sRMP

DK/H/2441/001-003/DC

aripiprazole

VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Schizophrenia is a mental disorder affecting about 7 per thousand of the adult population, mostly in the age group 15-35 years. Though the incidence (how frequently an event occurs in a population over a period of time) is low (3-10,000), the prevalence (the number of cases in a given population) is high due to chronicity. It may cause delusions, paranoia, hallucinations, disordered thinking and behavior, and catatonia. The symptoms usually begin between the ages of 16-30.

People with schizophrenia -- the most chronic and disabling of the major mental illnesses -- often have problems functioning in society, at work, at school, and in relationships. Schizophrenia can leave its sufferer frightened and withdrawn. It is a life-long disease that cannot be cured but usually can be controlled with proper treatment. It is characterized by disassociated thought process and disintegration of emotional responses. Schizophrenics may experience symptoms like hallucinations, paranoia, delusions, or disorganized speech and thinking.
The exact cause of schizophrenia is not yet known. Researchers have uncovered a number of factors that appear to play a role in the development of schizophrenia, including genetics, brain chemistry, brain abnormality and environmental factors.

Bipolar disorder, formerly called manic depression, is a mental illness that brings severe high and low moods and changes in sleep, energy, thinking, and behavior. People who have bipolar disorder can have periods in which they feel overly happy and energized (**mania**) and other periods of feeling very sad, hopeless, and sluggish (**depression**). In between those periods, they usually feel normal. Bipolar disorder can also cause changes in energy and behavior. Bipolar disorder is not the same as the normal ups and downs everyone goes through. Bipolar symptoms are more powerful than that. They can damage relationships and make it hard to go to school or keep a job. They can also be dangerous. Some people with bipolar disorder try to hurt themselves or attempt suicide. People with bipolar disorder can get treatment. With help, they can get better and lead successful lives.

Anyone can develop bipolar disorder. The illness usually lasts a lifetime.

VI.2.2 Summary of treatment benefits

Aripiprazole is one of a group of medicines called antipsychotics.

It is used to treat adults and adolescents aged 15 years and older who suffer from a disease characterized by symptoms such as hearing, seeing or sensing things which 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. The recommended starting dose for aripiprazole is 10 or 15 mg/day with a maintenance dose of 15 mg/day administered on a once-a-day schedule without regard to meals. Aripiprazole is effective in a dose range of 10 to 30 mg/day. Enhanced efficacy at doses higher than a daily dose of 15 mg has not been demonstrated although individual patients may benefit from a higher dose. The maximum daily dose should not exceed 30 mg.

Aripiprazole is further used to treat adults and adolescents aged 13 years and older who suffer from 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 the treatment with aripiprazole. The recommended starting dose for aripiprazole is 15 mg administered on a once-a-day schedule without regard to meals as monotherapy or combination therapy. Some patients may benefit from a higher dose. The maximum daily dose should not exceed 30 mg.

VI.2.3 Unknowns relating to treatment benefits

Aripiprazole is not recommended for use in patients with schizophrenia below 15 years of age due to insufficient data on safety and efficacy. Younger patients (<13 years) with bipolar disorder are at increased risk of experiencing adverse events associated with aripiprazole.

In patients with severe hepatic impairment, the data available are insufficient to establish recommendations. In these patients dosing should be managed cautiously.

Very limited safety data are available on concomitant use of aripiprazole and stimulants; therefore, extreme caution should be taken when these drugs are co-administered.

There are no adequate and well-controlled trials of aripiprazole in pregnant women. Patients should be advised not to breast feed if they are taking aripiprazole.

VI.2.4 Summary of safety concerns

Important identified risks

Important identified risks		
Risk	**What is known**	**Preventability**
Safety concern in lay language ***(medical term)***	**Brief summary in lay language**	**Whether risk can be minimised or mitigated, and how**
Inability to initiate movement, inability to remain motionless *(Extrapyramidal symptoms)* Involuntary, repetitive body movements *(Tardive dyskinesia)*	In clinical trials of one year or less duration, there were uncommon reports of treatment emergent dyskinesia during treatment with aripiprazole. In paediatric clinical trials of aripiprazole akathisia (inability to sit still or remain motionless) and parkinsonism were observed.	People who experienced uncontrolled twitching or jerking, or a constant urge to move will taking tablets should seek advice from a doctor. It may be necessary to close monitoring symptoms or discontinue drug administration.

A combination of fever, severe muscle stiffness, sweating or a lowered level of consciousness *(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, myoglobinuria (rhabdomyolysis), and acute renal failure. However, elevated creatine phosphokinase and rhabdomyolysis, not necessarily in association with NMS, have also been reported.	People who experienced muscle stiffness or inflexibility with high fever, sweating, altered mental status, or very rapid or irregular heart beat should immediately seek advice from a doctor. Treatment may need to be discontinued as the above mentioned adverse events may be signs of a potentially fatal symptom complex associated with antipsychotic medicinal products.

Important potential risks	
Risk	**What is known (Including reason why it is considered a potential r isk)**
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.
Hyperglycaemia/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 (patients treated with substance containing no medication). 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 adverse 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 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.
Orthostatic hypotension	Orthostatic hypotension, also known as postural hypotension, is a form of hypotension in which a person's blood pressure suddenly falls when standing up or stretching. In clinical trials of aripiprazole orthostatic hypotension was reported commonly (affects up to 1 in 10 people).
Dyslipidaemia	Dyslipidemia is an abnormal amount of lipids (e.g. cholesterol and/or fat) in the blood. In developed countries, most dyslipidemias are hyperlipidemias; that is, an elevation of lipids in the blood. Aripiprazole may be associated with changed in levels of total cholesterol, triglycerides, HDL and LDL although with a lower risk than other commonly used atypical antipsychotics.
Weight gain*	Weight gain is commonly seen in schizophrenic and bipolar mania patients due to comorbidities, use of antipsychotics known to cause weight gain, poorly managed life-style, and might lead to severe complications. Weight gain has been reported post-marketing among patients prescribed aripiprazole. When seen, it is usually in those with significant risk factors such as history of diabetes, thyroid disorder or pituitary adenoma. In clinical trials aripiprazole has not been shown to induce clinically relevant weight gain in adults. In clinical trials of adolescent patients with bipolar mania, aripiprazole has been shown to be associated with weight gain after 4 weeks of treatment. Weight gain should be monitored in adolescent patients with bipolar mania. If weight gain is clinically significant, dose reduction should be considered.
Fatigue and somnolence*	In the paediatric population somnolence and fatigue were observed more frequently in patients with bipolar disorder compared to patients with schizophrenia.

* Although these safety concerns do not appear to the "Summary of activities in the risk managemen t plan" they are presented here as there are additional risk minimisation measures applicable to them .

Important missing information	
Risk	**What is known**
Safety in pregnancy and lactation	<u>Pregnancy</u> There are no adequate and well-controlled trials of aripiprazole in pregnant women. Congenital anomalies have been reported; however, 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, this medicinal product should not be used in pregnancy unless the expected benefit clearly justifies the potential risk to the foetus. Neonates exposed to antipsychotics (including aripiprazole) during the third 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. <u>Breast-feeding</u> Aripiprazole is excreted in human breast milk. Patients should be advised not to breast feed if they are taking aripiprazole.
Safety in paediatric patients	Aripiprazole is not recommended for use in patients with schizophrenia below 15 years of age due to insufficient data on safety and efficacy. Younger patients with bipolar disorder are at increased risk of experiencing adverse events associated with aripiprazole. Therefore, aripiprazole is not recommended for use in patients below 13 years of age.

VI.2.5 Summary of risk minimisation measures by safety concern

This medicine has special conditions for its safe and effective use (additional risk minimisation measures).

These additional risk minimisation measures are for the following risks:

- **Use in adolescents 13 years and older for bipolar I disorder with special attention to weight gain, extrapyramidal symptoms, somnolence and fatigue.**

Risk minimisation measure(s)
These measures will enable the HCP to understand what [aripiprazole] is used for, be aware of important risks of weight gain, extrapyramidal symptoms, somnolence and fatigue in particular in the adolescents 13 years and older and how they should be mitigated and managed and understand what other tools are available to communicate and remind patients of these risks.
• Summary description of main additional risk minimisation measures – Aripiprazole is associated with the risks of weight gain, extrapyramidal symptoms, somnolence and fatigue in adolescents 13 years and older. It is therefore of great importance to adhere to the advice given in the product information.
Weight gain, extrapyramidal symptoms, somnolence and fatigue Healthcare Professional and patient education Objective and rationale Patients and HCPs to understand the risks of weight gain, extrapyramidal symptoms, somnolence and fatigue in adolescents 13 years and older and the procedures related to the appropriate management of this risk to minimise its occurrence and its severity. Proposed action: • HCP educational materials to be provided to prescribing physicians and pharmacists including advice on: ✓ aripiprazole therapeutic indications;

Risk minimisation measure(s)
✓ the populations that aripiprazole should be used; ✓ the recommended posology (10 mg/day for the paediatric population); ✓ the safety and tolerability profile of aripiprazole in particular at doses higher than the recommended and ✓ the communication of these risks to the patients and caregivers • Patients/caregivers brochure will have the following aims: ✓ familiarization with aripiprazole (why and how it is used); ✓ education of patients that aripiprazole should not be used below 13 years of age; ✓ instructions on the recommended dosages; ✓ information on the safety and tolerability profile of aripiprazole and ✓ familiarization with the symptoms that might be encountered

VI.2.6 Planned post authorisation development plan

Not applicable

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

Version	Date	Safety concerns	Change
1.0	04.06.2014	**Important identified risks** • Extrapyramidal Symptoms (EPS), including tardive dyskinesia • Neuroleptic Malignant Syndrome (NMS) **Important potential risks** • Seizures • Hyperglycaemia/diabetes • Suicide-related events • Orthostatic hypotension • Dyslipidaemia • Cardiovascular related disorders • Conduction abnormalities • Weight gain • Fatigue and somnolence • Dysphagia • Increased mortality and cerebrovascular adverse reactions in elderly patients with dementia • Concomitant use with potent CYP3A4 or CYP2D6 inhibitors or potent CYP3A4 inducers • Patients with ADHD comorbidity • Aspartame (applicable only for orodispersible tablets) **Missing information** • Pregnancy and breast-feeding	Initial version

		• Paediatric patients with schizophrenia (<15 years of age) and paediatric patients with bipolar disorder (<13 years of age)	
2.0	17.12.2014	**Important identified risks** • Extrapyramidal Symptoms (EPS), including tardive dyskinesia • Neuroleptic Malignant Syndrome (NMS) **Important potential risks** • Seizures • Hyperglycaemia/diabetes • Suicide-related events • Orthostatic hypotension • Dyslipidaemia • Cardiovascular related disorders • Conduction abnormalities • Weight gain • Fatigue and somnolence • Dysphagia (primarily applies to schizophrenia patients) • Increased mortality and cerebrovascular adverse reactions in elderly patients with dementia • Drug interactions • Patients with ADHD comorbidity • Aspartame (applicable only for orodispersible tablets) • Growth • Low prolactin in paediatric patients • Pathological gambling • Serotonin syndrome • Hepatic adverse events **Missing information** • Safety in pregnancy and lactation • Safety in paediatric patients with schizophrenia (<15 years of age) and paediatric patients with bipolar disorder (<13 years of age)	Implementation of Day 70 +100 assessors' comments for the DCP procedures DK/H/2440/001-004/DC and DK/2441/001-003/DC Implementation of Day 80 comments f or the Centralized p rocedure EMEA/H/C/004008
3.0	13.02.2015	**Important identified risks** • Extrapyramidal Symptoms (EPS), including tardive dyskinesia • Neuroleptic Malignant Syndrome (NMS) **Important potential risks** • Seizures • Hyperglycaemia/diabetes • Suicide-related events • Orthostatic hypotension • Dyslipidaemia **<u>Other potential risks</u>**	Implementation of CHMP Day 150 comments as well as assessment report as endorsed by PRAC for the Centralized procedure EMEA/H/C/004008

		• Cardiovascular related disorders • Conduction abnormalities • Weight gain • Fatigue and somnolence • Dysphagia (primarily applies to schizophrenia patients) • Increased mortality and cerebrovascular adverse reactions in elderly patients with dementia • Drug interactions • Patients with ADHD comorbidity • Aspartame (applicable only for orodispersible tablets) • Growth • Low prolactin in paediatric patients • Pathological gambling • Serotonin syndrome • Hepatic adverse events **Missing information** • Safety in pregnancy and lactation • Safety in paediatric patients with schizophrenia (<15 years of age) and paediatric patients with bipolar disorder (<13 years of age)	
4.0	15.04.2015	**Important identified risks** • Extrapyramidal Symptoms (EPS), including tardive dyskinesia • Neuroleptic Malignant Syndrome (NMS) **Important potential risks** • Seizures • Hyperglycaemia/diabetes • Suicide-related events • Orthostatic hypotension • Dyslipidaemia **Missing information** • Safety in pregnancy and lactation • Safety in paediatric patients with schizophrenia (<15 years of age) and paediatric patients with bipolar disorder (<13 years of age)	Implementation of comments from CHMP on CHMP (Co-) Rapporteur AR Implementation of Day 180 assessors' comments for the DCP procedures DK/H/2440/001-004/DC and DK/2441/001-003/DC