6 PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

6.1 VI.1: Summary of the Risk Management Plan for Aripiprazole

This is a summary of the risk management plan (RMP) for aripiprazole. The RMP details important risks of aripiprazole, how these risks can be minimised, and how more information will be obtained about aripiprazole's risks and uncertainties (missing information).

Aripiprazole's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how aripiprazole should be used.

This summary of the RMP for aripiprazole should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of aripiprazole’s RMP.

6.1.1 I: The Medicine and What it is Used for

Aripiprazole (Abilify) is authorised for schizophrenia in adults and in adolescents aged 15 years and older, moderate to severe manic episodes in Bipolar I Disorder and the prevention of a new manic episode in adults who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment, treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older and for rapid control of agitation and disturbed behaviours in patients with schizophrenia or in patients with manic episodes in Bipolar I Disorder, when oral therapy is not appropriate (see SmPC for the full indication). It contains aripiprazole as the active substance and it is given orally or intramuscularly. Forms and strengths are as follows:

- Abilify tablets: 1 mg, 2 mg, 3 mg, 5 mg, 6 mg, 10 mg, 12 mg, 15 mg, 20 mg and 30 mg
- Abilify orally disintegrating tablets: 3 mg, 5 mg, 6 mg, 10 mg, 12 mg, 15 mg, 20 mg, 24 mg and 30 mg
- Abilify oral solution: 1 mg/mL
- Abilify powder: 10 mg aripiprazole/1 g powder
- Abilify solution for injection (immediate release) for IM use: 7.5 mg/mL

Aripiprazole (Abilify Maintena) is authorised for maintenance treatment of schizophrenia in adult patients stabilised with oral aripiprazole (see SmPC for the full indication). It contains aripiprazole as the active substance and it is given intramuscularly in 300 mg/vial or pre-filled dual chamber syringe and 400 mg/vial or pre-filled dual chamber syringe.

Further information about the evaluation of aripiprazoles's benefits can be found in aripiprazole's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage

https://apac01.safelinks.protection.outlook.com/?url=http%3A%2F%2Fwww.ema.europa.eu%2Fema%2Findex.jsp%3Fcurl%3Dpages%2Fmedicines%2Fhuman%2Fmedicines%2F002755%2Fhuman_med_001711.jsp&data=02%7C01%7CRiddhima.Engineer%40otsuka-us.com%7Cf892cdf75cf44d3d3be708d5e5b29376%7C34ddb3397fd04f009041c2e47fbbc9f4%7C1%7C0%7C636667477501932245&sdata=FY7qfTbNzV1D7V8I0acV7iDuPDV1GkUhEZURsx6%2FCqM%3D&reserved=0

6.1.2 II: Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of aripiprazole, together with measures to minimise such risks and the proposed studies for learning more about aripiprazole's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

6.1.2.1 II.A: A List of Important Risks and Missing Information

Important risks of aripiprazole are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks

are concerns for which there is sufficient proof of a link with the use of aripiprazole. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

Table 6.1.2.1-1 II.A-1: List of Important Risks and Missing Information-Abilify	
Important Identified Risks	• EPS, including tardive dyskinesia
Important Potential Risks	• Orthostatic hypotension
Missing Information	• Use in Pregnancy and Lactation

Table 6.1.2.1-2 II.A-2: List of Important Risks and Missing Information-Abilify Maintena	
Important Identified Risks	• EPS, including tardive dyskinesia •
Important Potential Risks	• Orthostatic hypotension
Missing Information	• Use in Pregnancy and Lactation • Use in Elderly Patients above 65 Years of Age

6.1.2.2 II.B: Summary of Important Risks

Table 6.1.2.2-1 II.B-1: Important Identified Risk: EPS, including tardive dyskinesia	
Evidence for linking the risk to the medicine	
Risk factors and risk groups	<u>EPS Risk Factors:</u> Age, gender, diagnosis of mood disorder, cognitive difficulties, alcohol and substance abuse, exposure to antipsychotic treatments (type and dose), use of concomitant medications, and diabetes.[343] <u>Tardive Dyskinesia Risk Factors:</u> Presence or history of EPS, advanced age, diagnosis of mood disorders or cognitive difficulties, alcohol and substance abuse, antipsychotic treatment (type and dose), use of concomitant medications, and diabetes.[290,297,298]

Table 6.1.2.2-1 II.B-1: Important Identified Risk: EPS, including tardive dyskinesia	
Risk minimisation measures	**Routine risk minimisation measures:** - Warnings & Precautions, section 4.4 of SmPC - Undesirable effects, section 4.8 of the SmPC **Additional risk minimisation measures: None**
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** PASS Study No. 15893N- Extrpyramidal symptoms in patients being treated with Abilify Maintena® Cohort Study with a 2-year follow-up using European automated healthcare databases See section II.C of this summary for an overview of the post-authorisation development plan.

Table 6.1.2.2-2 II.B-2: Important Potential Risk: Orthostatic Hypotension	
Evidence for linking the risk to the medicine	SCS - Bipolar[178]; SCS - Low-dose[252]; SCS - Adjunctive MDD[253]; SCS - Solution for Injection[254]; SCS - Bipolar Pediatrics[253] CSR - 31-03-240[255]; CSR - 31-03-241[256]; SCS - Adjunctive Bipolar[257]; SCS - Autism[258]; CSR – 31-09-266[259]; CSR – 31-09-267[260]; CSR – 31-12-293[261]; CSR 31-12-294[262]; CSR – 31-97-303[263] <u>Aripiprazole IM Depot studies in adult schizophrenia</u>: CN138-020[264]; 031-07-002[301]; 31-05-244[266]; 31-11-289[267]; 31-07-246[268]; 31-07-247{CSR_247}; 31-08-248[270]; 031-08-003[265]; 031-10-002[271]; 31-11-283[272]; 31-11-284[302]; 31-10-270[273]; 31-11-290[274]; 31-12-298[275]; 31-12-291[276]; 31-12-297[277].
Risk factors and risk groups	• Advanced age • Use of psychotropic medications (e.g., dopaminergic drugs, antidepressants, neuroleptic agents)[251] • Use of antianginal drugs or antihypertensive and vasodilator therapy[249]

Table 6.1.2.2-2	II.B-2: Important Potential Risk: Orthostatic Hypotension
	• Medical conditions, including hypovolemia, defects of vasomotor reflexes, and autonomic nervous system dysfunction (as may occur in diabetes and Parkinsonism). Drug-induced orthostatic hypotension remains a concern[247,251] • Prolonged and severe orthostatic hypotension has been associated with stroke and myocardial infarction[304] • Drug-induced orthostatic hypotension and elderly patients: – Orthostatic hypotension is associated with significant morbidity and mortality, especially elderly patients in acute-care settings[249] ranging from mild symptoms (dizziness) to severe symptoms, such as syncope (leading to fractures or other injuries and immobility)[304] – Approximately one third of all falls in nursing homes are attributed to psychotropic drug use.[305]
Risk minimisation measures	**Routine risk minimisation measures:** - Warnings & Precautions, section 4.4 of SmPC - Undesirable effects, section 4.8 of the SmPC **Additional risk minimisation measures: None**

Table 6.1.2.2-3	II.B-3: Missing Information: Use in Pregnancy and Lactation
Risk minimisation measures	**Routine risk minimisation measures:** - Pregnancy and lactation, section 4.6 of the SmPC **Additional risk minimisation measures: None**

Table 6.1.2.2-4	II.B-4 Missing Information: Use in Elderly Patients above 65 Years of Age
Risk minimisation measures	**Routine risk minimisation measures:** - Posology and method of administration, section 4.2 of the SmPC -Warnings & Precautions, section 4.4 of SmPC **Additional risk minimisation measures: None**

6.1.2.3 II.C: Post-authorisation Development Plan

II.C.1 Studies which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of aripiprazole.

II.C.2 Other Studies in Post-authorisation Development Plan

PASS Study No. 15893N- Extrpyramidal symptoms in patients being treated with Abilify Maintena® Cohort Study with a 2-year follow-up using European automated healthcare databases.

Purpose of the study: further assess the risk of EPS-related events linked to the use of Abilify Maintena in clinical practice

Table 6.1.2.3-1 List of Studies in Post-Authorization Development Plan

Study/activity (including study number)	Objectives	Safety concerns /efficacy issue addressed	Status	Planned date for submission of (interim and) final results
Study No. 15893N- Extrpyramidal symptoms in patients being treated with Abilify Maintena® Cohort Study with a 2-year follow-up using European automated healthcare databases	Further characterize the risk of EPS-related events of aripiprazole IM depot	Further assess the risk of EPS-related events linked to the use of Abilify Maintena in clinical practice	Ongoing	31-Mar-2021

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