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Summary of the risk management plan (RMP) for Aripiprazole Sandoz (aripiprazole)

This is a summary of the risk management plan (RMP) for Aripiprazole Sandoz, which details the measures to be taken in order to ensure that Aripiprazole Sandoz is used as safely as possible. For more information on RMP summaries, see here.

This RMP summary should be read in conjunction with the EPAR summary and the product information for Aripiprazole Sandoz, which can be found on Aripiprazole Sandoz's EPAR page.

Overview of disease epidemiology

Aripiprazole Sandoz is a medicine used for the treatment of schizophrenia and bipolar I disorder.

Schizophrenia is a mental illness with a number of symptoms, including disorganised thinking and speech, hallucinations (hearing or seeing things that are not there), suspiciousness and delusions (false beliefs) that typically appear in adulthood. Men and women are affected equally though symptoms appear slightly earlier in men than in women. It is estimated that there are 24 million people with schizophrenia worldwide. In Europe about 15 in every 100,000 people (0.015%) are newly diagnosed with schizophrenia each year, and it is thought that about 1 in every 100 people (1%) have the disease at any one time.

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. Up to 2.4% of people worldwide are affected with bipolar I disorder at some point in their life.

Summary of treatment benefits

Aripiprazole Sandoz contains the active substance aripiprazole and is available as tablets (5, 10, 15, 20 and 30 mg). Aripiprazole Sandoz is a 'generic' and a 'hybrid' medicine. This means that it is similar to a 'reference medicine' already authorised in the European Union (EU), but it contains aripiprazole at a new strength in addition to existing strengths: while the reference medicine, Abilify, is available as 5, 10, 15 and 30 mg, Aripiprazole Sandoz is also available as 20 mg tablets.

Because Aripiprazole Sandoz is bioequivalent to the reference medicine, its benefits and risks are taken as being the same as the reference medicine's. The company carried out 'bioequivalence' studies to show that Aripiprazole Sandoz is bioequivalent to the reference medicine, Abilify. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

Unknowns relating to treatment benefits

There are no adequate and well-controlled trials of aripiprazole in pregnant and breastfeeding women. In addition, Aripiprazole Sandoz is not recommended for use in patients with schizophrenia below 15 years of age due to insufficient data on safety and efficacy.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Movement disorders including tardive dyskinesia (abnormal movements of the tongue, face, arms, or body)	Patients on Aripiprazole Sandoz are at risk of developing movement disorders (including tardive dyskinesia). There have been uncommon reports of tardive dyskinesia in clinical trials lasting up to one year. The likelihood of tardive dyskinesia becoming irreversible appears to increase with treatment duration and the total cumulative dose. Less commonly, the condition develops after relatively brief treatment periods at low doses. In paediatric clinical trials of aripiprazole with adolescents aged 13 years and older, akathisia (inability to sit still or remain motionless) and parkinsonism were observed especially with daily doses of 30 mg.	Consultation with the doctor before starting treatment regarding the presence of involuntary, irregular muscle movements, especially in the face, is required. Aripiprazole should be prescribed for the shortest duration necessary to produce a satisfactory clinical response to minimize the occurrence of movement disorders. If signs and symptoms appear, dose reduction or discontinuation should be considered.
Life-threatening neurological disorder called neuroleptic malignant syndrome	Neuroleptic malignant syndrome (NMS) is a potentially fatal condition associated with antipsychotic medicines. In clinical trials, rare cases of NMS were reported during treatment with aripiprazole. The symptoms may include fever, muscle stiffness, altered mental status, evidence of autonomic instability (irregular pulse or blood pressure), and acute kidney failure.	Doctors should monitor patients for symptoms, particularly early in the course of treatment. Patients who experienced muscle stiffness with high fever, sweating, altered mental status, or very rapid or irregular heart beat should immediately seek advice from a doctor. If a patient develops signs and symptoms indicative of NMS, or presents with unexplained high fever without additional clinical manifestations of NMS, all antipsychotic medicines, including Aripiprazole Sandoz, must be discontinued.

Important potential risks

Risk	What is known
Fits (seizures)	Fits (seizures) or convulsions have been reported in up to 1 in 100 patients taking aripiprazole. Therefore, Aripiprazole Sandoz should be used with caution in patients with a history of seizures or conditions with lower seizure threshold (e.g., Alzheimer dementia), which may be more prevalent in patients 65 years or older.
High blood levels of glucose (sugar) (hyperglycaemia and diabetes mellitus)	Blood sugar fluctuation and high blood sugar (hyperglycaemia) have been reported with atypical antipsychotic agents, including aripiprazole. 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 with placebo (a dummy treatment). Patients treated with any antipsychotic agents, including aripiprazole, should be observed for signs and symptoms of hyperglycaemia (such as excessive thirst, passing large amounts of urine, increased appetite and weakness) and patients with diabetes or with risk factors for diabetes should be monitored regularly for worsening of glucose control.
Suicide-related events	Suicide or thoughts of suicide are common in patients with psychotic illnesses and mood disorders, and in some cases has been reported early after starting or switching of antipsychotic therapy, including aripiprazole. Results of an epidemiological study suggested that there was no increased risk of suicidality with aripiprazole compared with other antipsychotics among adult patients with schizophrenia or bipolar disorder. Patients who are at high risk of suicidal behaviour should be closely monitored.
Low blood pressure upon standing (orthostatic hypotension)	When standing up quickly, it may take a second or two for the body to make adjustments to constrict blood vessels and push blood up to the brain. If there is a delay, then this time of relative low blood pressure (postural hypotension) may cause symptoms such as light headedness, falls and visual blurring. Postural hypotension has been reported with aripiprazole.
Abnormal amount of lipids in the blood (dyslipidaemia)	Dyslipidaemia has been reported in patients treated with atypical antipsychotics, including aripiprazole. However, there were no significant differences in the incidence rates of dyslipidaemia compared with placebo.
Weight gain	Weight gain is known to occur with certain antipsychotics; however it is also commonly seen in patients with schizophrenia and bipolar disorder due to other factors such as certain diseases or a poorly managed life-style. 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 (benign tumour of the pituitary gland,

	a gland located at the base of the brain). In clinical trials aripiprazole has not been shown to induce clinically relevant weight gain in adults. In clinical trials of adolescents with bipolar mania, aripiprazole has been shown to be associated with weight gain after 4 weeks of treatment. Weight gain should be monitored in adolescents with bipolar mania. If weight gain is clinically significant, dose reduction should be considered.
Sleepiness / tiredness (somnolence / fatigue)	In the paediatric population, somnolence and fatigue (tiredness) were observed more frequently in patients with bipolar disorder compared with patients with schizophrenia.

Missing information

Risk	**What is known**
Safety in pregnancy and lactation	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 doctor 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 Sandoz 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 movement disorders and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, increased or reduced muscle strength, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully. Aripiprazole is excreted in human breast milk and patients should be advised not to breastfeed if they are taking aripiprazole.
Safety in paediatrics (children)	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 for bipolar I disorder.

Summary of risk minimisation measures by safety concern

All medicines have a summary of product characteristics (SmPC) which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, and also describes the risks and recommendations for minimising them. Information for patients is available in lay language in the package leaflet. The measures listed in these documents are known as 'routine risk minimisation measures'.

The SmPC and the package leaflet are part of the medicine's product information. The product information for Aripiprazole Sandoz can be found on Aripiprazole Sandoz's EPAR page.

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimisation measures). Full details on these conditions and the key elements of any educational material can be found in Annex II of the product information which is published on Aripiprazole Sandoz's EPAR page; how they are implemented in each country however will depend upon agreement between the marketing authorisation holder and the national authorities.

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, movement disorders, somnolence and fatigue.

Risk minimization measure(s)
Summary description of main additional risk minimisation measures: Educational material for healthcare professionals (HCPs), patients and caregivers.
Objective and rationale: Patients and healthcare professionals to understand the possible risks of movement disorders, weight gain and increased drowsiness and fatigue in the paediatric population and the procedures related to the appropriate management of these risks to minimise their occurrence and severity.
Proposed action:
Healthcare professionals and patients educational materials will be provided to prescribing physicians and patients or their caregivers to convey the following key messages regarding the safety profile of aripiprazole in adolescents aged 13 years and older with respect to movement disorders, weight gain, somnolence and fatigue in the treatment for up to 12 weeks of moderate to severe manic episodes in bipolar I disorder: • Treatment with aripiprazole has been associated with dose-related movement disorders such as akathisia, parkinsonism and tardive dyskinesia. • Weight gain has been reported post-marketing among patients prescribed aripiprazole. Significant risk factors for weight gain are: – history of diabetes; – thyroid disorder; – pituitary adenoma. • There is a need for close monitoring and dosage adjustment if signs and symptoms of movement disorders and clinically significant weight gain appear in a patient taking Aripiprazole Sandoz. • In the paediatric population, somnolence and fatigue were observed more frequently in patients

with bipolar disorder compared with patients with schizophrenia.

- The indicated age range is 13–17 years and aripiprazole is not recommended for use in patients below 13 years of age due to safety concerns.

There is a greater potential for occurrence of adverse events with doses higher than 10 mg/day.

Planned post-authorisation development plan

None.

Summary of changes to the risk management plan over time

Not applicable.

This summary was last updated in 07-2015.