VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Schizophrenia

The prevalence (proportion of the population found to have a disease) of schizophrenia (a disease characterised by symptoms such as hearing, seeing or sensing things which are not there, suspiciousness, mistaken beliefs, incoherent speech and behaviour and emotional flatness) is generally consider to be 1%. Schizophrenia affects men and women equally. The beginning is later in women than in men and it happens between late adolescence and the middle 30s. The schizophrenia it affects usually people from developed countries and it is found more often in black people than in white people.[1]

Bipolar I Disorder

The prevalence (proportion of the population found to have a disease) of bipolar I disorder (a disease characterised by 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) is generally consider to be 0.6%.

The beginning of this disease may happen from childhood to 50s. Most cases commence around 15-19 years and 20-24 years. Bipolar I disorder occurs equally in both sexes and no racial differences exist.[2]

VI.2.2 Summary of treatment benefits

Schizophrenia[3]

One study performed on 420 patients with aggravation of schizophrenia (a disease characterised by symptoms such as hearing, seeing or sensing things which are not there, suspiciousness, mistaken beliefs, incoherent speech and behaviour and emotional flatness) was found to be effective. One hundred fourty two patients (34%) completed the six weeks of treatment. The conclusion of this study indicates that aripiprazole is more effective than placebo in schizophrenia.

Bipolar I Disorder[3]

One study performed on 262 bipolar disorder (a disease characterised by 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) patients treated for 3 weeks with aripiprazole or placebo (substance with no medicinal effect) was found to be effective. The completion rate was higher with aripiprazole 42% (110 patients) than with placebo 21% (55 patients). The conclusion of this study indicates that aripiprazole is more effective than placebo in bipolar I disorder.

Another study performed on 161 patients with bipolar I disorder treated for 26 weeks with aripiprazole or placebo (substance with no medicinal effect) was found to be effective. Aripiprazole was superior to placebo on delaying the time to fall back into disease. Even weight gain occurred in 7 (13%) aripiprazole-treated patients, aripiprazole is more effective than placebo in bipolar I disorder.

VI.2.3 Unknowns relating to treatment benefits

According to the SmPC, there is limited information regarding aripiprazole use in hepatic impairment, elderly, children and adolescents with Tourette's disorder/irritability associated with autistic disorder 6 to 18 years/below 18 years of age and in patients with schizophrenia below 15 years of age. However, based on current knowledge, there is no indication to suggest that treatment results would be different in any subgroup of the target population.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Involuntary, irregular muscle movements, especially in the face (extrapyramidal symptoms, including tardive dyskinesia)	Caution is needed for adolescents aged 13 years and older 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 to not overcome the daily dose because involuntary, irregular muscle movements, especially in the face can appear. In this case, the dose may be decreased and the patient needs to be under observation. New-born babies, of mothers that have used aripiprazole in the last three months of their pregnancy may experience shaking, muscle stiffness and/or weakness.	Yes, by monitoring for early symptoms. Dose reduction may be considered.
High fever, stiff muscles, changes in pulse, heart rate and blood pressure (Neuroleptic Malignant Syndrome)	Caution is needed for patients who suffer from muscle stiffness or inflexibility with high fever, sweating, altered mental status, or very rapid or irregular heartbeat.	Yes, by monitoring for early symptoms and stopping the treatment when symptoms appear.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Convulsions (seizures)	Caution is needed for patients taking aripiprazole if they have a history of seizures.
High blood sugars(hyperglycaemia/diabetes)	Caution is needed for patients taking aripiprazole if they have high blood sugar (characterised by symptoms such as excessive thirst, passing of large amounts of urine, increase in appetite, and feeling weak) or a family history of diabetes. Ketoacidosis (ketones in blood and urine), coma and death have been reported in patients treated with aripiprazole.
Suicide-related events	During treatment with aripiprazole, the patient may have thoughts or feelings about hurting himself. Suicidal thoughts and behaviours have been reported.
Light-headedness or fainting when rising too quickly from sitting or lying position (orthostatic hypotension)	Some people using aripiprazole may feel dizzy, especially when getting up from a lying or sitting position.

Risk	What is known (Including reason why it is considered a potential risk)
Abnormal amount of the lipids in the blood (dyslipidemia)	No medical important differences in lipid levels are reported in studies made in patients taking aripiprazole or placebo (substance with no medicinal effect).

Missing information

Risk	What is known
Limited information on use in pregnant women (Safety in pregnancy and lactation)	The doctor has to be informed if the patient becomes pregnant or intends to become pregnant during treatment with aripiprazole because it can cause harm to the developing baby when administered to pregnant women. Newborn babies, of mothers that have used aripiprazole in the last trimester (last three months of their pregnancy) may experience shaking, muscle stiffness and/or weakness, sleepiness, agitation, breathing problems, and difficulty in feeding. In this case, the doctor should be announced. Women taking aripiprazole should not breastfeed because the medicine is crossing in the milk.
Limited information on use in children and adolescents (Safety in paediatrics)	The patients with schizophrenia (disease characterised by symptoms such as hearing, seeing or sensing things which are not there, suspiciousness, mistaken beliefs, incoherent speech and behaviour and emotional flatness) below 15 years of age should not take aripiprazole because safety and efficacy effects have not been demonstrated. The patients with manic episodes in Bipolar I Disorder (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) below 13 years of age should not use aripiprazole due to risk of experiencing adverse events and should not take more than 30 mg every day because adverse events can occur. Children and adolescents aged below 18 years with irritability associated with autistic disorder (condition characterised by symptoms such as aggression, tantrums, rapidly changing moods and self-injurious behavior) should not take aripiprazole because safety and efficacy effects have not been demonstrated. Children and adolescents 6 to 18 years with tics (sudden, repetitive, nonrhythmic movements that involves discrete muscle groups) and associated with Tourette's disorder (condition characterised by multiple physical (motor) tics and at least one vocal (phonic) tic) should not take aripiprazole because safety and efficacy effects have not been demonstrated. Studies involving adolescents aged 13 years and older with schizophrenia have been conducted. Some reactions were reported more frequently in adolescents receiving aripiprazole than in adults: somnolence/sedation, extrapyramidal disorders (involuntary, irregular muscle movements, especially in the face), dry mouth, increased appetite, orthostatic hypotension (light-headedness or fainting when rising too quickly from sitting or lying position). Low serum prolactin levels in adolescents seem to be higher in males than in fe-

Risk	What is known
	males. Regarding manic episodes in Bipolar I Disorder, the adverse events are similar in adults and adolescents aged 13 years and older. Studies involving adolescents with Tourette's disorder has been conducted. No long term data are available regarding the safety and the efficacy of aripiprazole in this disorder.

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.

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 minimisation measures are for the following risks:

Involuntary, irregular muscle movements, especially in the face (extrapyramidal symptoms, including tardive dyskinesia)

Healthcare Professional and patient education
Objective and rationale: To minimise the occurrence and to mitigate the impact of extrapyramidal symptoms by reinforcing the need for HCPs to carefully consider the indicated age range, dose and duration of treatment when prescribing aripiprazole to children with bipolar I disorder, and by helping patients be vigilant for specific adverse reactions.
Proposed action: HCP brochure to be provided to prescribing physicians to clearly highlight the need to carefully consider the indicated age range, dose and duration of treatment before prescribing aripiprazole to a paediatric patient with bipolar I disorder. Furthermore, vigilance will be urged in the on-going evaluation of extrapyramidal symptoms. Patient brochure will inform patients about the possible appearance of extrapyramidal symptoms, which are these symptoms and the importance of informing their HCP if any occur.

Weight gain

Healthcare Professional and patient education
Objective and rationale: To minimise the occurrence and to mitigate the impact of weight gain by reinforcing the need for HCPs to carefully consider the indicated age range, dose and duration of treatment when prescribing aripiprazole to children with bipolar I disorder, and by helping patients be vigilant for specific adverse reactions.
Proposed action: HCP brochure to be provided to prescribing physicians to clearly highlight the need to carefully consider the indicated age range, dose and duration of treatment before prescribing aripiprazole to a paediatric patient with bipolar I disorder. Furthermore, vigilance will be urged in the on-going evaluation of weight gain.

Healthcare Professional and patient education
Patient brochure will inform patients about the possible appearance of weight gain and the importance of informing their HCP if this occurs.

Sleepiness/tiredness (somnolence/fatigue)

Healthcare Professional and patient education
Objective and rationale: To minimise the occurrence and to mitigate the impact of adverse events related to somnolence and fatigue by reinforcing the need for HCPs to carefully consider the indicated age range, dose and duration of treatment when prescribing aripiprazole to children with bipolar I disorder, and by helping patients be vigilant for specific adverse reactions.
Proposed action: HCP brochure to be provided to prescribing physicians to clearly highlight the need to carefully consider the indicated age range, dose and duration of treatment before prescribing aripiprazole to a paediatric patient with bipolar I disorder. Furthermore, vigilance will be urged in the on-going evaluation of adverse events related to somnolence and fatigue. Patient brochure will inform patients about the possible appearance of adverse events related to somnolence and fatigue and the importance of informing their HCP if this occurs.

VI.2.6 Planned post authorisation development plan

No post-authorisation safety or efficacy studies are ongoing or are planned to be conducted for aripiprazole.

VI.2.7 Summary of changes to the Risk Management Plan over time

Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
1.0	02-06-2014	Extrapyramidal symptoms, including tardive dyskinesia Neuroleptic Malignant Syndrome Seizures Hyperglycaemia/diabetes Suicide-related events Orthostatic hypotension Dyslipidemia Weight gain Somnolence/fatigue Cardiovascular-related disorders Conduction abnormalities Low prolactin in paediatric patients Dysphagia (primarily applies to schizophrenia population) Use in patients with lactose intolerance	Not approved

Version	Date	Safety Concerns	Comment
		ADHD comorbidity Drug interactions Increased mortality and CVA in elderly patients with dementia Pathological gambling Serotonin syndrome Hepatic adverse events Safety in pregnancy and lactation Safety in paediatrics	
2.0	18-12-2014	Growth has been added as a new important potential risk. A new CMS was added for this procedure. The mock ups for additional RMMs have been attached.	The safety concerns were updated according to Assessment report on procedure DK/H/2423/001-003/DC. Not approved
3.0	30-04-2015	In Part II Module SVIII, to be in line with the Innovator, only five safety concerns from the important potential risks were categorized like this (Seizures, Hyperglycemia/diabetes, Suicide-related events, Orthostatic hypotension, Dyslipidemia), the rest of them were categorized as non-important potential risks. In section VI.2.4 only five important potential safety concerns (Seizures, Hyperglycemia/diabetes, Suicide-related events, Orthostatic hypotension, Dyslipidemia) were mentioned. The other safety concerns not categorized as important were deleted. Two new CMSs were added: LT for the 10 mg strength and CY for the 30 mg strength.	The section VI.2.4 was updated according to Assessment Report on procedure DK/H/2423/001-003/DC