprazole. The patient was treated with aripiprazole 10 mg daily since the age of 25 years for paranoid schizophrenia, and he reported strong urges to gamble ever since starting aripiprazole treatment. A year after starting aripiprazole, his PG worsened after experiencing a "big win." When he was 29 years old he decided to initiate "specialized care." He discontinued aripiprazole when he was 30 years old, and after a few weeks, he reported a substantial decrease in gambling urges.

Reviewer's comments: This case describes increased gambling urges and PG that started after aripiprazole treatment was initiated. The gambling urges significantly decreased within weeks of discontinuing aripiprazole treatment.

Case 3 (Gaboriau et al):[39]

This case involves a 31 year old male with a history of schizoaffective disorder. The patient occasionally gambled (scratch cards) since he was 18 years old, but did not have a history of PG. On an unspecified date, the patient started aripiprazole 10 mg daily (route unspecified) for schizoaffective disorder. The dose was increased to aripiprazole 20 mg daily after a few months (date unspecified), which was "immediately followed by an irresistible urge to gamble." The patient received "specialized care" one year after the onset of PG. He was placed under legal guardianship, and the aripiprazole dose was decreased to 15 mg daily on an unspecified date. His PG resolved on an unspecified date after aripiprazole dose was decreased.

Reviewer's comments: This case describes a close temporal relationship (immediately/within days) between increased exposure to aripiprazole and new onset of PG. Additionally, PG resolved after aripiprazole dose was decreased, indicating a possible dose-dependent effect (i.e. aripiprazole at the high dose potentially acted more as a dopamine agonist, and at a low dose acted more as a dopamine antagonist). Other interventions, such as implementing legal guardianship, confounds this dechallenge.

Cohen et al.[36] describe three cases of PG associated with aripiprazole treatment. Two patients with schizophrenia and one patient with schizoaffective disorder experienced PG after initiating treatment with aripiprazole. In all three cases the authors ruled out "psychotic or a thymic decompensation" as the cause of PG. None of the three patients had a personal or family history of PG Table 1 summarizes the characteristics of the three cases.

Table 1. Characteristics of Patients from Cohen et al. Case Series[36]

	Patient 1	Patient 2	Patient 3
Sex	Male	Male	Male
Age (years)	30	20	19
Psychiatric diagnosis (DSM-IV code)	Schizoaffective disorder (295.7)	Paranoid schizophrenia (295.3)	Residual schizophrenia (295.6)
Duration of psychiatric condition (years)	10	6	1
Other psychiatric comorbidities	No	No	No
No. of DSM-IV PG criteria endorsed (out of 10)	7	6	8
Psychiatric treatment before the PG episode	- Risperidone 4 mg/d - Carbamazepine 800 mg/d	- Haloperidol 200 mg / 4 weeks (IM) - Pramazepam 60 mg/d	- Amisulpride 400 mg/d - Diazepam 30 mg/d
Treatment during PG	- Aripiprazole 15 mg/d - Carbamazepine 800 mg/d	- Aripiprazole 15 mg/d - Pramazepam 60 mg/d	- Aripiprazole 10 mg/d - Diazepam 30 mg/d - Amisulpride 400 mg/d

Table 1. Characteristics of Patients from Cohen et al. Case Series[36]			
	Patient 1	Patient 2	Patient 3
Treatment modification	- Risperidone 4 mg/d - Carbamazepine 800 mg/d	- Haloperidol 200 mg / 4 weeks (IM) - Pramazepam 80 mg/d	- Risperidone 4 mg/d - Diazepam 30 mg/d
PG onset after introduction of aripiprazole (days)	30	21	30
Gambling duration (months)	9	1	9
PG resolution after aripiprazole discontinuation (days)	25	7	21

All three cases describe a close temporal relationship between initiation of aripiprazole and onset of PG (21 to 30 days), as well as a positive dechallenge within 7-25 days after aripiprazole was discontinued. Additional strengths include medical confirmation of PG, ruling out of mania, and lack of gambling history prior to initiation of aripiprazole.

Smith et al.[37] published a case series of three case reports involving aripiprazole and PG. These three patients presented for cognitive-behavioral therapy for PG at the National Problem Gambling Clinic in England. The first of the three cases is described in Section 3.2. The other two cases are described below.

The second case of Smith et al.[37] involves a 28 year old male with a history of schizoaffective disorder. The patient had a history of gambling two or three times a week since adolescence, but his gambling behavior worsened after being switched from risperidone to aripiprazole 15 mg (route and frequency not specified). After three months of treatment with aripiprazole, the patient reported an escalation in gambling. He spent all of his money on gambling and considered it being "a reason to live." Even though he eventually limited his access to money, he would spend eight hours a day on the internet searching for free gambling opportunities. His psychiatrist switched him from aripiprazole to quetiapine on an unspecified date. The patient reported that the medication change had a "massive impact" on his gambling. After three months he was no longer preoccupied with gambling and did not have a compulsion to gamble.

Smith et al.'s[37] third case involves a 26 year old male with a history of schizophrenia. The patient had no history of gambling prior to starting treatment with aripiprazole. Approximately one year after starting aripiprazole, he started having strong urges to gamble, leading to significant financial loss. Because he had a history of only one psychotic episode that occurred more than seven years prior, aripiprazole was discontinued and no other antipsychotic was prescribed. At a one-month follow up visit after discontinuing aripiprazole, the patient reported no thoughts or a drive to gamble. The patient was able to maintain abstinence from gambling at the 6-month follow-up.

Reviewer's comments: These two cases describe a temporal relationship between aripiprazole initiation and onset of PG. In the second case, the patient had history of gambling, but gambling was not considered pathological until after starting aripiprazole. In the third case the patient did not have any history of gambling. There was a positive dechallenge in both cases after discontinuation of aripiprazole.

Gavaudan et al.[33] describe two cases of PG and criminal activity associated with aripiprazole. In the first case a 46 year old male with paranoid schizophrenia was initiated on aripiprazole 15 mg/day as adjunctive therapy to his current regimen of haloperidol 200 mg IM monthly and prazepam 60 mg daily. A few days after starting aripiprazole, his caregiver (sister) observed that he had increased gambling activity, anxiety, and aggression. The patient began stealing money from his sister. He reported having a craving for gambling which helped reduce his anxiety briefly. He was diagnosed with PG, and since PG first appeared after starting aripiprazole, aripiprazole was discontinued. His prazepam dose was also increased to 80 mg daily. One week after discontinuing aripiprazole, PG and anxiety had completely resolved ("entirely disappeared"). Prazepam dose was decreased back to 60 mg daily, and haloperidol 200 mg IM monthly was maintained. At the three-week follow-up, resolution of PG was maintained.

In the second case of Gavaudan et al.,[33] a 19 year old male with schizophrenia developed PG and committed theft after starting aripiprazole 10 mg daily. The patient's treatment regimen consisted of amisulpride 400 mg daily and diazepam 30 mg daily. A few weeks after initiating aripiprazole the patient started gambling which progressively worsened over the course of seven months in terms of frequency and betting amounts. At seven months, he physically assaulted a woman on the street and stole her mobile phone. He was arrested a few minutes later trying to sell the mobile phone at a betting shop. Amisulpride and aripiprazole were discontinued, and replaced with risperidone 4 mg daily. PG and aggressive behavior resolved within three weeks. At the four-month follow-up, resolution of PG was maintained.

Reviewer's comments: Both cases describe a temporal relationship between the initiation of aripiprazole and the onset of PG that led to criminal activity. Both cases also demonstrate a positive dechallenge for PG after aripiprazole was discontinued. In both cases, the reason aripiprazole was added to the patient's treatment regimen was to target negative symptoms after initial improvement in psychotic symptoms with antipsychotic treatment (haloperidol in case 1 and amisulpride in case 2). Since aripiprazole was not initiated in response to overall decompensation, this strengthens the case that the PG behavior was not caused by a lack of treatment response or by disease progression.

Roxanas[35] published a case of a 64 year old female who developed PG and compulsive eating after initiating aripiprazole. The patient did not have a history of drug or alcohol abuse, novelty-seeking behavior, or PD. She had a 31 year history of schizophrenia that was "well managed" with pimozide. She was switched from pimozide to aripiprazole for an unspecified reason. Initial aripiprazole dose was 10 mg daily and after five months, the dose was increased to 15 mg daily. Six months after the aripiprazole dose was increased, she developed an irresistible urge to gamble, which resulted in great financial loss. The patient described, "I just wanted to keep putting money in, it was an urgency. I would go high…and I seemed to lose all reason." The patient also experienced a compulsion to eat, particularly for "sweets and cakes," and gained

nine kilograms in weight in a six month period. The patient denied compulsive shopping or hypersexuality, and was not taking any other medications. She was switched off of aripiprazole to ziprasidone 40 mg twice daily. After one month, the gambling urges stopped and she also lost two kilograms in weight.

Reviewer's comments: This case describes a temporal relationship between PG and compulsive eating after an aripiprazole dose increase. The events abated within one month of aripiprazole discontinuation, indicating a positive dechallenge.

Cheon et al.[38] reported two cases of hypersexuality and aripiprazole. The first case involves a 37 year old female with schizophrenia. The patient was switched from risperidone to aripiprazole 20 mg daily (initially 10 mg daily titrated up to 20 mg daily) due to experiencing galactorrhea and amenorrhea with risperidone. She experienced increased libido within a month of being treated with aripiprazole 20 mg daily, and exhibited hypersexuality in the form of demanding daily sexual intercourse and frequent use of online pornography. She never exhibited these behaviors prior to aripiprazole therapy. Physical examination and laboratory investigations were all within normal limits. Aripiprazole was discontinued and the patient was switched back to risperidone. The patient was lost to follow-up, but 5 months later was re-admitted to the hospital for a psychotic episode and was treated with quetiapine 800 mg daily. Resolution of hypersexuality was sustained as evidenced by no reports of increased demand for sexual relations during her two month hospitalization.

Cheon et al.'s[38] second case involves a 36 year old female with schizophrenia. Her medical history was significant for obsessive-compulsive and avoidant personality traits. She had never engaged in sexual relationships. She was switched from risperidone to aripiprazole 20 mg daily due to weight gain with risperidone. Concomitant medications included fluoxetine 40 mg daily. An unspecified time after switching to aripiprazole, the patient exhibited increased sexual urges and activities. "For example, she engaged in masturbation and sexual fantasies, and watched pornographic materials more frequently." She also experienced unprovoked spontaneous sexual urges toward strangers. These new sexual behaviors embarrassed the patient and she became anxious and guilty. The patient insisted switching back to risperidone. After discontinuing aripiprazole and restarting risperidone 6 mg daily, "her high libido level rapidly subsided to her baseline level."

Reviewer's comments: Both cases describe a close temporal relationship between the initiation of aripiprazole and the onset of compulsive sexual behavior. Both cases also describe a positive dechallenge. The second case specifies that the compulsive sexual behaviors were so distressing to the patient that she insisted to switch off of aripiprazole.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

OFIR N NEVO
03/10/2016

ALLEN D BRINKER
03/10/2016

IDA-LINA DIAK
03/10/2016

CINDY M KORTEPETER
03/10/2016

ROBERT L LEVIN
03/10/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021436
NDA 021713
NDA 021729
NDA 021866
NDA 202971

SAFETY LABELING CHANGE NOTIFICATION

OTSUKA PHARMACEUTICAL CO LTD
C/O OTSUKA PHARMACEUTICAL DEVELOPMENT AND COMMUNICATIONS INC
Attention: Dana Cahill, PhD
Associate Director, Global Regulatory Affairs
2440 Research Blvd.
Rockville, MD 20850

Dear Dr. Cahill:

Please refer to your New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Abilify (aripiprazole) 2, 5, 10, 15, 20, 30 mg tablets (NDA 21436); Abilify (aripiprazole) 1mg/mL oral solution (NDA 21713); Abilify (aripiprazole) 10 and 15 mg Orally Disintegrating Tablets (NDA 21729); Abilify (aripiprazole) 9.75 mg/1.3 mL injection for IM use (NDA 21866); and Abilify Maintena (aripiprazole) for extended-release injectable suspension, for intramuscular injection 300 mg/vial and 400 mg/vial (NDA 202971).

Section 505(o)(4) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to make safety related label changes based upon new safety information that becomes available after approval of the drug or biological product.

Since aripiprazole was approved on November 15, 2002, we have become aware of an association between aripiprazole and pathological gambling as a result of regulatory action taken by Health Canada in November, 2015. Further, we identified reports in the FDA Adverse Event Reporting System (FAERS) database and medical literature supporting an association between aripiprazole and other impulse-control problems beyond just pathological gambling. We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

We acknowledge that we recently reviewed labeling supplements for Abilify products that provided for the addition of the adverse event term "pathological gambling" (as well as "hiccups") to Section 6.2 (Postmarketing Experience) of labeling. This review was conducted by

the Division of Psychiatry Products based on the data presented in those submissions. These supplements were approved on January 15, 2016. Please note that the above review of FAERS and literature data was conducted independently by our Office of Surveillance and Epidemiology (OSE) and was prompted by foreign regulatory actions based on reports of pathological gambling. This broader review identified not only reports of impulsive gambling but also other impulsive behaviors, as described below. Therefore, the FDA review and the actions requested below will supersede the January 15, 2016, approval action with respect to the pathological gambling component of the approved supplements.

In accordance with section 505(o)(4) of the FDCA, we are notifying you that based on the new safety information described above, we believe that the new safety information should be included in the labeling for aripiprazole as follows:

The addition of the following language under Warnings and Precautions immediately following the subsection titled "Metabolic Changes:"

> **Pathological Gambling and Impulse-Control Problems**
> Post-marketing case reports suggest that patients can experience intense urges, particularly for gambling, and the inability to control these urges while taking aripiprazole. Other urges, reported less frequently than gambling, include: uncontrolled sexual urges, uncontrolled spending, binge or compulsive eating, and other urges with impulsive and compulsive features. These urges were reported to have stopped when the dose was reduced or the medication was discontinued. Because patients may not recognize these behaviors as abnormal, it is important for prescribers to ask patients or their caregivers specifically about the development of new or increased gambling urges, uncontrolled sexual urges, uncontrolled spending, binge or compulsive eating, or other urges while being treated with aripiprazole. If left unrecognized, these urges may result in harm to the patient and to others. Consider dose reduction or stopping the medication if a patient develops such urges while taking aripiprazole.

In addition, add the following language to the Patient Counseling Information immediately following the subsection titled "Clinical Worsening of Depression and Suicide Risk":

> **Impulse Control Symptoms Including Compulsive Behaviors**
> Alert patients and their caregivers to the possibility that they may experience intense urges to spend money, intense urges to gamble, increased sexual urges, binge eating and/or other intense urges and the inability to control these urges while taking aripiprazole.

In accordance with section 505(o)(4), within 30 days of the date of this letter, you must submit a supplement proposing changes to the approved labeling in accordance with the above direction, or notify FDA that you do not believe a labeling change is warranted, and submit a rebuttal statement detailing the reasons why such a change is not warranted. If you submit a supplement that includes only language identical to that specified above, the supplement may be submitted as a changes being effected (CBE-0) supplement. If the supplement includes proposed language that differs from that above, submit a prior approval supplement (PAS). Requirements under section 505(o)(4) apply to NDAs, BLAs, and ANDAs without a currently marketed reference listed drug approved under an NDA, including discontinued products, unless approval of an application has been withdrawn in the Federal Register. Therefore, the requirements described in this letter apply to you, unless approval of your application has been withdrawn in the Federal Register.

Under section 502(z), failure to submit a response in 30 days may subject you to enforcement action, including civil money penalties under section 303(f)(4)(A) and an order to make whatever labeling changes FDA deems appropriate to address the new safety information.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

SAFETY LABELING CHANGES UNDER 505(o)(4) - PRIOR APPROVAL SUPPLEMENT

OR

SAFETY LABELING CHANGES UNDER 505(o)(4) – CHANGES BEING EFFECTED

OR

SAFETY LABELING CHANGES UNDER 505(o)(4) – REBUTTAL (CHANGE NOT WARRANTED)."

Prominently identify subsequent submissions related to the safety labeling changes supplement with the following wording in bold capital letters at the top of the first page of the submission:

SUPPLEMENT <<insert assigned #>>
SAFETY LABELING CHANGES UNDER 505(o)(4) - AMENDMENT

If you do not submit electronically, please send 5 copies of the submission.

If you have any questions, call Simran Parihar, Regulatory Project Manager, at (301) 301-796-7545 or Simran.Parihar@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Marc Stone, M.D.
Deputy Director for Safety (Acting)
Division of Psychiatry Products
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARC B STONE
05/03/2016