SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Aripiprazole Otsuka 720 mg prolonged-release suspension for injection in pre-filled syringe

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Aripiprazole Otsuka 720 mg prolonged-release suspension for injection in pre-filled syringe

Each pre-filled syringe contains 720 mg aripiprazole per 2.4 mL (300

mg/mL).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release suspension for injection in pre-filled syringe

The suspension is white to off-white. The suspension is pH neutral (approximately 7.0).

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Aripiprazole Otsuka is indicated for maintenance treatment of schizophrenia in adult patients stabilised with aripiprazole.

4.2 Posology and method of administration

Posology
For patients who have never taken aripiprazole, tolerability with aripiprazole must be established prior to initiating treatment with Aripiprazole Otsuka.

Titration of the dose for Aripiprazole Otsuka is not required.

Starting regimen
The recommended starting dosing regimen when transitioning from Aripiprazole Otsuka 400 mg once monthly is Aripiprazole Otsuka 960 mg no sooner than 26 days after previous injection of Aripiprazole Otsuka 400 mg. Aripiprazole Otsuka 960 mg should then be dosed once every 2 months (every 56 days).
Initiation may also be started by following one of two additional regimens:

- One injection start: On the day of initiation following oral therapy, one injection of Aripiprazole Otsuka 960 mg should be administered and treatment with 10 mg to 20 mg oral aripiprazole per day for 14 consecutive days should be continued to maintain therapeutic aripiprazole concentrations during initiation of therapy.

- Two injection start: On the day of initiation following oral therapy, one injection of Aripiprazole Otsuka 960 mg and one injection of Aripiprazole Otsuka 400 mg should be administered at two different injection sites (see method of administration), along with one 20 mg dose of oral aripiprazole.

Dosing interval and dosing adjustments
After the injection start, the recommended maintenance dose is one injection of Aripiprazole Otsuka 960 mg every second month. Inject Aripiprazole Otsuka 960 mg once every two months as a single injection 56 days after the previous injection. Patients may be given the injection up to 2 weeks before or 2 weeks after the scheduled 2-month dose.
If there are adverse reactions with the Aripiprazole Otsuka 960 mg dose, reduction to Aripiprazole Otsuka 720 mg once every two months should be considered.

Missed doses
If more than 8 weeks and less than 14 weeks have elapsed since the last injection, the next dose of Aripiprazole Otsuka 960 mg/720 mg should be administered as soon as possible. The once every two months schedule should then be resumed. If more than 14 weeks have elapsed since the last injection, the next dose of Aripiprazole Otsuka 960 mg/720 mg should be administered with concomitant oral aripiprazole for 14 days or with 2 separate injections (one each of Aripiprazole Otsuka 960 mg and Aripiprazole Otsuka 400 mg or one each Aripiprazole Otsuka 720 mg and Aripiprazole Otsuka 300 mg) administered together with one 20 mg oral aripiprazole dose. The once every two months schedule should then be resumed.

Special populations
Elderly

The safety and efficacy of Aripiprazole Otsuka 960 mg/720 mg in the treatment of schizophrenia in patients 65 years of age or older has not been established (see section 4.4). No recommendations on dosing can be made.

Renal impairment

No dose adjustment is required for patients with renal impairment (see section 5.2).

Hepatic impairment

No dose adjustment is required for patients with mild or moderate hepatic impairment. In patients with severe hepatic impairment, the data available are insufficient to establish recommendations. In these patients dosing should be managed cautiously. Oral formulation should be preferred (see section 5.2).

Known CYP2D6 poor metabolisers
In patients who are known to be CYP2D6 poor metabolisers:

- Patients transitioning from Aripiprazole Otsuka 300 mg once monthly: The starting dose should be one injection of Aripiprazole Otsuka 720 mg g, no sooner than 26 days after previous injection of Aripiprazole Otsuka 300 mg.

- One injection start (following transition from oral therapy): The starting dose should be one injection of Aripiprazole Otsuka 720 mg and treatment should be continued with the prescribed dose of oral aripiprazole per day for 14 consecutive days.

- Two injection start (following transition from oral therapy): The starting dose should be 2 separate injections; one Aripiprazole Otsuka 720 mg and one Aripiprazole Otsuka 300 mg injection, together with a single dose of 20 mg oral aripiprazole (see method of administration).

Thereafter, a maintenance dose of Aripiprazole Otsuka 720 mg should be administered once every two months as a single injection.

Maintenance dose adjustments due to interactions with CYP2D6 and/or CYP3A4 inhibitors and/or CYP3A4 inducers

Maintenance dose adjustments should be made in patients taking concomitant strong CYP3A4 inhibitors or strong CYP2D6 inhibitors for more than 14 days. If the CYP3A4 inhibitor or CYP2D6 inhibitor is withdrawn, the dose may need to be increased to the previous dose (see section 4.5). In case of adverse reactions despite dose adjustments of Aripiprazole Otsuka 960 mg, the necessity of concomitant use of CYP2D6 or CYP3A4 inhibitor should be reassessed.

Concomitant use of CYP3A4 inducers with Aripiprazole Otsuka 960 mg/720 mg for more than 14 days should be avoided because the blood levels of aripiprazole are decreased and may be below the effective levels (see section 4.5).

Aripiprazole Otsuka 960 mg/720 mg should not be used in patients who are known to be CYP2D6 poor metabolisers and concomitantly use a strong CYP2D6 and/or CYP3A4 inhibitor.

Table 1: Maintenance dose adjustments of Aripiprazole Otsuka in patients who are taking concomitant strong CYP2D6 inhibitors, strong CYP3A4 inhibitors, and/or CYP3A4 inducers for more than 14 days

	Adjusted 2-monthly dose
Patients taking Aripiprazole Otsuka 960 mg*	
Strong CYP2D6 or strong CYP3A4 inhibitors	720 mg
Strong CYP2D6 and strong CYP3A4 inhibitors	Avoid use
CYP3A4 inducers	*Avoid use*

*Avoid use in patients who already take 720 mg, e.g. due to adverse rections to the higher dose.

Paediatric population

The safety and efficacy of Aripiprazole Otsuka 960 mg/720 mg in children and adolescents aged 0 to 17 years have not been established. No data are available.

Method of administration

Aripiprazole Otsuka 960 mg and 720 mg is only intended for gluteal intramuscular injection and must not be administered intravenously or subcutaneously. It must only be administered by a healthcare professional.

The suspension must be injected slowly as a single injection (doses must not be divided) into the gluteal muscle, alternating the injections between the right and left side. Care must be taken to avoid inadvertent injection into a blood vessel.

If initiating with any of the options that require two injections (one Aripiprazole Otsuka 960 mg or 720 mg and one Aripiprazole Otsuka 400 mg or 300 mg), inject into two different sites. DO NOT inject both injections concomitantly into the same gluteal muscle.

Full instructions for use and handling of Aripiprazole Otsuka *960 mg/720 mg* are provided in the package leaflet (information intended for healthcare professionals).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

During antipsychotic treatment, improvement in the patient's clinical condition may take several days to some weeks. Patients should be closely monitored throughout this period.

Use in patients who are in an acutely agitated or severely psychotic state
Aripiprazole Otsuka should not be used to manage acutely agitated or severely psychotic states when immediate symptom control is warranted.

Suicidality
The occurrence of suicidal behaviour is inherent in psychotic illnesses, and in some cases has been reported early after initiation or switch of antipsychotic treatment, including treatment with aripiprazole (see section 4.8). Close supervision of high-risk patients should accompany antipsychotic treatment.

Cardiovascular disorders
Aripiprazole should be used with caution in patients with known cardiovascular disease (history of myocardial infarction or ischaemic heart disease, heart failure, or conduction abnormalities),

cerebrovascular disease, conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medicinal products) or hypertension, including accelerated or malignant. Cases of venous thromboembolism (VTE) have been reported with antipsychotic medicinal products. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with aripiprazole and preventive measures undertaken (see section 4.8).

QT prolongation

In clinical trials of treatment with oral aripiprazole, the incidence of QT prolongation was comparable to placebo. Aripiprazole should be used with caution in patients with a family history of QT prolongation (see section 4.8).

Tardive dyskinesia

In clinical trials of one year or less duration, there were uncommon reports of treatment emergent dyskinesia during treatment with aripiprazole. If signs and symptoms of tardive dyskinesia appear in a patient on aripiprazole, dose reduction or discontinuation should be considered (see section 4.8). These symptoms can temporally deteriorate or can even arise after discontinuation of treatment.

Neuroleptic malignant syndrome (NMS)

NMS is a potentially fatal symptom complex associated with antipsychotics. 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. If a patient develops signs and symptoms indicative of NMS or presents with unexplained high fever without additional clinical manifestations of NMS, all antipsychotics, including aripiprazole, must be discontinued (see section 4.8).

Seizure

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 (see section 4.8).

Elderly patients with dementia-related psychosis

Increased mortality

In three placebo-controlled trials of oral aripiprazole in elderly patients with

psychosis associated with Alzheimer's disease (n = 938; mean age: 82.4 years; range: 56 to 99 years), patients treated with aripiprazole were at an increased risk of death compared to placebo. The rate of death in oral aripiprazole-treated patients was 3.5 % compared to 1.7 % in placebo. Although the causes of deaths were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature (see section 4.8).

Cerebrovascular adverse reactions
In the same trials with oral aripiprazole, cerebrovascular adverse reactions (e.g., stroke, transient ischaemic attack), including fatalities, were reported in patients (mean age: 84 years; range: 78 to 88 years). Overall, 1.3 % of oral aripiprazole-treated patients reported cerebrovascular adverse reactions compared with 0.6 % of placebo-treated patients in these trials. This difference was not statistically significant. However, in one of these trials, a fixed-dose trial, there was a significant dose- response relationship for cerebrovascular adverse reactions in patients treated with aripiprazole (see section 4.8). Aripiprazole is not indicated for the treatment of patients with dementia-related psychosis.

Hyperglycaemia and diabetes mellitus

Hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with aripiprazole. No specific studies have been conducted with Aripiprazole Otsuka in patients with hyperglycaemia or diabetes mellitus. Risk factors that may predispose patients to severe complications include obesity and family history of diabetes. Patients treated with 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 (see section 4.8).

Hypersensitivity

Hypersensitivity reactions, characterised by allergic symptoms, may occur with aripiprazole (see section 4.8).

Weight gain

Weight gain is commonly seen in schizophrenic patients due to use of antipsychotics known to cause weight gain, co-morbidities, poorly managed lifestyle and might lead to severe complications. Weight gain has been reported post-marketing among patients prescribed oral 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 (see section 4.8).

Dysphagia

Oesophageal dysmotility and aspiration have been associated with the use of aripiprazole. Aripiprazole should be used cautiously in patients at risk for aspiration pneumonia.

Gambling disorder and other impulse control disorders

Patients can experience increased urges, particularly for gambling, and the inability to control these urges while taking aripiprazole. Other urges reported include increased sexual urges, compulsive shopping, binge or compulsive eating, and other impulsive and compulsive behaviours. It is important for prescribers to ask patients or their caregivers specifically about the development of new or increased gambling urges, sexual urges, compulsive shopping, binge or compulsive eating, or other urges while being treated with aripiprazole. It should be noted that impulse-control symptoms can be associated with the underlying disorder; however, in some cases, urges were reported to have stopped when the dose was reduced or the medicinal product was discontinued. Impulse control disorders may result in harm to the patient and others if not recognised. A dose reduction or stopping of the medicinal product should be considered if a patient develops such urges (see section 4.8).

Falls
Aripiprazole may cause somnolence, postural hypotension, motor and sensory instability, which may lead to falls. Caution should be taken when treating patients at higher risk, and a lower starting dose should be considered (e.g., elderly or debilitated patients; see section 4.2).

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed with Aripiprazole Otsuka. The information below is obtained from studies with oral aripiprazole. The 2- month dosing interval and long half-life of aripiprazole after dosing with Aripiprazole Otsuka 960 mg or 720 mg should also be considered when assessing the drug-drug interaction potential.

Due to its α1-adrenergic receptor antagonism, aripiprazole has the potential to enhance the effect of certain antihypertensive medicinal products.

Given the primary central nervous system (CNS) effects of aripiprazole, caution should be used when aripiprazole is administered in combination with alcohol or other CNS medicinal products with overlapping adverse reactions such as sedation (see section 4.8).

If aripiprazole is administered concomitantly with medicinal products known to cause QT prolongation or electrolyte imbalance, caution

should be used.

Potential for other medicinal products to affect aripiprazole

Quinidine and other strong CYP2D6 inhibitors
In a clinical trial of oral aripiprazole in healthy subjects, a strong inhibitor of CYP2D6 (quinidine) increased aripiprazole AUC by 107 %, while C_{max} was unchanged. The AUC and C_{max} of dehydro-aripiprazole, the active metabolite, decreased by 32 % and 47 %, respectively. Other strong inhibitors of CYP2D6, such as fluoxetine and paroxetine, may be expected to have similar effects and similar dose reduction should, therefore, be applied (see section 4.2).

Ketoconazole and other strong CYP3A4 inhibitors
In a clinical trial of oral aripiprazole in healthy subjects, a strong inhibitor of CYP3A4 (ketoconazole) increased aripiprazole AUC and C_{max} by 63 % and 37 %, respectively. The AUC and C_{max} of dehydro-aripiprazole increased by 77 % and 43 %, respectively. In CYP2D6 poor metabolisers, concomitant use of strong inhibitors of CYP3A4 may result in higher plasma concentrations of aripiprazole compared to that in CYP2D6 extensive metabolisers (see section 4.2). When considering concomitant administration of ketoconazole or other strong CYP3A4 inhibitors with aripiprazole, potential benefits should outweigh the potential risks to the patient. Other strong inhibitors of CYP3A4, such as itraconazole and HIV protease inhibitors may be expected to have similar effects and similar dose reductions should, therefore, be applied (see section 4.2). Upon discontinuation of the CYP2D6 or CYP3A4 inhibitor, the dose of aripiprazole should be increased to the dose prior to the initiation of the concomitant therapy. When weak inhibitors of CYP3A4 (e.g., diltiazem) or CYP2D6 (e.g., escitalopram) are used concomitantly with aripiprazole, modest increases in plasma aripiprazole concentrations may be expected.

Carbamazepine and other CYP3A4 inducers
Following concomitant administration of carbamazepine, a strong inducer of CYP3A4, and oral aripiprazole to patients with schizophrenia or schizoaffective disorder, the geometric means of C_{max} and AUC for aripiprazole were 68 % and 73 % lower, respectively, compared to when oral aripiprazole (30 mg) was administered alone. Similarly, for dehydro- aripiprazole the geometric means of C_{max} and AUC after carbamazepine co- administration were 69 % and 71 % lower, respectively, than those following treatment with oral aripiprazole alone. Concomitant administration of Aripiprazole Otsuka 960 mg/720 mg and other inducers of CYP3A4 (such as rifampicin, rifabutin, phenytoin, phenobarbital, primidone, efavirenz, nevirapine and St. John's Wort) may be expected to have similar effects. The concomitant use of CYP3A4 inducers with Aripiprazole Otsuka 960 mg/720 mg should be avoided because the blood levels of aripiprazole are decreased and may be below the effective levels.

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 serotonergic medicinal products, such as Selective Serotonin Reuptake Inhibitor/Serotonin Noradrenaline Reuptake Inhibitor (SSRI/SNRI), or with medicinal products that are known to increase aripiprazole concentrations (see section 4.8).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Plasma exposure to aripiprazole after a single dose of Aripiprazole Otsuka is expected to remain for up to 34 weeks (see section 5.2). This should be taken into account when initiating treatment in women of childbearing potential, considering a possible future pregnancy or breast-feeding. Aripiprazole Otsuka should only be used in women planning to become pregnant if clearly necessary.

Pregnancy
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 (see section 5.3). Patients must be advised to notify their physician if they become pregnant or intend to become pregnant during treatment with aripiprazole.

Prescribers need to be aware of the long-acting properties of Aripiprazole Otsuka. Aripiprazole has been detected in plasma in adult patients up to 34 weeks after a single-dose administration of the prolonged-release suspension.

New-born infants 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, new-born infants should be monitored carefully (see section 4.8).

Maternal exposure to Aripiprazole Otsuka before and during pregnancy may lead to adverse reactions in the newborn child. Aripiprazole Otsuka should not be used during pregnancy unless clearly necessary.

Breast-feeding
Aripiprazole/metabolites are excreted in the breast milk to such an extent that effects on the breast-fed infant are likely if Aripiprazole Otsuka is administered to breast-feeding women. Since a single dose of Aripiprazole Otsuka is expected to remain for up to 34 weeks in plasma (see section 5.2),

breast-fed infants may be at risk even from Aripiprazole Otsuka administration long before breast- feeding. Patients currently under treatment or who have been treated in the past 34 weeks with Aripiprazole Otsuka should not breast feed.

Fertility

Aripiprazole did not impair fertility based on data from reproductive toxicity studies with aripiprazole.

4.7 Effects on ability to drive and use machines

Aripiprazole has minor to moderate influence on the ability to drive and use machines due to potential nervous system and visual effects, such as sedation, somnolence, syncope, vision blurred, diplopia (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The safety profile of Aripiprazole Otsuka 960 mg and Aripiprazole Otsuka 720 mg for the treatment of schizophrenia in adults is based on adequate and well- controlled studies of Aripiprazole Otsuka 400 mg and Aripiprazole Otsuka 300 mg. In general, the observed adverse drug reactions (ADRs) in Aripiprazole Otsuka 960 mg/720 mg clinical trials were similar to the ADRs observed in the Aripiprazole Otsuka 400 mg/300 mg clinical trials.

The most frequently observed ADRs reported in ≥ *5 % of* patients in two double-blind, long-term trial of Aripiprazole Otsuka 400 mg/300 mg were weight increased (9.0%), akathisia (7.9%) and insomnia (5.8%). In the Aripiprazole Otsuka 960 mg/720 mg clinical trials, weight increased (22.7%), injection site pain (18.2%) akathisia (9.8 %), anxiety (8.3 %), headache (7.6 %), insomnia (7.6 %), and constipation (6.1 %) were the most frequently observed ADRs.

Tabulated list of adverse reactions

The incidences of the ADRs associated with Aripiprazole Otsuka 400 mg/300 mg and Aripiprazole Otsuka 960 mg/720 mg are tabulated below. The table is based on adverse reactions reported during clinical trials and/or post-marketing use.

All ADRs are listed by system organ class and frequency; very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000), and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

The ADRs listed under the frequency "not known" were reported during post- marketing use.

System organ class	Common	Uncommon	Not known
Blood and lymphatic system disorders		Neutropenia Anaemia Thrombocytopenia Neutrophil count decreased White blood cell count decreased	Leukopenia
Immune system disorders		Hypersensitivity	Allergic reaction (e.g. anaphylactic reaction, angioedema including swollen tongue, tongue oedema, face oedema, pruritus, or urticaria)
Endocrine disorders		Blood prolactin decreased Hyperprolactinaemia	Diabetic hyperosmolar coma Diabetic ketoacidosis
Metabolism and nutrition disorders	Weight increased[a] Diabetes mellitus Weight decreased	Hyperglycaemia Hypercholesterolaemia Hyperinsulinaemia Hyperlipidaemia Hypertriglyceridaemia Appetite disorder	Anorexia Decreased appetite[b] Hyponatraemia
Psychiatric disorders	Agitation Anxiety Restlessness Insomnia	Suicidal ideation Psychotic disorder Hallucination Delusion Hypersexuality Panic reaction Depression Affect lability Apathy Dysphoria Sleep disorder Bruxism Libido decreased Mood altered	Completed suicide Suicide attempt Gambling disorder Impulse-control disorder Binge eating Compulsive shopping Poriomania Nervousness Aggression

System organ class	Common	Uncommon	Not known
Nervous system disorders	Extrapyramidal disorder Akathisia Tremor Dyskinesia Sedation Somnolence Dizziness Headache	Dystonia Tardive dyskinesia Parkinsonism Movement disorder Psychomotor hyperactivity Restless legs syndrome Cogwheel rigidity Hypertonia Bradykinesia Drooling Dysgeusia Parosmia	Neuroleptic malignant syndrome Generalised tonic-clonic seizure Serotonin syndrome Speech disorder
Eye disorders		Oculogyric crisis Vision blurred Eye pain Diplopia Photophobia	
Cardiac disorders		Ventricular extrasystoles Bradycardia Tachycardia Electrocardiogram T wave amplitude decreased Electrocardiogram abnormal Electrocardiogram T wave inversion	Sudden death Cardiac arrest Torsades de pointes Ventricular arrhythmia QT prolonged
Vascular disorders		Hypertension Orthostatic hypotension Blood pressure increased	Syncope Venous embolism (including pulmonary embolism and deep vein thrombosis)
Respiratory, thoracic and mediastinal disorders		Cough Hiccups	Oropharyngeal spasm Laryngospasm Aspiration pneumonia

System organ class	Common	Uncommon	Not known
Gastrointestinal disorders	Dry mouth	Gastrooesophageal reflux disease Dyspepsia Vomiting Diarrhoea Nausea Abdominal pain upper Abdominal discomfort Constipation Frequent bowel movements Salivary hypersecretion	Pancreatitis Dysphagia
Hepatobiliary disorders		Liver function test abnormal Hepatic enzyme increased Alanine aminotransferase increased Gamma-glutamyltransferase increased Blood bilirubin increased Aspartate aminotransferase increased	Hepatic failure Jaundice Hepatitis Alkaline phosphatase increased
Skin and subcutaneous tissue disorders		Alopecia Acne Rosacea Eczema Skin induration	Rash Photosensitivity reaction Hyperhidrosis Drug reaction with eosinophilia and systemic symptoms (DRESS)

System organ class	Common	Uncommon	Not known
Musculoskeletal and connective tissue disorders	Musculoskeletal stiffness	Muscle rigidity Muscle spasms Muscle twitching Muscle tightness Myalgia Pain in extremity Arthralgia Back pain Joint range of motion decreased Nuchal rigidity Trismus	Rhabdomyolysis
Renal and urinary disorders		Nephrolithiasis Glycosuria	Urinary retention Urinary incontinence
Pregnancy, puerperium and perinatal conditions			Drug withdrawal syndrome neonatal
Reproductive system and breast disorders	Erectile dysfunction	Galactorrhoea Gynaecomastia Breast tenderness Vulvovaginal dryness	Priapism
General disorders and administration site conditions	Injection site pain[a] Injection site induration Fatigue	Pyrexia Asthenia Gait disturbance Chest discomfort Injection site reaction Injection site erythema Injection site swelling Injection site discomfort Injection site pruritus Thirst Sluggishness	Temperature regulation disorder (e.g. hypothermia, pyrexia) Chest pain Peripheral oedema

System organ class	Common	Uncommon	Not known
Investigations	Blood creatine phosphokinase increased	Blood glucose increased Blood glucose decreased Glycosylated haemoglobin increased Waist circumference increased Blood cholesterol decreased Blood triglycerides decreased	Blood glucose fluctuation

a: Reported as very common in Aripiprazole Otsuka 960 mg/720 mg clinical trials.

b: Reported only in Aripiprazole Otsuka 960 mg/720 mg clinical trial program

Description of selected adverse reactions

Injection site reactions

The percentage of patients in an open-label study reporting any injection site-related adverse reaction (all reported as injection site pain) was 18.2 % for patients treated with Aripiprazole Otsuka 960 mg and 9.0 % for patients treated with Aripiprazole Otsuka 400 mg. In both treatment groups, the majority of the reported injection site pain occurred with the first injection of Aripiprazole Otsuka 960 mg patients (21 of 24 patients) or Aripiprazole Otsuka 400 mg (7 of 12 patients), resolved within 5 days, and were reported with decreasing frequency and severity upon subsequent injections. The overall mean site visual analog scale scores (0 = no pain to 100 = unbearably painful) for patient reported rating of pain were similar in both treatment groups at the last injection: 0.8 pre-dose and 1.4 post-dose for the Aripiprazole Otsuka 960 mg group compared to 1.3 post-dose for the Aripiprazole Otsuka 400 mg group.

Neutropenia
Neutropenia has been reported in the clinical program with Aripiprazole Otsuka 400 mg/300 mg and typically started around day 16 after first injection, and lasted a median of 18 days.

Extrapyramidal Symptoms (EPS)
In trials in stable patients with schizophrenia, Aripiprazole Otsuka 400 mg/300 mg was associated with a higher frequency of EPS symptoms (18.4 %) than oral aripiprazole treatment (11.7 %). Akathisia was the most frequently observed symptom (8.2 %) and typically started around Day 10 after first injection, and lasted a median of 56 days. Subjects with akathisia typically received anti-cholinergic medicines as treatment, primarily benzatropine mesilate and trihexyphenidyl. Less often substances such as propranolol and benzodiazepines (clonazepam and diazepam) were administered to control akathisia. Parkinsonism events followed in frequency of 6.9 % for Aripiprazole Otsuka 400 mg/300 mg, 4.2 % for oral aripiprazole 10 mg to 30 mg tablets and 3.0 % for placebo, respectively.

Data from an open-label study of patients treated with Aripiprazole Otsuka 960 mg, showed minimal change from baseline in EPS scores, as assessed by the Simpson-Angus Rating scale (SAS), the Abnormal Involuntary Movement Scale (AIMS) and the Barnes Akathisia Rating Scale (BARS). The incidence of reported EPS-related events for patients treated with Aripiprazole Otsuka 960 mg was 18.2 % compared to the incidence of patients treated with Aripiprazole Otsuka 400 mg, which was 13.4 %.

Dystonia
Class effect: Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic medicinal products. An elevated risk of acute dystonia is observed in males and younger age groups.

Weight
During the double-blind, active-controlled phase of the 38-week long-term trial (see section 5.1), the incidence of weight gain of ≥ 7 % from baseline to last visit was 9.5 % for Aripiprazole Otsuka 400 mg/300 mg and 11.7 % for the oral aripiprazole tablets 10 mg to 30 mg. The incidence of weight loss of ≥ 7 % from baseline to last visit was 10.2 % for Aripiprazole Otsuka 400 mg/300 mg and 4.5 % for oral aripiprazole tablets 10 mg to 30 mg. During the double-blind, placebo-controlled phase of the 52-week long-term trial (see section 5.1), the incidence of weight gain of ≥ 7 % from baseline to last visit was 6.4 % for Aripiprazole Otsuka 400 mg/300 mg and 5.2 % for placebo. The incidence of weight loss of ≥ 7 % from baseline to last visit was 6.4 % for Aripiprazole Otsuka 400 mg/300 mg and 6.7 % for placebo. During double-blind treatment, mean change in body weight from baseline to last visit was −0.2 kg for Aripiprazole Otsuka 400 mg/300 mg and −0.4 kg for placebo (p = 0.812).

In an open-label, multiple-dose, randomised study in adult patients with schizophrenia (and bipolar I disorder) in which two months presentation.

Aripiprazole Otsuka 960 mg was evaluated against monthly Aripiprazole Otsuka 400 mg, the overall incidence of weight gain ≥ 7 % from baseline was comparable between Aripiprazole Otsuka 960 mg *(*40.6 %) and Aripiprazole Otsuka 400 mg *(*42.9 %). The mean change in body weight from baseline to last visit was 3.6 kg for Aripiprazole Otsuka 960 mg and 3.0 kg for Aripiprazole Otsuka 400 mg.

Prolactin

In clinical trials for the approved indications and in post-marketing data both increase and decrease in serum prolactin as compared to baseline was observed with aripiprazole (section 5.1).

Gambling disorder and other impulse control disorders

Gambling disorder, hypersexuality, compulsive shopping and binge or compulsive eating can occur in patients treated with aripiprazole (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

No cases of overdose associated with adverse reactions were reported in clinical studies with aripiprazole. While experience with aripiprazole overdose is limited, among the few cases of overdose (accidental or intentional) reported in clinical trials and post marketing experience with oral aripiprazole, the highest estimated ingestion was a total of 1260 mg with no fatalities.

The potential for dose dumping has been evaluated by simulation of aripiprazole plasma concentrations after an Aripiprazole Otsuka 960 mg dose is entirely absorbed in the systemic circulation. Based on the results of the simulation, if dose dumping would occur, aripiprazole concentrations may reach up to 13.5 times the concentrations that are achieved by a therapeutic dose of Aripiprazole Otsuka 960 mg without dose dumping. Furthermore, aripiprazole concentrations following dose dumping would decline within 5 days to concentrations normally observed following the administration of

Aripiprazole Otsuka 960 mg.

Signs and symptoms

Care must be taken to avoid inadvertent injection of this medicinal product into a blood vessel. Following any confirmed or suspected accidental overdose/inadvertent intravenous administration with aripiprazole, close observation of the patient is needed. The potentially medically significant signs and symptoms observed in overdose included lethargy, increased blood pressure, somnolence, tachycardia, nausea, vomiting and diarrhoea.

Management of overdose

There is no specific antidote to aripiprazole. Management of overdose should concentrate on supportive care, including close medical supervision and monitoring. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. Use supportive and symptomatic measures.

Treatment should consist of general measures employed in the management of overdose with any medicinal product. Consider the possibility of multiple medicinal product overdose.

Consider the long-acting nature of the medicinal product and the long elimination half-life of aripiprazole when assessing treatment needs and recovery.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psycholeptics, other antipsychotics, ATC code: N05AX12

Mechanism of action

It has been proposed that aripiprazole's efficacy in schizophrenia is mediated through a combination of partial agonism at dopamine D_2 and serotonin 5- HT_{1A} receptors and antagonism at serotonin 5-HT_{2A} receptors. Aripiprazole exhibited antagonist properties in animal models of dopaminergic hyperactivity and agonist properties of dopaminergic hypoactivity.

Aripiprazole exhibits high binding affinity in vitro for dopamine D_2 and D_3, serotonin 5-HT_{1A} and 5-HT_{2A} receptors and has moderate affinity for dopamine D_4, serotonin 5-HT_{2C} and 5-HT_7, alpha-1 adrenergic, and histamine H_1 receptors. Aripiprazole also exhibited moderate binding affinity for the serotonin reuptake site and no

appreciable affinity for cholinergic muscarinic receptors. Interaction with receptors other than dopamine and serotonin subtypes may explain some of the other clinical effects of aripiprazole.

Aripiprazole oral doses ranging from 0.5 mg to 30 mg administered once a day to healthy subjects for 2 weeks produced a dose-dependent reduction in the binding of ^{11}C-raclopride, a D_2/D_3 receptor ligand, to the caudate and putamen detected by positron emission tomography.

Clinical efficacy and safety

Maintenance treatment of schizophrenia in adults
The efficacy of Aripiprazole Otsuka 960 mg, administered once every two months, was established in part, on the basis of pharmacokinetic bridging through an open-label, multiple-dose, randomized, parallel-arm multi-centre study. The study demonstrated that Aripiprazole Otsuka 960 mg provides similar aripiprazole concentrations, and thus similar effectiveness, to Aripiprazole Otsuka 400 mg over the dosing interval (see section 5.2).

The similarity of aripiprazole plasma concentrations of Aripiprazole Otsuka 960 mg to Aripiprazole Otsuka 400 mg is presented in table 1.

Table 2: Geometric mean ratio and confidence interval (CI) following the fourth administration of Aripiprazole Otsuka 960 mg or the seventh and eighth Aripiprazole Otsuka 400 mg in the open-label study

Parameter	Ratio (Aripiprazole Otsuka 960 mg/Aripiprazole Otsuka 400 mg)	90 % CI
AUC_{0-56} [a]	1.006[c]	0.851 - 1.190
C_{56}/C_{28} [b]	1.011[d]	0.893 - 1.145
C_{max} [b]	1.071[c]	0.903 - 1.270

[a] AUC_{0-56} following the fourth administration of Aripiprazole Otsuka 960 mg or the sum of AUC_{0-28} following the seventh and eighth administration of Aripiprazole Otsuka 400 mg.

[b] Aripiprazole plasma concentrations following the fourth administration of Aripiprazole Otsuka 960 mg (C_{56}) or the eighth administration of Aripiprazole Otsuka 400 mg (C_{28}).

[c] Aripiprazole Otsuka 960 mg (n = 34), Aripiprazole Otsuka 400 mg (n = 32)

[d] Aripiprazole Otsuka 960 mg (n = 96), Aripiprazole Otsuka 400 mg (n = 82).

The effectiveness of Aripiprazole Otsuka 960 mg/720 mg in the treatment of schizophrenia is further supported by the established effectiveness of Aripiprazole Otsuka 400 mg/300 mg, as summarised

below:

Efficacy of Aripiprazole Otsuka 400 mg/300 mg
The efficacy of Aripiprazole Otsuka 400 mg/300 mg in the maintenance treatment of patients with schizophrenia was established in two randomised, double-blind, long-term trials.

The pivotal trial was a 38 week, randomised, double-blind, active-controlled trial designed to establish the efficacy, safety, and tolerability of this medicinal product administered as monthly injections compared to once daily oral aripiprazole tablets 10 mg to 30 mg as maintenance treatment in adult patients with schizophrenia. This trial consisted of a screening phase and 3 treatment phases: Conversion phase, oral stabilisation phase, and double-blind, active-controlled phase.

Six-hundred and sixty-two patients eligible for the 38-week double-blind, active-controlled phase were randomly assigned in a 2:2:1 ratio to double-blind treatment to one of 3 treatment groups: 1) Aripiprazole Otsuka 2) the stabilisation dose of oral aripiprazole 10 mg to 30 mg, or 3) aripiprazole long-acting injectable 50 mg/25 mg. The aripiprazole long-acting injectable 50 mg/25 mg dose was included as a low dose aripiprazole to test assay sensitivity for the non-inferiority design.

The results of analysis of the primary efficacy endpoint, the estimated proportion of patients experiencing impending relapse by end of week 26 of the double-blind, active-controlled phase, showed that Aripiprazole Otsuka 400 mg/300 mg is non-inferior to aripiprazole oral tablets 10 mg to 30 mg.

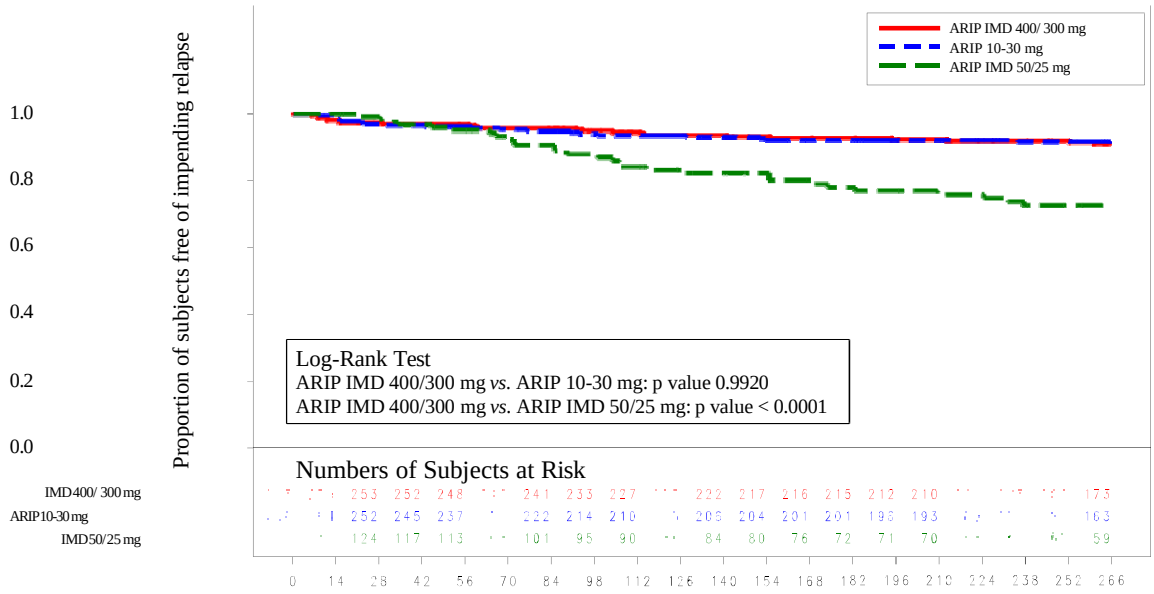
The estimated relapse rate by end of week 26 was 7.12 % for Aripiprazole Otsuka 400 mg/300 mg, and 7.76 % for oral aripiprazole tablets 10 mg to 30 mg, a difference of −0.64 %.

The 95 % CI (−5.26, 3.99) for the difference in the estimated proportion of patients experiencing impending relapse by end of week 26 excluded the predefined non-inferiority margin, 11.5 %. Therefore, Aripiprazole Otsuka 400 mg/300 mg is non-inferior to aripiprazole oral tablets 10 mg to 30 mg.

The estimated proportion of patients experiencing impending relapse by end of week 26 for Aripiprazole Otsuka 400 mg/300 mg was 7.12 %, which was statistically significantly lower than in aripiprazole long-acting injectable 50 mg/25 mg (21.80 %; p = 0.0006). Thus, superiority of Aripiprazole Otsuka 400 mg/300 mg over the aripiprazole long-acting injectable 50 mg/25 mg was established, and the validity of the trial design was confirmed.

The Kaplan-Meier curves of the time from randomisation to impending relapse during the 38-week, double-blind, active-controlled phase for Aripiprazole Otsuka 400 mg/300 mg, oral aripiprazole 10 mg to 30 mg, and aripiprazole long-acting injectable 50 mg/25 mg are shown in figure 1.

Figure 1: Kaplan-Meier product limit plot for time to exacerbation of psychotic symptoms/impending relapse



NOTE: ARIP IMD 400/300 mg = Aripiprazole Otsuka; ARIP 10 mg to 30 mg = oral aripiprazole; ARIP IMD 50/25 mg = Aripiprazole long-acting injectable

Further, the non-inferiority of Aripiprazole Otsuka compared to oral aripiprazole 10 mg to 30 mg is supported by the results of the analysis of the positive and negative syndrome scale score (PANSS).

Table 3: PANSS total score – change from baseline to week 38-Last Observation Carried Forward (LOCF): randomised efficacy sample[a, b]

	Aripiprazole Otsuka 400 mg/300 mg (n = 263)	Oral aripiprazole 10-30 mg/day (n = 266)	Aripiprazole long-acting injectable 50 mg/25 mg (n = 131)
Mean baseline (SD)	57.9 (12.94)	56.6 (12.65)	56.1 (12.59)
Mean change (SD)	−1.8 (10.49)	0.7 (11.60)	3.2 (14.45)
P-value	NA	0.0272	0.0002

[a] Negative change in score indicates improvement.

[b] Only patients having both baseline and at least one post baseline were included. P-values were derived from comparison for change from baseline within analysis of covariance model with treatment as term and baseline as covariate.

The second trial was a 52-week, randomised, withdrawal, double-blind, trial conducted in US adult patients with a current diagnosis of

schizophrenia. This trial consisted of a screening phase and 4 treatment phases: Conversion, oral stabilisation, IM stabilisation, and double-blind placebo-controlled. Patients fulfilling the oral stabilisation requirement in the oral stabilisation phase were assigned to receive, in a single-blind fashion, Aripiprazole Otsuka 400 mg/300 mg and began an IM phase for a minimum of 12 weeks and a maximum of 36 weeks. Patients eligible for the double-blind, placebo- controlled phase were randomly assigned in a 2:1 ratio to double-blind treatment with Aripiprazole Otsuka 400 mg/300 mg or placebo, respectively.

The final efficacy analysis included 403 randomised patients and 80 exacerbations of psychotic symptoms/impending relapse events. In the placebo group 39.6 % of the patients had progressed to impending relapse, whilst in the Aripiprazole Otsuka 400 mg/300 mg group impending relapse occurred in 10 % of the patients; thus, patients in the placebo group had a 5.03-fold greater risk of experiencing impending relapse.

Prolactin

In the double-blind, active-controlled phase of the 38-week trial, from baseline to last visit there was a mean decrease in prolactin levels in Aripiprazole Otsuka 400 mg/300 mg (−0.33 ng/mL) compared with a mean increase in oral aripiprazole tablets 10 mg to 30 mg (0.79 ng/mL; $p < 0.01$). The incidence of Aripiprazole Otsuka 400 mg/300 mg patients with prolactin levels > 1 time the upper limit of normal range (ULN) at any assessment was 5.4 % compared with 3.5 % of the patients on oral aripiprazole tablets 10 mg to 30 mg.

Male patients generally had a higher incidence than female patients in each treatment group.

In the double-blind placebo-controlled phase of the 52-week trial, from baseline to last visit there was a mean decrease in prolactin levels in Aripiprazole Otsuka 400 mg/300 mg a (−0.38 ng/mL) compared with a mean increase in placebo (1.67 ng/mL). The incidences of Aripiprazole Otsuka 400 mg/300 mg patients with prolactin levels > 1 time the ULN was 1.9 % compared to 7.1 % for placebo patients.

Acute treatment of schizophrenia in adults

The efficacy of Aripiprazole Otsuka 400 mg/300 mg in acutely relapsed adult patients with schizophrenia was established in a short-term (12-week), randomised, double-blind, placebo-controlled trial

(n = 339). The primary endpoint (change in PANSS total score from baseline to week 10) showed superiority of Aripiprazole Otsuka 400 mg/300 mg (n = 167) over placebo (n = 172). Similar to the PANSS total score, both the PANSS positive and negative subscale scores also showed an improvement (decrease) from baseline over time.

Table 4: PANSS total score – change from baseline to week 10: randomised efficacy sample [a]

	Aripiprazole Otsuka 400 mg/300 mg	**Placebo**
Mean baseline (SD)	102.4 (11.4) n = 162	103.4 (11.1) n = 167
LS mean change (SE)	−26.8 (1.6) n = 99	−11.7 (1.6) n = 81
P-value	< 0.0001	
Treatment difference[b] (95 % CI)	−15.1 (−19.4, −10.8)	

[a] Data were analysed using a mixed model repeated measures (MMRM) approach. The analysis included only subjects who were randomly assigned to treatment, given at least one injection, had baseline and at least one post- baseline efficacy assessment.

[b] Difference (Aripiprazole Otsuka minus placebo) in least squares mean change from baseline.

Aripiprazole Otsuka 400 mg/300 mg also showed statistically significant improvement in symptoms represented by Clinical Global Impressions Severity, CGI-S (CGI-S) score change from baseline to week 10.

Personal and social functioning were evaluated using the Personal and Social Performance (PSP) scale. The PSP is a validated clinician-rated scale that measures personal and social functioning in four domains: socially useful activities (e.g., work and study), personal and social relationships, self-care, and disturbing and aggressive behaviours. There was a statistically significant treatment difference in favour of Aripiprazole Otsuka 400 mg/300 mg compared to placebo at week 10 (+7.1, $p < 0.0001$, 95 % CI: 4.1, 10.1 using an ANCOVA model (LOCF)).

The safety profile was consistent with that known to Aripiprazole Otsuka 400 mg/300 mg. Nevertheless, there were differences from what has been observed with maintenance use in the treatment of schizophrenia. In a short- term (12-week), randomised, double-blind, placebo-controlled trial with Aripiprazole Otsuka 400 mg/300 mg treated subjects the symptoms which had at least twice the incidence of placebo were increased weight and akathisia. The

incidence of weight gain of ≥ 7 % from baseline to last visit (Week 12) was 21.5 % for Aripiprazole Otsuka 400 mg/300 mg compared with the placebo group 8.5 %. Akathisia was the most frequently observed EPS symptom (Aripiprazole Otsuka 400 mg/300 mg 11.4 % and placebo group 3.5 %).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Aripiprazole Otsuka in all subsets of the paediatric population in schizophrenia (see section 4.2 for information on paediatric use).

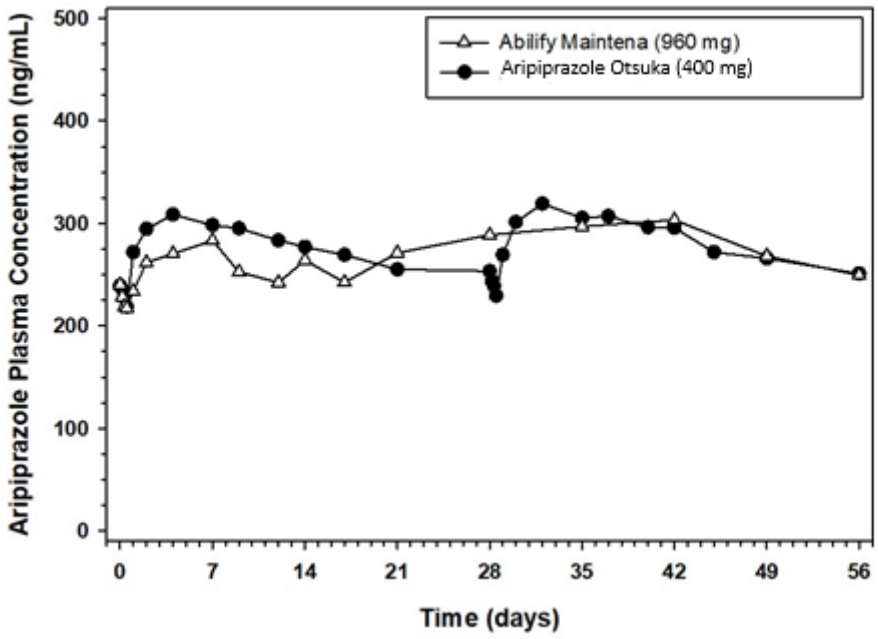
5.2 Pharmacokinetic properties

The pharmacokinetics of aripiprazole after administration of Aripiprazole Otsuka, presented below, are based on gluteal administration.

Aripiprazole Otsuka 960 mg/720 mg delivers aripiprazole over a 2-month period, compared to Aripiprazole Otsuka 400 mg/300 mg. Aripiprazole Otsuka doses of 960 mg and 720 mg, administered in the gluteal muscle, result in aripiprazole total exposure ranges that are encompassed within the exposure range corresponding to 300 mg and 400 mg doses of Aripiprazole Otsuka (dosed once a month), respectively. Additionally, mean observed maximum plasma concentrations (C_{max}) and plasma concentrations of aripiprazole at the end of the dosing interval were similar for Aripiprazole Otsuka 960 mg/720 mg as compared to corresponding doses of Aripiprazole Otsuka 400 mg/300 mg (see section 5.1).

The mean aripiprazole plasma concentration compared to the time profiles following the fourth administration of Aripiprazole Otsuka 960 mg (n = 102) or the seventh and eighth administration of Aripiprazole Otsuka 400 mg (n = 93) in the gluteal muscle of patients with schizophrenia (and bipolar I disorder) are shown in figure 2.

Figure 2: Mean Aripiprazole plasma concentration vs. time profile following the fourth administration of Aripiprazole Otsuka 960 mg or the seventh and eighth administration of Aripiprazole Otsuka 400 mg



Absorption/Distribution

Aripiprazole absorption into the systemic circulation is slow and prolonged following gluteal injection due to low solubility of aripiprazole particles. The release profile of aripiprazole from Aripiprazole Otsuka *960 mg/720 mg* results in sustained plasma concentrations over 2 months following gluteal injection(s). The release of the active substance after a single 780 mg dose of 2-monthly aripiprazole ready-to-use long-acting-injectable starts Day 1 and lasts for as long as 34 weeks.

Biotransformation

Aripiprazole is extensively metabolised by the liver primarily by three biotransformation pathways: dehydrogenation, hydroxylation, and N-dealkylation. Based on *in vitro* studies, CYP3A4 and CYP2D6 enzymes are responsible for dehydrogenation and hydroxylation of aripiprazole, and N-dealkylation is catalysed by CYP3A4. Aripiprazole is the predominant medicinal product moiety in systemic circulation. Following administration of multiple doses of Aripiprazole Otsuka 960 mg/720 mg, dehydro-aripiprazole, the active metabolite, represents approximately 30 % of aripiprazole AUC in plasma.

Elimination

Following a single oral dose of [^{14}C]-labelled aripiprazole, approximately 25 % and 55 % of the administered radioactivity was recovered in the urine faeces, respectively. Less than 1 % of unchanged aripiprazole was excreted in the urine and approximately 18 % was recovered unchanged in the faeces.

Pharmacokinetics in special patient groups

No specific studies have been performed with Aripiprazole Otsuka in special patient groups.

CYP2D6 poor metabolisers
Based on population pharmacokinetic analysis, the plasma concentrations of aripiprazole is around 2-fold higher in poor metabolisers of CYP2D6 compared with normal CYP2D6 metabolisers. (see section 4.2).

Elderly
After oral administration of aripiprazole, there are no differences in the pharmacokinetics of aripiprazole between healthy elderly and younger adult subjects. Similarly, there was no detectable effect of age in a population pharmacokinetic analysis of aripiprazole in schizophrenia patients.

Gender
After oral administration of aripiprazole, there are no differences in the pharmacokinetics of aripiprazole between healthy male and female subjects. Similarly, there was no clinically relevant effect of gender in a population pharmacokinetic analysis of aripiprazole in clinical trials in patients with schizophrenia.

Smoking
Population pharmacokinetic evaluation of oral aripiprazole has revealed no evidence of clinically relevant effects from smoking on the pharmacokinetics of aripiprazole.

Race
Population pharmacokinetic evaluation showed no evidence of race-related differences on the pharmacokinetics of aripiprazole.

Renal impairment
In a single-dose study with oral administration of aripiprazole, the pharmacokinetic characteristics of aripiprazole and dehydro-aripiprazole were found to be similar in patients with severe renal disease compared to that in young healthy subjects.

Hepatic impairment
A single-dose study with oral administration of aripiprazole to subjects with varying degrees of liver cirrhosis (Child-Pugh Classes A, B, and C) did not reveal a significant effect of hepatic impairment on the pharmacokinetics of aripiprazole and dehydro-aripiprazole, but the study included only 3 patients with Class C liver cirrhosis, which is insufficient to draw conclusions on their metabolic capacity.

5.3 Preclinical safety data

The toxicological profile for aripiprazole administered to experimental animals by intramuscular injection is generally similar to that seen following oral administration at comparable plasma levels. With intramuscular injection, however an inflammatory response was seen at the injection site, and consisted of granulomatous inflammation,

foci (deposited active substance), cellular infiltrates, oedema (swelling) and, in monkeys, fibrosis. These effects gradually resolved with discontinuation of dosing.

Non-clinical safety data for orally administered aripiprazole reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

Oral aripiprazole

For oral aripiprazole, toxicologically significant effects were observed only at doses or exposures that were sufficiently in excess of the maximum human dose or exposure, indicating that these effects were limited or of no relevance to clinical use. These included: dose-dependent adrenocortical toxicity in rats after 104 weeks of oral administration at approximately 3- to 10-times the mean steady-state AUC at the maximum recommended human dose and increased adrenocortical carcinomas and combined adrenocortical adenomas/carcinomas in female rats at approximately 10-times the mean steady-state AUC at the maximum recommended human dose. The highest non-tumorigenic exposure in female rats was approximately 7-times the human exposure at the recommended dose.

An additional finding was cholelithiasis as a consequence of precipitation of sulphate conjugates of hydroxy-metabolites of aripiprazole in the bile of monkeys after repeated oral dosing at 25 mg/kg/day to 125 mg/kg/day or approximately 16- to 81-times the maximum recommended human dose based on mg/m^2.

However, the concentrations of the sulphate conjugates of hydroxy-aripiprazole in human bile at the highest dose proposed, 30 mg per day, were no more than 6 % of the bile concentrations found in the monkeys in the 39-week study and are well below (6 %) their limits of in vitro solubility.

In repeated dose studies in juvenile rats and dogs, the toxicity profile of aripiprazole was comparable to that observed in adult animals, and there was no evidence of neurotoxicity or adverse events on development.

Based on results of a full range of standard genotoxicity tests, aripiprazole was considered non-genotoxic in humans. Aripiprazole did not impair fertility in reproductive toxicity studies.

Developmental toxicity, including dose-dependent delayed foetal ossification and possible teratogenic effects, were observed in rats at doses resulting in sub-therapeutic exposures (based on AUC) and in rabbits at doses resulting in exposures approximately 3- and 11-times the mean steady-state AUC at the maximum recommended clinical dose. Maternal toxicity occurred at doses similar to those eliciting developmental toxicity.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Carmellose sodium
Macrogol
Povidone (E1201)
Sodium chloride
Sodium dihydrogen phosphate monohydrate (E339)
Sodium hydroxide (for pH adjustment) (E524)
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not freeze.

6.5 Nature and contents of container

Pre-filled syringe (cyclic-olefin-copolymer) with bromobutyl plunger stopper and bromobutyl tip-cap and polypropylene plunger rod and finger grip.

Aripiprazole Otsuka 720 mg prolonged-release suspension for injection in pre-filled syringe

Each 720 mg pack contains one pre-filled syringe, and two sterile safety needles: one 38 mm (1.5 inch) 22 gauge and one 51 mm (2 inch) 21 gauge.

6.6 Special precautions for disposal

Tap the syringe on your hand at least 10 times. After tapping, shake the syringe vigorously for at least 10 seconds.

Gluteal muscle administration
The recommended needle for gluteal administration is a 38 mm (1.5 inch), 22 gauge sterile safety needle; for obese patients (Body mass index > 28 kg/m^2), a 51 mm (2 inch), 21 gauge sterile safety needle should be used.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Full instructions for use and handling of Aripiprazole Otsuka 960 mg/720 mg are provided in the package leaflet (information intended for healthcare professionals).

7 MARKETING AUTHORISATION HOLDER

Otsuka Pharmaceutical Netherlands B.V.

Herikerbergweg 292

1101 CT, Amsterdam

Netherlands

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 50697/0034

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26/04/2024

10 DATE OF REVISION OF THE TEXT

21/08/2025