VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Schizophrenia typically presents between the ages of 15 and 45, and includes positive symptoms such as delusions, hallucinations and disorganized thoughts, negative symptoms such as social withdrawal and lack of motivation, and disturbances in basic cognitive functions such as working memory (Grady et al, 2003). Its annual incidence averages 15 per 100,000, the point prevalence averages approximately 4.5 per population of 1000, and the risk of developing the illness over one's lifetime averages 0.7% (Tandon et al, 2008).

Bipolar disorder (BP) is a chronic, multistage mood disorder. BP type I (BP-I) is characterised by at least one manic episode, with periods of major depression. Its main symptoms in children and adolescents are poor concentration, little need for sleep, poor temper control, reckless behaviour and lack of self-control, euphoria/very elevated mood, grandiosity and irritability (Uttley et al, 2013). BPs type I and II affect about 2% of the world's population, with subthreshold forms of the disorder affecting another 2% (Geddes et al, 2013). In the case of BP-I, the aggregate lifetime prevalence is 0.6% and twelve-month prevalences is 0.4% (Merikangas et al, 2011). Approximately half of those with BP-I and subthreshold BP report onset before age 25 years, the mean (SE) ages at onset was 18.4 (0.7) years (Merikangas et al, 2011).

VI.2.2 Summary of treatment benefits

Adults:

Schizophrenia:

The efficacy of aripiprazole has been demonstrated in three short-term (four- and six-week) trials involving 1,228 patients. Significant improvements in symptoms of schizophrenia were observed in patients receiving aripiprazole (10, 15, 20 and 30 mg) versus those receiving placebo. The drug was significantly more effective than placebo in preventing relapse in patients with stable chronic schizophrenia in a 26-week, randomised trial. In a 52-week trial in patients with acute relapse of schizophrenia, the percentage of responders was similar between aripiprazol and haloperidol (73 vs. 77%). The overall completion rate was significantly higher for patients on aripiprazole (43%) than for haloperidol (30%). Scores in rating scales used as secondary endpoints showed a significant improvement over haloperidol.

Manic episodes in Bipolar I Disorder:

The efficacy of aripiprazole monotherapy in BP-I was demonstrated in four (two 3-week and two 12-week) placebo or active-controlled trials. Aripiprazole was superior to placebo in reduction of manic symptoms over 3 weeks and similar maintenance of effect to lithium or haloperidol at week 12. Also, addition of aripiprazol as adjunctive therapy resulted in superior efficacy in reduction of manic symptoms in patients partially non-responsive to lithium or valproate monotherapy for 2 weeks.

Both as monotherapy (26-week, placebo-controlled trial, followed by a 74-week extension) and as adjunctive therapy to lithium or valproate (52-week, placebo-controlled trial) aripiprazole was superior to placebo in preventing recurrence into mania but failed to demonstrate superiority over placebo in preventing recurrence into depression.

Paediatric population

Schizophrenia in adolescents

In a 6-week placebo-controlled trial involving 302 schizophrenic adolescent patients (13-17 years), aripiprazole significantly improved psychotic symptoms compared to placebo. In a sub-analysis (ages of 15 to 17 years) maintenance of effect was observed over the 26-week open-label extension trial.

Manic episodes in BP-I in children and adolescents

In a 30-week placebo-controlled trial involving 296 children and adolescents (10-17 years), with BP-I, including 139 patients with co-morbid diagnosis of ADHD, aripiprazole was superior to placebo in symptoms improvement in the patients with associated co-morbidity of ADHD compared to the group without ADHD, where there was no difference from placebo.

A long-term maintenance trial was performed in patients with a stable response to aripiprazol (13-26 week) who were either maintained on aripiprazole or substituted to placebo for further 16 weeks. Hazard ratio for relapse within 16 weeks (aripiprazole/placebo) was 0.57 (non-statistically significant difference).

VI.2.3 Unknowns relating to treatment benefits

Treatment of schizophrenia in adolescents aged 15 years and older is effective in a dose range of 10 to 30 mg/day. Enhanced efficacy at doses higher than a daily dose of 10 mg has not been demonstrated although individual patients may benefit from a higher dose.

The treatment of BP-I in adolescents aged 13 years and older must not exceed 12 weeks and doses higher than 10 mg/day should only be used in exceptional cases and with close clinical monitoring (due to substantially higher incidence of significant undesirable effects without proven enhanced efficacy).

Effectiveness in the treatment of schizophrenia and BP-I in patients aged 65 years and older has not been established.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	**What is known**	**Preventability**
Movement disorders, including involuntary, repetitive body movements with slow or belated onset (Extrapyramidal syndrome, including tardive dyskinesia)	Blockade of dopamine receptors in the basal ganglia by dopamine antagonists (i.e. haloperidol. olanzapine, aripiprazole, etc.) may induce Parkinson-like symptoms such as slow movement, tremor, psychomotor agitation, etc. These neurological disorders most frequently occur as the result of long-term or high-dose use of antipsychotic drugs. In the case of aripiprazole, in clinical trials of one year or less duration there were uncommon reports of treatment emergent dyskinesia (repetitive body movements with slow or belated onset) during treatment. These symptoms can temporally deteriorate or can even arise after discontinuation of	By using the product with caution following the SPC and PIL indications, if signs and symptoms of these or other movement disorders appear in a patient taking aripiprazole, dose reduction and close clinical monitoring should be considered (including therapy discontinuation if necessary)

Risk	What is known	Preventability
	treatment with aripiprazole. In paediatric clinical trials, akathisia (a syndrome characterized by an inability to remain motionless) and parkinsonism were also observed.	
Reaction to neuroleptic drugs that causes a combination of fever, muscle stiffness, faster breathing, excessive sweating/salivation, reduced consciousness and sudden changes in blood pressure and heart rate (Neuroleptic Malignant Syndrome, NMS)	NMS is an uncommon and potentially fatal side effect of antipsychotic medications. A sudden and marked reduction in dopaminergic activity secondary to neuroleptic-induced dopamine blockade is considered the key mechanism mediating the symptoms of the syndrome. Virtually all neuroleptics, including atypical antipsychotics, are capable of inducing this syndrome and the incidence of NMS has been estimated to be between 0.2 and 3.23 percent of psychiatric inpatients receiving neuroleptics. Rare cases of NMS were reported during treatment with aripiprazole. If a patient develops signs and symptoms indicative of NMS, or presents with unexplained high fever without additional clinical manifestations of NMS, all antipsychotic medicinal products, including aripiprazole, must be discontinued.	By using the product with caution following the SPC and PIL indications. If signs and symptoms of NMS appears aripiprazole must be discontinued.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Seizures	Seizures are provoked by a sudden, abnormal electrical activity in the brain. Seizures can provoke convulsions or just have mild symptoms (i.e. patient feels confused and wanders around). Most last a short time (a few seconds or minutes) and stop by themselves. About 10% of the population will experience a seizure in their lifetime. Most of these seizures are directly attributable to an acute, active insult to the central nervous system and are often referred as acute symptomatic seizures. Acute symptomatic seizures represent ~40% of all seizures and have an incidence of 29 to 39 per 100,000 person years Acute symptomatic seizures

Risk	What is known (Including reason why it is considered a potential risk)
	can be provoked by several medicines, i.e. antidepressants, lidocaine, or all the antipsychotics. For this reason, aripiprazole, an atypical antipsychotic, should be used with caution in patients who have a history of seizure disorder or have conditions associated with seizures.
Hyperglycemia/diabetes	Hyperglycaemia, 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 family history of diabetes. In clinical trials with aripiprazole, there were no significant differences in the incidence rates of hyperglycaemia-related adverse reactions (including diabetes) or in abnormal glycaemia laboratory values compared to placebo. Precise risk estimates for hyperglycaemia-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 hyperglycaemia (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 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. Close supervision of high-risk patients should accompany antipsychotic therapy. Results of an epidemiological study suggested that there was no increased risk of suicidality with aripiprazole compared to other antipsychotics among adult patients with schizophrenia or bipolar disorder. There are insufficient paediatric data to evaluate this risk in younger patients (below 18 years of age), but there is evidence that the risk of suicide persists beyond the first 4 weeks of treatment for atypical antipsychotics, including aripiprazole.
Orthostatic hypotension (dizzy spells)	Many antipsychotics can cause orthostatic hypotension, colloquially known as dizzy spells, and that consists in a transitory fall in blood pressure when suddenly the person stands up. This adverse effect can difficult the process to find the dose necessary to control psychotic symptoms. The risk of orthostatic hypotension associated with antipsychotic therapy is increased in patients with disorders of the autonomic nervous system, fluid imbalance and concomitant drug therapy that affect haemodynamic tone.
Dyslipidemia	Treatment with antipsychotic medications may be associated with increased risks for dyslipidemia. Possible underlying causes of lipid dysregulation include weight gain, dietary changes, and glucose intolerance. Ziprasidone, risperidone, and aripiprazole appear to be associated with a relatively low risk for hyperlipidemia when compared to other antipsychotic medications. Comparisons between aripiprazole and placebo in the proportions of patients

Risk	What is known (Including reason why it is considered a potential risk)
	experiencing potentially clinically significant changes in routine laboratory and lipid parameters revealed no medically important differences.

Missing information

Risk	What is known
Limited information on use in pregnancy and lactation.	There are no adequate and well-controlled trials of aripiprazole in pregnant women. Animal studies could not exclude potential developmental toxicity. Due to insufficient safety information in humans and concerns raised by animal reproductive studies, this medicinal product should not be used in pregnancy unless the expected benefit clearly justifies the potential risk to the foetus. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder in neonates exposed to antipsychotics (including aripiprazole) during the third trimester of pregnancy. Consequently, newborns should be monitored carefully. Aripiprazole is excreted in human breast milk. Patients should not to breast feed if they are taking aripiprazole.
Limited information on use in paediatric patients	Due to insufficient data on safety and efficacy, aripiprazole is not recommended for use in patients with schizophrenia below 15 years of age or in the treatment of manic episodes in Bipolar I Disorder in patients below 13 years of age. In this last indication, the treatment duration should not exceed 12 weeks and doses higher than 10 mg/day should only be used in exceptional cases and with close clinical monitoring, due to substantially higher incidence of significant undesirable effects.

VI.2.5 Summary of risk minimisation measures by safety concern

The Summary of Product Characteristics (SmPC) of Aripiprazole, which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them, as well as an abbreviated version of this in the form of a package leaflet (PL), can be found in the Health Agencies web pages and are also included in Annex II of this RMP.

Aripiprazole has special requirement conditions and restrictions for its safe and effective use and thus additional risk minimisation measures are deemed necessary.

VI.2.6 Planned post authorisation development plan

Currently, no further post-authorisation efficacy studies are planned.

No study have been imposed as a condition of the marketing authorisation

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

Not applicable. This is the first version of Aripiprazole RMP.