6.2 Elements for Public Summary - Abilify

6.2.1 Overview of Disease Epidemiology

Bipolar I Disorder

Reported prevalence rates for bipolar I disorder differ due to local variations in psychiatric practice, variations in the criteria that define a specific bipolar disorder, and because of the diverse manner in which bipolar I disorder manifests at any given time (chronic or recurrent). Therefore, depending upon geographical region and the criteria used to make the diagnosis, an estimated 1% to 6% of the adult population may have bipolar disorder. As a result of the challenges and varying professional views regarding the diagnosis of bipolar mania in children, the diagnosis of pediatric bipolar I/mania, particularly among pre-adolescent patients, is complex and remains controversial. Hence, the reported incidence of bipolar mania in children and adolescents varies widely and remains uncertain, with reported estimates internationally ranging from < 1% to 2%, and to as high as 27%.

Bipolar disorder occurs with equal frequency among males and females; however, among pre-adolescent cases, it appears to occur more frequently in males. A family history of bipolar disorder represents the greatest risk factor for developing bipolar mania. The age of onset, although variable, appears to be earlier in males than in females. The incidence of mania peaks in early adult life, but may develop earlier or even later in adulthood. Early-onset cases of bipolar disorder are associated with a more severe course of illness. In addition, over 50% of individuals may display aggressive behavior during the course of their first episode of bipolar mania.

Suicide and co-morbidities constitute a major health risk among bipolar patients and contribute to the high mortality rate observed among individuals with bipolar disorder. Risk of suicide is reported to be approximately 15 to 22 times higher for bipolar disorder patients than for the general population.

Schizophrenia

Schizophrenia occurs at a relatively low frequency, occurring in < 1% of the population, but there is substantial international variability in the incidence of this psychiatric illness. Incidence rates have shown considerable heterogeneity in terms of gender, age, ethnic group, and geographical region; international estimates have been reported to range widely from 7.7 to 43/100,000/year, with a median estimate of 15.2/100,000/year.

Schizophrenia is approximately 4 times more common in males than females, and in cases where the development of the disease is considered sporadic, onset typically occurs at an earlier age for males (mean age of onset is in the early 20's) than for females (mean age of onset is in the mid-to-late 20's). In contrast, in instances where patients have an affected first-degree relative (i.e., where there is genetic predisposition for developing schizophrenia), the age of onset is similar for both genders. The prognosis of schizophrenia appears to be worse for early-onset disease.

Family history is a well-established risk factor for schizophrenia. In addition, ethnic minority status is associated with a 2- to 5-fold higher incidence of schizophrenia, which may in part be attributed to psychosocial factors, such as poor socioeconomic status, social

marginalization, or adversity, discrimination, and stress associated with integration into a different culture.

It has been estimated that, globally, schizophrenia reduces life expectancy by an average of 10 years. The causes of the observed excess mortality are believed to be due to the mental disorder itself, as well as to unhealthy lifestyle practices (poor diet, smoking, alcohol, or other substance abuse) among schizophrenic patients. Risk of suicide is estimated to be approximately 9 times higher for schizophrenic patients than for the general population, and suicide is the largest single cause of excess mortality in schizophrenia. Suicide is significantly higher among men than women, and occurs most frequently in the year following the diagnosis of schizophrenia. Premature death among patients with schizophrenia is also attributed to various psychiatric and medical co-morbid conditions that are prevalent among this group.

Major Depressive Disorder

Major depressive disorder (MDD) is a relatively common mental illness, although estimates on the frequency with which it occurs vary widely. The highest rates of depression have been reported for South American countries; intermediate rates for the US and Western Europe, and the lowest rates have been reported among Asian countries. It has been estimated that approximately 20% of individuals may suffer from major depression during their lifetime. MDD occurs approximately twice as often in females than in males. Moreover, women often experience more severe symptoms of the illness than do men. A family history of major depression is a risk factor for developing the condition and accounts for an estimated 30% to 40% of cases. Family history is also is associated with an earlier age of disease onset.

MDD is a highly recurrent syndrome and up to 70% to 80% of adolescents and adults, respectively, who experience one episode of major depression will experience at least one recurrence within the next several years. Moreover, the probability of recurrence increases with both the severity of the first episode and with earlier age of onset. Early onset depression is associated with greater functional impairment, greater burden of both medical and psychiatric co-morbidity, and higher frequency of suicide-related events than depression with later age onset.

An estimated 29% to 46% of depressed patients fail to respond fully with antidepressant treatment. Treatment resistant depression tends to occur in patients who are older, have more severe and/or chronic illness, or in those who suffer from a co-morbid psychiatric or general medical condition.

Chronic physical illness, smoking, alcohol abuse, and suicide and accidents are commonly associated with depression and increased mortality. Mortality, particularly from unnatural causes, is higher for individuals with MDD than for the general population.

Autistic Disorder

Autism Spectrum Disorders (ASD) includes 3 diagnoses: autistic disorder, Asperger's disorder, and pervasive developmental disorder not otherwise specified (PDD-NOS).

The rate of autism and ASD vary widely with international reports ranging from <1 to 72 per 10,000 for autistic disorder, and from 3 to 270 per 10,000 for ASD. Based upon recent data, the average prevalence has been estimated to be 20 per 10,000 for autistic disorder and 60-70

per 10,000 for ASD. Autism spectrum disorders have consistently been reported to occur much more frequently in males than females. There has been an observed increase in the incidence of autism/ASD in recent decades. While the reasons for the apparent increase are not clear, it is believed to be mainly due to greater awareness of the condition and changes in methods and criteria for clinical diagnosis, although an aetiologic basis to which the increase may be partly attributable has not been ruled out.

The functional impairment observed in autism/ASD is due not only to the disorder itself, but also to the co-morbid conditions from which autistic children are known to suffer (e.g., Attention Deficit Hyperactivity Disorder; anxiety disorder; Obsessive Compulsive Disorder; oppositional defiant disorder; depression)**.** The risk of mortality among individuals with autism is approximately 2 to 5.6 times that expected for the general population.

6.2.2 Summary of Treatment Benefits

Aripiprazole is one of a group of medicines called antipsychotics. It is used to treat adults and adolescents 15 years and older who have a disease characterized by symptoms such as hearing, seeing or sensing things that are not there, suspiciousness, mistaken beliefs, incoherent speech, and behavior and emotional flatness. People with this condition may also feel depressed, guilty, anxious, or tense.

Aripiprazole is used to treat adults and adolescents 13 years and older who have a condition with symptoms such as feeling "high," having excessive amounts of energy, needing much less sleep than usual, talking very quickly with racing ideas, and sometimes, severe irritability. In adults, it also prevents this condition from returning in patients who have responded to treatment with aripiprazole.

6.2.3 Unknowns Relating to Treatment Benefits

Aripiprazole is indicated for the treatment of schizophrenia in adults and in adolescents aged 15 years and older.

Aripiprazole is indicated for the treatment of moderate to severe manic episodes in Bipolar I Disorder and for the prevention of a new manic episode in adults who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment.

Aripiprazole is indicated for the treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older.

Aripiprazole is also indicated for adjunctive treatment of MDD in adults (US only).

Aripiprazole solution for injection is indicated for the rapid control of agitation and disturbed behaviors in patients with schizophrenia or in patients with manic episodes in bipolar I disorder, when oral therapy is not appropriate. Treatment with aripiprazole Solution for Injection should be discontinued as soon as clinically appropriate and the use of oral aripiprazole should be initiated.

Within these indications, aripiprazole has been studied in a wide range of patients, across races, genders, and ages.

Several of the clinical trials were conducted in broader populations than the indications listed above. The limitations of the trials included the following.

Children

- Schizophrenia: Aripiprazole is not recommended for use in patients with schizophrenia < 15 years of age due to insufficient data on the safety and efficacy of these patients.
- Manic episodes in bipolar I disorder in adolescents: Younger patients are at increased risk of experiencing AEs associated with aripiprazole; therefore, it is not recommended for use in patients < 13 years of age.

Elderly patients

- The effectiveness of aripiprazole in the treatment of schizophrenia and bipolar I disorder in patients 65 years and older has not been established.
- In patients with severe hepatic impairment, the data available are insufficient to establish recommendations. In these patients dosing should be managed cautiously.

6.2.4 Summary of Safety Concerns

6.2.4.1 Important Identified Risks

Table 6.2.4.1-1: Important Identified Risks

Risk	What is known	Preventability
Involuntary, irregular muscle movements, especially in the face (extrapyramidal symptoms [EPS], including tardive dyskinesia)	Extrapyramidal disorder is a common undesirable effect (frequency: ≥ 1/100 to < 1/10) in adults treated with aripiprazole, and a more common undesirable effect (frequency: 18.4%) in adolescents 13 years and older in clinical trials. Tardive dyskinesia: in clinical trials of 1 year or less duration, there were uncommon reports of treatment-emergent dyskinesia during treatment with aripiprazole. Other EPS: in pediatric clinical trials of aripiprazole, akathisia and Parkinsonism were observed.	Yes, by lowering the aripiprazole dose and adding anticholinergic drugs. If signs and symptoms appear in a patient treated with aripiprazole, dose reduction or discontinuation may be considered.
High fever, stiff muscles, confusion, sweating, changes in pulse, heart rate , and blood pressure (neuroleptic malignant syndrome [NMS])	NMS is a potentially fatal symptom complex associated with antipsychotic medicinal products. In clinical trials, rare cases of NMS were reported during treatment with aripiprazole. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase (CPK), myoglobinuria (rhabdomyolysis), and acute renal failure. However, elevated CPK and rhabdomyolysis, not necessarily in association with NMS, have also been reported.	Yes, by monitoring for early symptoms. If a patient develops signs and symptoms indicative of NMS, or presents with an unexplained high fever without additional clinical manifestations of NMS, all antipsychotic medicinal products, including aripiprazole, must be discontinued.

6.2.4.2 Important Potential Risks

Table 6.2.4.2-1: Important Potential Risks

Risk	What is known
Convulsions (seizures)	In clinical trials, uncommon cases of seizure were reported during treatment with aripiprazole. Therefore, aripiprazole should be used with caution in patients who have a history of seizure disorder or have conditions associated with seizures.
High blood sugar (hyperglycemia/diabetes)	Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotic agents, including aripiprazole. Risk factors that may predispose patients to severe complications include obesity and a family history of diabetes. In clinical trials with aripiprazole, there were no significant differences in the incidence rates of hyperglycemia-related adverse reactions (including diabetes) or in abnormal glycemic laboratory values compared to placebo. Precise risk estimates for hyperglycemia-related adverse reactions in patients treated with aripiprazole and with other atypical antipsychotic agents are not available to allow direct comparisons. Patients treated with any antipsychotic agents, including aripiprazole, should be observed for signs and symptoms of hyperglycemia (such as polydipsia, polyuria, polyphagia, and weakness), and patients with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control.
Suicide-related events	The occurrence of suicidal behavior is inherent in psychotic illnesses and mood disorders, and in some cases has been reported early after initiation or switch of antipsychotic therapy, including treatment with aripiprazole. Close supervision of high-risk patients should accompany antipsychotic therapy. Results of an epidemiologic study suggested that there was no increased risk of suicidality with aripiprazole compared to other antipsychotics among patients with schizophrenia or bipolar disorder.
Lightheadedness or fainting when rising too quickly from a sitting or lying position (orthostatic hypotension)	Orthostatic hypotension is an uncommon adverse reaction (frequency: ≥ 1/1,000 to < 1/100) in adults treated with aripiprazole, and a common adverse reaction (frequency ≥ 1/100, < 1/10) in adolescents 15 years and older treated with aripiprazole in clinical trials. Antipsychotic drugs, including aripiprazole, may increase the effect of medicines used to lower the blood pressure. Be sure to tell your doctor if you take a medicine to keep your blood pressure under control.
Abnormal amount of lipids in the blood (dyslipidemia)	In a pooled analysis on lipid parameters from placebo-controlled clinical trials in adults, aripiprazole has not been shown to induce clinically relevant alterations in levels of total cholesterol, triglycerides, HDL, and LDL. Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.

6.2.4.3 Missing Information

Table 6.2.4.3-1: Missing Information

Risk	What is known
Use in pregnancy and lactation	There are no adequate and well-controlled trials of aripiprazole in pregnant women. Congenital anomalies have been reported; however, a causal relationship with aripiprazole could not be established. Animal studies could not exclude potential developmental toxicity. Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during treatment with aripiprazole. Due to insufficient safety information in humans, and concerns raised by animal reproductive studies, aripiprazole should not be used in pregnancy unless the expected benefit clearly justifies the potential risk to the fetus. Neonates exposed to antipsychotics, including aripiprazole, during the third

Table 6.2.4.3-1: Missing Information

Risk	What is known
	trimester of pregnancy are at risk of adverse reactions, including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully.
	Aripiprazole is excreted in human breast milk. Patients are advised not to breast feed if they are taking aripiprazole.
Use in pediatrics	Aripiprazole is indicated for the treatment of schizophrenia in adolescents 15 years and older, and it is not recommended for use in patients with schizophrenia < 15 years of age due to insufficient data on safety and efficacy.
	Aripiprazole is indicated for the treatment of manic episodes in bipolar I disorder in adolescents 13 years and older, and it is not recommended for use in patients with bipolar I disorder < 13 years of age due to insufficient data on safety and efficacy.

6.2.5 Summary of Additional Risk Minimization Measures by Safety Concern

These additional risk minimization measures are for the following risks: EPS, weight gain, and AEs related to somnolence and fatigue.

Table 6.2.5-1: Involuntary, Irregular Muscle Movements, Especially in the Face (Extrapyramidal Symptoms)/Weight Gain/Adverse Events Related to Somnolence and Fatigue

Risk minimization measure(s)
Objective and Rationale
Patients and healthcare professionals (HCPs) to understand the risk of EPS, weight gain, and AEs related to somnolence/fatigue and the procedures related to the appropriate management of these risks to minimize their occurrence and their severity.

6.2.6 Planned Post Authorization Development Plan

Table 6.2.6-1: List of Studies in Post-Authorization Development Plan

Study/activity (including study number)	Objectives	Safety concerns /efficacy issue addressed	Status	Planned date for submission of (interim and) final results
A post-authorization safety study to assess the effectiveness of the educational program for bipolar I disorder in adolescents 13 years and older urging vigilance in the ongoing evaluation of extrapyramidal symptoms (EPS), weight gain, and AEs	To assess the effectiveness of the educational program (e.g., whether the educational material effectively communicates and reinforces the core safety messages conveyed in the SmPC and PIL to carefully consider the indicated age range, dose, and duration of treatment	EPS, weight gain, and AEs related to somnolence / fatigue	Final CSR was submitted.	June 2016

Table 6.2.6-1: List of Studies in Post-Authorization Development Plan

Study/activity (including study number)	Objectives	Safety concerns /efficacy issue addressed	Status	Planned date for submission of (interim and) final results
related to somnolence/fatigue	before considering aripiprazole for patients with pediatric bipolar disorder).			
Study 31-09-266 is a double-blind, randomized, multicenter placebo-controlled study to evaluate the long-term efficacy, safety, and tolerability of aripiprazole as maintenance treatment in adolescents 13 to < 18 years of age with schizophrenia	Primary objective: To evaluate the efficacy of aripiprazole compared with placebo, as measured by time to exacerbation of psychotic symptoms / impending relapse, in adolescent schizophrenic subjects who have maintained stability of response for 2 consecutive weekly time points on oral aripiprazole with at least 7 weeks of treatment. Secondary objective: To evaluate the safety and tolerability of oral aripiprazole as maintenance treatment in adolescent subjects with schizophrenia.	Long-term efficacy, safety, and tolerability of aripiprazole as maintenance treatment	Final CSR was submitted.	2014
Study 31-09-267 is a long-term, multicenter, open-label study to evaluate the safety and tolerability of flexible-dose oral aripiprazole (OPC-14597) as maintenance treatment in adolescent patients with schizophrenia or children and adolescents with bipolar I disorder, manic or mixed with or without psychotic features	To further characterize the long-term safety and tolerability of aripiprazole in adolescent subjects with schizophrenia and child and adolescent subjects with Bipolar I Disorder, manic or mixed episode, with or without psychotic features	Long-term safety, and tolerability of aripiprazole as maintenance treatment	Final CSR was submitted	2015

None of the above studies are conditions of the marketing authorization.