VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Schizophrenia

Schizophrenia is a mental illness with a number of symptoms, including confused or unclear thinking and speech, hallucinations (hearing or seeing things that are not there), suspiciousness and delusions (false beliefs). It is often characterized by abnormal social behaviour (inactivity and reduced social engagement and emotional expression) and failure to recognize what is real. Genetics, early environment, psychological and social processes appear to be important contributory factors. Schizophrenia affects around 0.3–0.7% of people at some point in their life, or 24 million people worldwide as of 2011. It occurs 1.4 times more frequently in males than females and typically appears earlier in men—the peak ages of onset are 25 years for males and 27 years for females.

Bipolar I Disorder

Bipolar I disorder is a mental illness in which patients have manic episodes (periods of abnormally high mood), alternating with periods of normal mood. They may also have episodes of depression. About 3% of people have bipolar disorder worldwide, a proportion consistent for both men and women and across racial and ethnic groups. Bipolar disorder affects more than 30 million people worldwide, and is among the top 20 leading causes of disability (WHO 2004). Up to 2% of Europeans will have a bipolar disorder at some point in their life, of which approximately half will develop bipolar I disorder. The cause is not clearly understood, but both genetic and environmental risk factors are believed to play a role.

VI.2.2 Summary of treatment benefits

Schizophrenia

There were three main short-term studies lasting four to six weeks, which involved 1,203 adults and compared aripiprazole tablets with placebo (a dummy treatment). The effectiveness of aripiprazole in preventing symptoms from returning was assessed in three studies lasting up to a year, two of which used haloperidol (another antipsychotic medicine) as a comparator. Aripiprazole tablets were also compared with placebo in one study involving 302 patients aged between 13 and 17 years. All of the studies measured the change in the patient's symptoms using a standard scale for schizophrenia.

When used to treat schizophrenia, aripiprazole was more effective than placebo in the short-term adult studies. In the long-term studies, aripiprazole was more effective than placebo, and as effective as haloperidol, after up to a year of treatment. Aripiprazole was also more effective than placebo over six weeks in the study of adolescents, and the effect of aripiprazole was maintained for at least six months in patients aged over 15 years.

Bipolar I disorder

There were eight studies looking at aripiprazole taken by mouth in adults. Five of these compared aripiprazole with placebo over three weeks (total of 1,900 adults) two of which continued for further 9 weeks and used haloperidol and lithium (another antipsychotic medicine) as comparators. The sixth study compared aripiprazole with haloperidol over 12 weeks in 347 adults, and the seventh compared Aripiprazole with placebo in the prevention of recurrence in 160 adults whose manic symptoms had already been stabilised using aripiprazole. The eighth study looked at the effect of adding aripiprazole or placebo to existing treatment with lithium or valproate (antipsychotic medicine) in 384 adults. Aripiprazole was also compared with placebo in one study involving 296 children and adolescents.

The studies showed that aripiprazole was more effective than placebo at reducing manic symptoms in four of the five short-term studies in adults. Aripiprazole also had a similar effect to haloperidol and to lithium over three weeks. This effect was maintained for up to 12 weeks. Aripiprazole was also more effective than placebo at preventing manic episodes returning in previously treated adults for up to 74 weeks, and when it was used as an add-on to existing treatment. In the study in children and adolescents, aripiprazole was also more effective than placebo at reducing the manic symptoms of bipolar disorder.

VI.2.3 Unknowns relating to treatment benefits

Not applicable.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Involuntary, irregular muscle movements, especially in the face, uncontrollable twitching or jerking, uncontrolled movements of the limbs, restlessness **(Extrapyramidal symptoms [EPS], including tardive dyskinesia)**	In adult patients, uncontrollable twitching or jerking movements, restlessness, and shaking may affect up to 1 in 10 people. Adolescents aged 13 years and older experienced side effects that were similar in frequency and type to those in adults except that uncontrollable twitching or jerking movements were very common (may affect more than 1 in 10 people) and muscle twitching, uncontrolled movements of the limbs were common (may affect up to 1 in 10 people).	If you notice you are developing unusual movements, please tell your doctor. Lowering the aripiprazole dose and adding another drug (anticholinergic drugs) may be necessary. 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**	Neuroleptic malignant syndrome (a combination of fever, muscle stiffness, faster breathing, sweating, reduced consciousness and sudden changes in blood pressure and heart rate) has been reported	Tell your doctor immediately if you suffer from muscle stiffness or inflexibility with high fever, sweating, altered mental status, or very rapid or irregular heartbeat.

Risk	What is known	Preventability
syndrome [NMS])	since the marketing of aripiprazole but the frequency for them to occur is not known.	Monitoring for early symptoms must be concerned. 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.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Seizures, fits **(Convulsions)**	Seizures have been reported since the marketing of aripiprazole but the frequency for them to occur is not known (frequency cannot be estimated from the available data). 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 **(Hyperglycaemia/ diabetes)**	High blood sugar, onset or worsening of diabetes, ketoacidosis (ketones in the blood and urine) or coma have been reported since the marketing of aripiprazole but the frequency for them to occur is not known. Risk factors that may predispose patients to severe complications include obesity and a family history of diabetes. Patients treated with aripiprazole should be observed for signs and symptoms of hyperglycaemia (such as excessive drinking, excessive or abnormally large production or passage of urine, excessive hunger, 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	Thoughts of suicide, suicide attempt and suicides, as other behaviours related to it have been reported by patients being treated with aripiprazole since the marketing of the drug but the frequency for them to occur is not known (frequency cannot be estimated from the available data). Depression has also been reported with use of aripiprazole, it is uncommon side effect (may affect up to 1 in 100 people). The occurrence of suicidal behaviour 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. Tell your doctor immediately if you are having any thoughts or feelings about hurting yourself.
Light-headedness or fainting when rising too quickly from a sitting or lying position **(Orthostatic hypotension)**	Light-headedness may affect up to 1 in 10 people and some people may feel dizzy, especially when getting up from a lying or sitting position (may affect up to 1 in 100 people). 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. In adolescents aged 13 years and older feeling dizzy, especially when getting up from a lying or sitting position, was common (may affect up to 1 in 10 people).

Risk	What is known (Including reason why it is considered a potential risk)
Abnormal amount of lipids in the blood **(Dyslipidaemia)**	Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics. However, 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.

Missing information

Risk	What is known
Safety in pregnancy and lactation	There are no adequate and well-controlled trials of aripiprazole in pregnant women. Birth defects in new-born babies have been reported; however, causal relationship with aripiprazole could not be established. You should not take aripiprazole if you are pregnant unless you have discussed this with your doctor. Be sure to tell your doctor immediately if you are pregnant, think you may be pregnant, or if you are planning to become pregnant. The following symptoms may occur in new-born babies, of mothers that have used aripiprazole in the last trimester (last three months of their pregnancy): shaking, muscle stiffness and/or weakness, sleepiness, agitation, breathing problems, and difficulty in feeding. If your baby develops any of these symptoms you may need to contact your doctor.
Safety in children (paediatrics)	Aripiprazole is not for use in children and adolescents under 13 years. 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.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

Applicable only to countries where indication of aripiprazole for the treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older will be launched:

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimisation measures); how they are implemented in each country, however, will depend upon agreement between the manufacturer and the national authorities.

These additional risk minimization measures are for the following risks (in adolescents aged 13 years and older): involuntary, irregular muscle movements, especially in the face; weight gain, and adverse events related to sleepiness and tiredness:

Risk minimisation measure(s)
Objective and rationale Patients and healthcare professionals to understand the risk of involuntary, irregular muscle movements, weight gain, and adverse events related to sleepiness and tiredness, and the procedures related to the appropriate handling of these risks to minimize their appearance and their severity.
Main additional risk minimisation measures Healthcare professional and patient education for bipolar I disorder in adolescents 13 years and older in the ongoing evaluation of involuntary, irregular muscle movements, weight gain, and adverse events related to sleepiness and tiredness: • Educational leaflet to be provided to prescribers to clearly point out the need for careful consideration of the need of the treatment regarding the age, dose, and duration of treatment before prescribing aripiprazole to children with bipolar disorder. Furthermore, precaution will be urged in the ongoing evaluation of involuntary, irregular muscle movements, especially in the face, weight gain, and adverse events related to sleepiness and tiredness. • Patient booklet will help patients to better understand and recognize specific adverse events.

VI.2.6 Planned post authorisation development plan

Not applicable.

VI.2.7 Summary of changes to the risk management plan over time

Not applicable.