

VI.2 Elements for a public summary

For sake of completeness, with reference to article 11 of the Directive 2001/83, the applicant retains the option to carve out the indication for bipolar disorder in the national marketing authorisations, if carving is necessary to avoid infringement of national patents in certain countries. Carving out will not have any negative impact on risk assessment.

VI.2.1 Overview of disease epidemiology

Incidence and prevalence of target indication	Schizophrenia is a mental disorder characterized by a breakdown of thought processes and by impaired emotional responses. Common symptoms are delusions including paranoia and auditory hallucinations, disorganized thinking reflected in speech, and a lack of emotional intelligence. It accounts for 20 % of all chronic medical disability and affects 1% of the population worldwide, with equal frequency in men and women. The onset of symptoms typically occurs in young adulthood, with a global lifetime prevalence of about 0.3–0.7%. Diagnosis is based on observed behavior and the patient's reported experiences. Bipolar disorder, also known as bipolar affective disorder, manic-depressive disorder, or manic depression, is a mental illness classified by psychiatry as a mood disorder. Individuals with bipolar disorder experience episodes of an elevated or agitated mood known as mania alternating with episodes of depression. 2.4 percent of the world's population may have some form of the disease. Mania can occur with different levels of severity. At milder levels of mania, known as hypomania, individuals appear energetic, excitable, and may be highly productive. As mania becomes more severe, individuals begin to behave erratically and impulsively, often making poor decisions due to unrealistic ideas about the future, and may have great difficulty with sleep. At the most severe level, individuals can experience distorted beliefs about the world known as psychosis. A study from first admission for mania or mixed episode (representing the hospitalized and therefore most severe cases) found that 50% achieved syndromal recovery (no longer meeting

	criteria for the diagnosis) within six weeks and 98% within two years. Within two years, 72% achieved symptomatic recovery (no symptoms at all) and 43% achieved functional recovery (regaining of prior occupational and residential status). However, 40% went on to experience a new episode of mania or depression within 2 years of syndromal recovery, and 19% switched phases without recovery.

VI.2.2 Summary of treatment benefits

For the treatment of schizophrenia, there were three main short-term studies lasting four to six weeks, which involved 1.203 adults and compared aripiprazole 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 was also compared with placebo in one study involving 302 patients aged between 13 and 17 years.

For the treatment of bipolar disorder, there were eight main studies looking at aripiprazole in adults. Five of these compared aripiprazole with placebo over three weeks in a total of 1,900 adults, two of which continued for a further nine weeks to look at the maintenance of the effect 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 (another antipsychotic medicine) in 384 adults. Aripiprazole was also compared with placebo in one study involving 296 children and adolescents.

Clinical studies showed that patients can be switched to and from aripiprazole without much difficulty.

Compliance and adherence to treatment have a significant influence on relapse prevention and long-term treatment outcome in patients treated with antipsychotics therefore treatments with minimal side effects are desirable. Aripiprazole efficacy is clearly superior to that of placebo, is similar to that of haloperidol or perphenazine, and appears to have similar efficacy to risperidone and olanzapine. It has a benign side-effect profile, particularly regarding to extrapyramidal symptoms.

VI.2.3 Unknowns relating to treatment benefits

Not applicable. This is a generic medicine and its benefits and risks are taken as being the same as of innovator's product.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Movement disorders with symptoms similar to Parkinson's disease, including involuntary muscle twitches that occur after prolonged treatment (**Extrapyramidal symptoms, including tardive dyskinesia**)	Movement disorders similar to symptoms of Parkinson's disease have been reported commonly (they may affect up to 1 in 10 people). Symptoms include uncontrollable twitching or jerking movements, difficulty starting muscle movements, shaking, feeling restless or muscle stiffness without pain. If signs and symptoms of the movement disorder appear, dose reduction or discontinuation of aripiprazole should be considered. In clinical trials of one year or less duration late-onset involuntary muscle twitches (tardive dyskinesia) occurred uncommonly (may affect up to 1 in 100 people). In those cases symptoms can worsen or even arise after discontinuation of treatment.	Tell your doctor if you develop unusual movements, including involuntary, irregular muscle movements, especially in the face. Your doctor may consider dose reduction with close monitoring or discontinuation of aripiprazole.

Life-threatening neurological disorder **(Neuroleptic malignant syndrome)**	The life-threatening neurological disorder neuroleptic malignant syndrome (NMS) is most often caused by a side effect of neuroleptic or antipsychotic drugs, including aripiprazole. Rare cases were reported in clinical studies with aripiprazole. It typically consists of muscle stiffness or inflexibility with high fever, sweating, altered mental status, or very rapid or irregular heart beat. Additional signs may include elevations of muscle break-down products in the blood (creatine phosphokinase) and urine (myoglobinuria), which can sometimes lead to kidney failure (acute renal failure).	Tell your doctor immediately if you suffer from muscle stiffness or inflexibility with high fever, sweating, altered mental status, or very rapid or irregular heart beat as these can all be symptoms of the life-threatening neurological disorder neuroleptic malignant syndrome. If a patient develops signs and symptoms indicative of NMS, or presents with unexplained high fever without additional symptoms, all antipsychotic medicinal products, including aripiprazole, must be discontinued.

Potential risks (*Important potential risk):

Risk	What is known (Including reason why it is considered a potential risk)
Convulsions or fits **(Seizures)***	In clinical trials with aripiprazole uncommon cases of seizures were reported. Therefore, aripiprazole should be used with caution in patients who have a history of seizure disorder or have conditions associated with seizures.
Increases in blood sugar and diabetes **(Hyperglycemia/diabetes)***	Increases in blood sugar (Hyperglycaemia) and/or development or exacerbation of diabetes occasionally associated with a very severe consequences, called ketoacidosis or coma or even death, have been reported in patients treated with atypical antipsychotic medicines including aripiprazole. However, in studies with aripiprazole no significant increase of these events compared to placebo were found.
Events associated with wanting to kill yourself **(Suicide-related events)***	Suicidal behavior is often present in psychotic illnesses and mood disorders. Some cases have been reported early after starting antipsychotic therapy, including aripiprazole. Results of a study suggested that the risk of suicidality with aripiprazole treatment was not increased compared to other antipsychotics.

Low blood pressure when standing up **(Orthostatic hypotension)***	As some cases have been identified, this adverse event is considered a potential risk.
Changes/increases in the content of certain fats in the blood **(Dyslipidemia)***	No medically important differences were detected when comparing aripiprazole- vs. placebo (= no drug, just a sugar-pill)-treated patients.
Weight gain	Weight gain is commonly seen in patients due to co-morbidities, use of antipsychotics known to cause weight gain, poorly managed life-style, and might lead to severe complications. Among patients prescribed aripiprazole, when seen, it is usually in those with significant risk factors. In clinical trials aripiprazole has not been shown to induce clinically relevant weight gain in adults, while in 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 and if it is clinically significant, dose reduction should be considered.
Sleepiness/tiredness **(Somnolence/fatigue)**	Adolescents aged 13 years and older experienced sleepiness and tiredness very commonly (greater than 1 in 10 patients), especially patients with bipolar disorder compared to patients with schizophrenia. The frequency of these adverse events in the adult patient population was common (less than 1 in 10 patients).
Disorders of the heart and/or blood vessels **(Cardiovascular-related disorders)**	Aripiprazole should be used with caution in patients with known disorders of the heart and/or blood vessels (i.e.heart attack, heart failure, or abnormalities of the heart rhythm, diseases of blood vessels in the brain, including stroke) and in conditions which would predispose patients to low blood pressure (hypotension) (i.e. dehydration, lowered blood volume, and treatment with blood-pressure lowering medicinal products) or high blood pressure (hypertension).
Abnormalities of the heart rhythm **(Conduction abnormalities)**	In clinical trials of aripiprazole, the incidence of a life-threatening abnormality of the heart rhythm (QT prolongation) was comparable to placebo(= no drug, just a sugar-pill). However, as with other antipsychotics, aripiprazole should be used with caution in patients with a family history of this life-threatening abnormality of the heart rhythm (QT prolongation).
Growth	Aripiprazole is not for use in children and adolescents under 13 years. In children and adolescents (the pediatric population) aripiprazole is indicated for the treatment of schizophrenia in adolescents aged 15 years and older as well as for the treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older, where the treatment duration should be the minimum necessary for symptom control and must not exceed 12 weeks and daily dose of 10 mg should not be exceeded.

Low concentration of the milk-forming hormone prolactin in the blood of children and adolescents **(Low prolactin in paediatric patients)**	In studies low prolactin concentrations were noted in the blood of 13-17 year-old adolescents with schizophrenia who have been treated for up to 2 years, as well as in the paediatric bipolar population (10 17 years) who have been treated for up to 30 weeks. "
Difficulty swallowing **(Dysphagia (primarily applies to schizophrenia population))**	Difficulty swallowing and aspiration (when the food goes down the wrong pipe, reaching the lungs instead of the stomach) as its consequence have been associated with antipsychotic treatment, including aripiprazole. Therefore, aripiprazole should be used cautiously in patients at risk for aspiration pneumonia.
Intolerance to sugar from milk **(Lactose intolerance)**	This medicinal product contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.
Disorder of attention combined with hyperactivity in addition to the condition treated with aripiprazole **(ADHD co-morbidity)**	Very limited safety data are available on concomitant use of aripiprazole and stimulants used in the treatment of ADHD; therefore, extreme caution should be taken when these drugs are taken together.
Effects one drug has on another's activity when both drugs are administered together **(Drug interactions)**	A potential for drug interactions exists.
Higher likelihood of death and stroke-related events (CVA-cerebrovascular events) in patients, who are suffering from dementia (loss of brain function) **Increased mortality and CVA in elderly patients with dementia**	Data from trials demonstrated that there is an increased likelihood of death and stroke-related events in patients, who are suffering from dementia (loss of brain function) and are being treated with aripiprazole as compared to placebo (= no drug, just a sugar-pill). Therefore aripiprazole is not indicated for the treatment of dementia-related psychosis (i.e. a mental state with symptoms involving a "loss of contact with reality as a consequence of loss of brain function (dementia)).
Pathological gambling	Rare reports of pathological gambling have been reported among patients prescribed aripiprazole, regardless of whether these patients had a prior history of gambling. Patients with a prior history of pathological gambling may be at increased risk and should be monitored carefully.
A life-threatening syndrome that develops due to high levels of the chemical serotonin **(Serotonin syndrome)**	Cases of serotonin syndrome have been reported in patients taking aripiprazole, and possible signs and symptoms for this condition can occur especially in cases of concomitant use with other medications (serotonergic drugs, i.e. triptans, tramadol, tryptophan, SSRIs (such as paroxetine and fluoxetine), tricyclics (such as clomipramine, amitriptyline), pethidine, St John's Wort and venlafaxine) that increase the

	levels of the chemical serotonin, such as antidepressants, or with drugs that are known to increase aripiprazole concentrations. Serotonin syndrome symptoms typically occur within several hours of taking a new drug or increasing the dose of a drug you're already taking. Signs and symptoms include: Agitation or restlessness, confusion, rapid heart rate and high blood pressure, dilated pupils, loss of muscle coordination or twitching muscles, heavy sweating, diarrhea, headache, shivering, and goose bumps. Severe serotonin syndrome can be life-threatening. Signs and symptoms include: High fever, seizures, irregular heartbeat, and unconsciousness.
Adverse events involving the liver **(Hepatic adverse events)**	The frequency of these reactions is considered not known (cannot be estimated from the available data).

Missing information:

Risk	**What is known**
Safety in pregnancy and lactation	There is no adequate well-controlled study in pregnant women therefore aripiprazole should not be used in pregnancy unless really necessary. Babies exposed to antipsychotics during the third trimester of pregnancy are at increased risk of developing side effects. Aripiprazole is excreted in milk therefore the patients should not breastfeed if they are taking aripiprazole.
Safety in paediatrics	In children and adolescents (the pediatric population) aripiprazole is indicated for the treatment of schizophrenia in adolescents aged 15 years and older as well as for the treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older, where the treatment duration should be the minimum necessary for symptom control and must not exceed 12 weeks and daily dose of 10 mg should not be exceeded. Younger patients 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. Aripiprazole is not recommended for use in patients with schizophrenia below 15 years of age due to lack of information on safety and efficacy.

VI.2.5 Summary of additional 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.
The Summary of Product Characteristics and the Package leaflet for this product can be found at the agency's EPAR page.

This is a generic application.

However, the originator has additional risk minimisation measures: In each Member State where the new 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 is launched the Marketing Authorisation Holder (MAH) shall agree an educational programme with the National Competent Authority. The MAH shall ensure that, following discussions and agreement with the National Competent Authorities in each Member State where the new 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 is launched all healthcare professionals who are expected to prescribe aripiprazole are provided with an information pack containing the following items:
• Summary of Product Characteristics (SmPC) and Package Leaflet
• Educational material for the healthcare professionals
• Educational material for the patients and their caregivers

Key elements of the Healthcare Professional FAQ Brochure (Q&A format) intended for Healthcare Providers treating adolescent patients with bipolar mania:
• Brief introduction to aripiprazole indication and the purpose of the tool
• Instructions reinforcing that the indicated age range is 13-17 years and that aripiprazole is *not* recommended for use in patients below 13 years of age due to safety concerns
• Instructions that the recommended dose is 10 mg/day and that enhanced efficacy at higher doses has not been demonstrated
• Information regarding the safety and tolerability profile of aripiprazole, in particular potential consequences regarding adverse effects at doses higher than 10 mg/day, in particular with respect to:
- Weight gain, including a recommendation to monitor patients
- Extrapyramidal symptoms
- Somnolence
- Fatigue
• Reminder to educate patients/caregivers and distribute the Patient/Caregiver Information Brochure

Key elements of the Patients/Caregiver Information Brochure:
• Brief introduction to aripiprazole indication and the purpose of the tool
• Information that the indicated age range is 13-17 years and that aripiprazole is *not* recommended for use in patients below 13 years of age
• Information that aripiprazole can cause adverse effects at doses higher than 10 mg/day, in particular with respect to:
- Weight gain, including a recommendation to monitor patients
- Extrapyramidal symptoms
- Somnolence

- Fatigue
• Request to inform the physician of all medical conditions before treatment
• The importance of not attempting to self-treat any symptoms without consulting their Healthcare professional

VI.2.6 Planned post authorisation development plan (if applicable)
Not applicable. No postauthorisation studies are planned.