NEW ZEALAND DATA SHEET

1 PRODUCT NAME

Aripiprazole Lupin

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Aripiprazole tablets 5, 10, 15, 20, 30 mg

3 PHARMACEUTICAL FORM

Aripiprazole Lupin tablets 5 mg are white, round, biconvex, bevelled edged tablets
Aripiprazole Lupin tablets 10 mg are white, oval shaped, bevelled edged tablets
Aripiprazole Lupin tablets 15 mg are white, round, bevelled edged tablets
Aripiprazole Lupin tablets 20 mg are white, round, biconvex, tablets
Aripiprazole Lupin tablets 30 mg are white, round, biconvex, bevelled edged tablets

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Aripiprazole Lupin tablets are indicated for the treatment of schizophrenia including maintenance of clinical improvement during continuation therapy.

Aripiprazole Lupin tablet monotherapy is indicated for acute and maintenance treatment of manic and mixed episodes with Bipolar I Disorder with or without psychotic features.

Aripiprazole Lupin tablets are indicated as an adjunctive therapy to either lithium or valporate for the acute treatment of manic and mixed episodes associated with Bipolar I Disorder with or without psychotic features.

4.2 Dose and Method of Administration

Recommended Dosage

Schizophrenia

Adults

The recommended starting dose for Aripiprazole Lupin tablets is 10 or 15 mg/day administered on a once-a-day schedule without regard to meals. Doses in the range of 10 to 30 mg/day have been effective in clinical trials. Daily dosage may be adjusted on the basis of individual clinical status within the range of 10-30 mg daily. Dosage increases should not be made before 2 weeks, the time needed to achieve steady state. There is no evidence that doses higher than 15 mg/day are more effective than the recommended starting dose of 10-15 mg.

The maintenance dose for Aripiprazole Lupin tablets is 15 mg/day.

Bipolar Disorder
Acute Treatment
Adults
The recommended starting and target dose is 15 mg as monotherapy or as adjunctive therapy with lithium or valporate given once a day, without regard to meals. The dose can be increased to 30 mg/day based on clinical response. The safety of doses above 30 mg/day has not been evaluated in clinical trials.

Maintenance Therapy
Adults
Maintenance of efficacy in Bipolar I disorder was demonstrated in a trial involving patients who had been symptomatically stable on aripiprazole tablets (15 mg/day or 30 mg/day, as monotherapy) for at least 6 consecutive weeks. These patients were discontinued from those medications and randomised to either aripiprazole tablets, at the same dose they were stabilised on, or placebo, and observed for relapse. Patients should be periodically reassessed to determine the continued need for maintenance treatment.

Renal Impairment
No dosage adjustment is required in adult patients with renal impairment.

Hepatic Impairment
No dosage adjustment is required for adult patients with hepatic impairment (Child-Pugh Class A, B or C).

Paediatric
The safety and effectiveness of Aripiprazole Lupin tablets in patients under 18 years of age has not been established.

Elderly
No dosage adjustment is required for patients ≥65 years of age.

Gender
No dosage adjustment is required for female adult patients relative to male adult patients.

Concomitant Medications
Dosage adjustment for patients taking Aripiprazole Lupin tablets concomitantly with potential CYP3A4 inhibitors: When concomitant administration of a potent CYP3A4 inhibitor with Aripiprazole Lupin tablets occurs, the Aripiprazole Lupin tablet dose should be decreased. When the CYP3A4 inhibitor is withdrawn from the combination therapy, the Aripiprazole Lupin tablet dose should then be increased.

Dosage adjustment for patients taking Aripiprazole Lupin tablets concomitantly with potential CYP2D6 inhibitors: When concomitant administration of potential CYP2D6 inhibitors such as quinidine, fluoxetine, or paroxetine with Aripiprazole Lupin tablets occurs, the Aripiprazole Lupin tablet dose should be halved. When the CYP2D6 inhibitor is withdrawn from the combination therapy, the Aripiprazole Lupin tablet dose should then be increased.

Dosage adjustment for patients taking Aripiprazole Lupin tablets concomitantly with multiple medications that inhibit CYP3A4 and CYP2D6: Although no clinical studies have been conducted in which aripiprazole tablets were taken together with multiple drugs that inhibit CYP3A4 and CYP2D6, consideration should be given to reducing the daily dose of Aripiprazole Lupin tablets in individual circumstances.

Dosage adjustment for patients taking Aripiprazole Lupin tablets concomitantly with potential CYP3A4 inducers: When a potent CYP3A4 inducer such as carbamazepine is added to Aripiprazole Lupin tablet therapy, the Aripiprazole Lupin tablet dose should be increased. Additional dose increases should be based on clinical evaluation. When the CYP3A4 inducer is withdrawn from the combination therapy, the Aripiprazole Lupin tablet dose should then be reduced.

Smoking Status

No dosage adjustment is required for smoking patients relative to non-smoking patients.

Switching from Other Antipsychotics

Any of the following methods can be used safely for switching patients to Aripiprazole Lupin tablets from another antipsychotic monotherapy:

- immediate discontinuation of the patient's current antipsychotic regimen and immediate initiation of Aripiprazole Lupin tablets;
- immediate initiation of Aripiprazole Lupin tablets while tapering off the current antipsychotic regimen over a 2-week period;
- upward titration of Aripiprazole Lupin tablets over a 2-week period and simultaneous tapering off of the patient's current antipsychotic regimen over the same 2-week period.

4.3 Contraindications

Aripiprazole Lupin tablets are contraindicated in patients who are hypersensitive to aripiprazole or any of the excipients.

For specific information about the contraindications of mood stabilisers refer to the Contraindications section of the prescribing information for these products when adjunctive therapy is indicated.

4.4 Special Warnings and Precautions for Use

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10- week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature.

In three placebo-controlled trials of aripiprazole tablets in elderly patients with psychosis associated with Alzheimer's disease, cerebrovascular adverse events (e.g. stroke, transient ischaemic attack), including fatalities, occurred in 1.3% (8/595) of aripiprazole-treated patients compared with 0.6% (2/343) of placebo-treated patients during the 10-week double-blind period or within 30 days of the last dose for those who discontinued the study during the double-blind phase. The all cause mortality rate in the same trials over the same period was 3.5% (21/595) in aripiprazole -treated patients and 1.7% (6/343) in the placebo group.

Aripiprazole is not approved for the treatment of patients with dementia-related psychosis.

General

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

Suicide

The possibility of a suicide attempt is inherent in psychotic illnesses and Bipolar Disorder, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for Aripiprazole Lupin tablets should be written for the smallest quantity consistent with good patient management, in order to reduce the risk of overdose.

Tardive Dyskinesia

The risk of tardive dyskinesia increases with long-term exposure to antipsychotic treatment. If signs and symptoms of tardive dyskinesia appear in a patient on Aripiprazole Lupin tablets, a dose reduction or drug discontinuation should be considered. These symptoms can temporally deteriorate or even arise after discontinuation of treatment.

Neuroleptic Malignant Syndrome

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs including Aripiprazole Lupin tablets. Rare cases of NMS occurred during aripiprazole treatment in the worldwide clinical database. 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 kinase, myoglobinuria (rhabdomyolysis), and acute renal failure. If a patient develops signs and symptoms indicative of NMS,or presents with unexplained high fever without additional clinical manifestations of NMS, all antipsychotic drugs, including Aripiprazole Lupin tablets must be discontinued.

Seizure

In short-term, placebo-controlled trials, seizures occurred in 0.1% (3/2,467) of adult patients treated with aripiprazole.

As with other antipsychotic drugs, Aripiprazole Lupin tablets should be used cautiously in patients who have a history of seizure disorder or have conditions associated with seizures.

Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients with Dementia- Related Psychosis

In placebo-controlled clinical studies (2 flexible dose and 1 fixed dose study) of dementia-related psychosis, there was an increased incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, in aripiprazole-treated patients (mean age: 84 years; range: 78-88 years). In the fixed dose study, there was a statistically significant dose response relationship for cerebrovascular adverse events in patients treated with aripiprazole.

Aripiprazole is not approved for the treatment of patients with dementia-related psychosis. (See also **Section 4.4 Special Warnings and Precautions for Use - Increased Mortality in Elderly Patients with Dementia-Related Psychosis and Use in Patients with Concomitant Illness: Safety Experience in Elderly Patients with Psychosis Associated with Alzheimer's Disease**.)

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 atypical antipsychotic agents including aripiprazole. In clinical trials with aripiprazole tablets, there were no significant differences in the incidence rates of hyperglycaemia-related adverse events (including diabetes) or in abnormal glycaemia laboratory values compared to placebo. Precise risk estimates for hyperglycaemia-related adverse events in patients treated with aripiprazole tablets and with other atypical antipsychotic agents are not available to allow direct comparisons. Patients treated with any antipsychotic agents, including Aripiprazole Lupin tablets, should be observed for signs and symptoms of hyperglycaemia (such as polydipsia, polyphagia and

weakness) and patients with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control.

Cardiovascular Adverse Events

Potentially due to its α1-adrenergic receptor antagonism, Aripiprazole Lupin tablets may be associated with orthostatic hypotension.

The incidence of orthostatic hypotension-associated events from short-term, placebo-controlled trials of adult patients on oral aripiprazole (n=2,467) included (aripiprazole incidence, placebo incidence): orthostatic hypotension (1%, 0.3%), postural dizziness (0.5%, 0.3%), and syncope (0.5%, 0.4%).

Orthostatic hypotension occurred in 0.8% (112/13,543) of oral aripiprazole-treated patients during clinical trials.

As with other atypical antipsychotics, Aripiprazole Lupin tablets 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 or conditions which would predispose patients to hypotension (dehydration, hypovolaemia, and treatment with antihypertensive medications).

Venous Thromboembolism

Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. 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 aripriprazole and preventive measures taken.

Weight Gain

Weight gain is commonly seen in schizophrenic and bipolar mania patients due to co-morbidities, use of antipsychotics known to cause weight gain, poorly managed life-style and might lead to severe complications. Weight gain has been reported post-marketing among patients prescribed aripiprazole. When seen, it is usually in those with significant risk factors such as history of diabetes, thyroid disorder or pituitary adenoma. In clinical trials aripiprazole has not been shown to induce clinically relevant weight gain in adults.

Body Temperature Regulation

Disruption of the body's ability to increase or reduce core body temperature has been attributed to antipsychotic agents, including aripiprazole tablets. Appropriate care is advised when prescribing Aripiprazole Lupin tablets for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

Patients should be advised regarding appropriate care in avoiding overheating and dehydration.

Dysphagia

Oesophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aripiprazole Lupin tablets and other antipsychotic drugs should be used cautiously in patients at risk of aspiration pneumonia (e.g. elderly patients).

Akathisia

Class effect: The presentation of akathisia may be variable and comprises subjective complaints of restlessness and an overwhelming urge to move and either distress or motor phenomena such as pacing, swinging of the legs while seated, rocking from foot to foot, or both. Particular attention should be paid

to the monitoring for such symptoms and signs as, left untreated, akathisia is associated with poor compliance and an increased risk of relapse.

Leukopenia, Neutropenia and Agranulocytosis

Class Effect: In clinical trial and/or post-marketing experience, events of leucopenia/neutropenia have been reported temporally related to antipsychotic agents, including aripiprazole.
Agranulocytosis has also been reported.

Possible risk factors for leucopenia/neutropenia include pre-existing low white blood cell count (WBC) and history of drug-induced leucopenia/neutropenia. Patients with a history of a clinically significant low WBC or drug-induced leucopenia/neutropenia should have their complete blood cell (CBC) monitored frequently during the first few months of therapy and discontinuation of aripiprazole should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Patients with clinically significant neutopenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutopenia (absolute neutorphil count <1000/mm^3) should discontinue aripiprazole and have their WBC followed until recovery.

Potential for Cognitive and Motor Impairment

Aripiprazole Lupin tablets, like other antipsychotics, may have the potential to impair judgment, thinking, or motor skills. In short-term, placebo-controlled trials, somnolence (including sedation) was reported as follows (aripiprazole incidence, placebo incidence): in adult patients (n=2,467) treated with oral aripiprazole (11%, 6%). Somnolence (including sedation) led to discontinuation in 0.3% (8/2,467) of adult patients on oral aripiprazole in short-term, placebo-controlled trials.

Despite the relatively modest increased incidence of these events compared to placebo, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that therapy with aripiprazole does not affect them adversely.

Pathological gambling and 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 spending, 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 spending, 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 medication was discontinued. Impulse control disorders may result in harm to the patient and others if not recognized. Consider dose reduction or stopping the medication if a patient develops such urges while taking aripiprazole (See **Section 4.8 Adverse Effects (Undesirable Effects)**).

Use in Patients with Concomitant Illness

Clinical experience with aripiprazole tablets in patients with certain concomitant systemic illnesses is limited. (See **Section 5.1 Pharmacodynamic Properties - Renal Impairment and Hepatic Impairment**).

Aripiprazole has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies.

Safety Experience in Elderly Patients with Psychosis Associated with Alzheimer's Disease: In three, 10-week, placebo-controlled studies of aripiprazole in elderly patients with psychosis associated

with Alzheimer's disease (n=938; mean age: 82.4 years; range: 56-99 years), the treatment-emergent adverse events that were reported at an incidence of ≥5% and aripiprazole incidence at least twice that for placebo were lethargy [placebo 2%, aripiprazole 5%], somnolence (including sedation) [placebo 3%, aripiprazole 8%] and incontinence (primarily, urinary incontinence) [placebo 1%, aripiprazole 5%].

The safety and efficacy of Aripiprazole Lupin tablets in the treatment of patients with psychosis associated with dementia have not been established. Aripiprazole Lupin tablets are not indicated for the treatment of psychosis associated with Alzheimer's disease. (See also **Section 4.4 Special Warnings and Precautions for Use- Increased Mortality in Elderly Patients with Dementia-Related Psychosis and Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients with Dementia-Related Psychosis**).

Drug Abuse and Dependence

Aripiprazole has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. In self-administration studies in rats and monkeys, Aripiprazole demonstrated marginal to no abuse potential. In physical dependence studies in rats and monkeys, modest withdrawal symptoms were observed upon abrupt cessation of dosing. While the clinical trials did not reveal any tendency for any drug-seeking behaviour, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed.

Consequently, patients should be evaluated carefully for a history of drug abuse and such patients should be observed closely for signs of Aripiprazole Lupin misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behaviour).

Use in Labour and Delivery

The effect of aripiprazole on labour and delivery has not been studied.

Use in Children

Safety and effectiveness in patients under 18 years of age have not been established.

Use in the Elderly

Placebo-controlled studies of aripiprazole in schizophrenia or Bipolar Mania did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Of the 13,543 patients treated with oral aripiprazole in clinical trials, 1,073 (8%) were ≥65 years old and 799 (6%) were ≥75 years old. The majority (81%) of the 1,073 patients were diagnosed with Dementia of the Alzheimer's Type.

Studies of elderly patients with psychosis associated with Alzheimer's disease have suggested that there may be a different tolerability profile in this population compared to younger patients with schizophrenia (see **Section 4.4 Special Warnings and Precautions for Use** - Increased Mortality in Elderly Patients with Dementia-Related Psychosis and Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients with Dementia-Related Psychosis and Use in Patients with Concomitant Illness). The safety and efficacy of Aripiprazole Lupin tablets in the treatment of patients with psychosis associated with Alzheimer's disease has not been established. Aripiprazole Lupin tablets are not indicated for the treatment of psychosis associated with Alzheimer's disease.

There was no effect of age on the pharmacokinetics of a single, 15-mg dose of aripiprazole. Aripiprazole clearance was decreased by 20% in elderly subjects (>65 years) compared to younger adult subjects (18 to 64 years), but there was no detectable effect of age in the population pharmacokinetic analysis in schizophrenia patients.

Concomitant Medication

Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions. (See **Sections 4.4 Special Warnings and Precautions for Use**, **Section 4.5 Interactions with Other Medicines and Other Forms of Interactions** and **Section 4.2 Dose and Method of Administration – Concomitant Medications**)

4.5 Interactions with Other Medicines and Other Forms of Interactions

CNS Drugs (including Alcohol)

Given the primary CNS effects of Aripiprazole Lupin tablets, caution should be used when Aripiprazole Lupin tablets are taken in combination with other centrally acting drugs and alcohol. Patients should be advised to avoid alcohol while taking Aripiprazole Lupin tablets.

Co-administration of lithium titrated upwards from a starting dose of 900 mg until serum lithium concentrations near the upper end of the lithium therapeutic concentration range (1.0 – 1.4 mmol/l) were achieved and maintained for at least 5 days or until dose-limiting adverse events were observed and valproate (divalproex sodium) titrated upwards from a starting dose of 250 mg twice daily to achieve serum concentrations within the therapeutic range of 50 – 125 μg/mL for at least 14 days, with 30 mg Aripiprazole Lupin tablets once daily had no clinically significant effects on the pharmacokinetics of aripiprazole. Nor was there any clinically significant change in valproic acid or lithium pharmacokinetics when aripiprazole 30 mg once daily was administered concomitantly for 7 days with either divalproex sodium 500 mg every 12 hours or controlled release lithium 450 mg every 12 hours.

Antihypertensive Agents

Due to its α1-adrenergic receptor antagonist activity, Aripiprazole Lupin tablets have the potential to enhance the effect of certain antihypertensive agents.

Inhibitors and Inducers of CYP2D6 & CYP3A4

Aripiprazole is metabolized by multiple pathways primarily involving the CYP2D6 and CYP3A4 enzymes. In clinical studies with healthy subjects, potent inhibitors of CYP2D6 (quinidine) and 3A4 (ketoconazole) decreased oral clearance of aripiprazole by 52% and 38%, respectively. Other potent inhibitors of CYP3A4 and CYP2D6 may be expected to have similar effects. When concomitant administration of quinidine or ketoconazole with aripiprazole occurs, the aripiprazole dose should be halved. When the inhibitor is withdrawn from the combination therapy, the aripiprazole dose should then be increased. (See **Section 4.2 Dose and Method of Administration - Concomitant Medication**)

No data are available for use of Aripiprazole Lupin tablets with other inhibitors of CYP3A4 or CYP2D6. Examples of medicines or substances that have the potential to inhibit CYP3A4 or CYP2D6 include, but are not limited to, clarithromycin, erythromycin, itraconazole, fluconazole, ritonavir, indinavir, nefazodone, cyclosporin, amiodarone, cimetidine, fluoxetine, paroxetine and grapefruit juice.

In a clinical study in patients with schizophrenia or schizo-affective disorder, co-administration of carbamazepine (200 mg twice daily), a potent CYP3A4 inducer, with aripiprazole (30 mg daily) resulted in an approximate 70% decrease in AUC values of both aripiprazole and its active metabolite, dehydro-aripiprazole. Other potent inducers of CYP3A4 and CYP2D6 may be expected to have similar effects. When a potent inducer like carbamazepine is added to aripiprazole therapy, the aripiprazole dose should be increased. Additional dose increases should be based on clinical evaluation. When the inducer is withdrawn from the combination therapy, the aripiprazole dose should then be reduced. (See **Section 4.2 Dose and Method of Administration – Dosage adjustment for patients taking CYP3A4 inducers**)

Inhibitors and Inducers of CYP1A1, CYP1A2, CYP2C9, and CYP2C19

Aripiprazole is not metabolized by CYP1A1, CYP1A2, CYP2C9, and CYP2C19 in vitro, suggesting that interactions with medications or other factors (e.g., smoking), which are inhibitors or inducers of these enzymes, are unlikely.

Effects of Aripiprazole Lupin tablets on Substrates for CYP2D6, CYP2C9, CYP2C19, CYP3A4, & CYP1A2

Aripiprazole and dehydro-aripiprazole were weak inhibitors of CYP2C9, CYP2C19, CYP2D6, and CYP3A4-mediated metabolism in vitro (IC50 values 2.4 –25 µM). Neither aripiprazole nor dehydro-aripiprazole inhibited CYP1A2 -mediated metabolism in vitro (IC50 value >50 – 66 µM).

In clinical studies, 10-30 mg/day doses of aripiprazole tablets had no significant effect on metabolism of substrates of CYP2D6 (dextromethorphan), CYP2C9 (warfarin), CYP2C19 (omeprazole, warfarin), and CYP3A4 (dextromethorphan). Thus, Aripiprazole Lupin tablets are unlikely to cause clinically important drug interactions mediated by these enzymes.

Famotidine

There was no significant effect of the H_2 antagonist famotidine, a potent gastric acid blocker, on the pharmacokinetics of aripiprazole.

Food

Aripiprazole Lupin tablets can be administered without regard to meals. Following administration of a 15-mg Aripiprazole Lupin tablets tablet with a standard hi-fat meal, the C_{max} of aripiprazole and its active metabolite, dehydro-aripiprazole, increased by 11%. The AUC of aripiprazole was increased by 18% and that of the active metabolite by 14%. Food delayed T_{max} by 3 hours for aripiprazole and 12 hours for the active metabolite.

4.6 Fertility, Pregnancy and Lactation

Pregnancy (Category B3)

In animal studies aripiprazole demonstrated developmental toxicity, including possible teratogenic effects, in rats and rabbits.

Pregnant rats were treated with oral doses of 3, 10, and 30 mg/kg/day (1, 3, and 9 times the MRHD on a mg/m^2 basis) of aripiprazole during the period of organogenesis. At 30 mg/kg, treatment was associated with slightly prolonged gestation, and a slight delay in foetal development as evidenced by decreased foetal weight, un-descended testes, and delayed skeletal ossification. There were no adverse effects on embryo-foetal or pup survival. Delivered offspring had increased incidences of hepatodiaphragmatic nodules and diaphragmatic hernia at 30 mg/kg (the other doses were not examined for these findings). (A low incidence of diaphragmatic hernia was also seen in the foetuses exposed to 30 mg/kg). Post-natally, decreased pup weight (persisting into adulthood) was seen at 30 mg/kg, delayed vaginal opening was seen at 10 and 30 mg/kg, and impaired reproductive performance (decreased fertility rate, corpora lutea, implants, and live foetuses, and increased post-implantation loss, likely mediated through effects on female offspring) was seen at 30 mg/kg. Maternal toxicity was seen at 30 mg/kg, which was similar to doses eliciting embryotoxicity.

Pregnant rabbits were treated with oral doses of 10, 30, and 100 mg/kg/day (2, 3, and 11 times human exposure at MRHD based on AUC and 8, 24, and 81 times the MRHD based on mg/m^2) of aripiprazole during the period of organogenesis. Decreased maternal food consumption, and increased abortions were seen at 100 mg/kg. Treatment caused increased foetal mortality (100 mg/kg), decreased foetal weight (30 mg and 100 mg/kg), increased incidence of a skeletal abnormality (fused sternebrae at 100 mg/kg) and minor skeletal variations (100 mg/kg).

Rats were treated with oral doses of 3, 10, and 30 mg/kg/day (1, 3, and 9 times the MRHD on a mg/m^2 basis) of aripiprazole from late gestation through weaning. At 30 mg/kg, maternal toxicity, slightly prolonged gestation, an increase in stillbirths, poor postnatal care/nursing, and decreases in pup weight (persisting into adulthood) and survival were seen.

Neonates exposed to antipsychotic drugs (including aripiprazole) during the third trimester of pregnancy are at risk of experiencing extrapyramidal neurological disturbances and/or withdrawal symptoms following delivery. There have been post-market reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self- limited, in other cases neonates have required additional medical treatment or monitoring.

Aripiprazole Lupin tablets should be used during pregnancy only if the anticipated benefit outweighs the risk and the administered dose and duration of treatment should be as low and as short as possible.

Patients should be advised to notify their doctors if they become pregnant or intend to become pregnant.

Breast feeding

Aripiprazole and/or its metabolites have been found in the milk of lactating rats. Aripiprazole is excreted in breast milk. Patients should be advised not to breast-feed if they are taking Aripiprazole Lupin tablets.

Fertility

Aripiprazole had no effect on fertility in female rats treated orally with 2, 6, and 20 mg/kg/day (0.6, 2, and 6 times the MRHD based on mg/m^2) for 2 weeks prior to mating through gestation day 7. Drug-related effects (persistent dioestrus and increased mating time pre-implantation losses, and corpora lutea) observed at all doses were considered the result of perturbed oestrous cyclicity secondary to drug-mediated hyperprolactinaemia.

Aripiprazole had no effect on fertility in male rats treated with PO doses of 20, 40, and 60 mg/kg/day (6, 12, and 18 times the MRHD based on mg/m^2) for 9 weeks prior to mating through mating. Disturbances of spermatogenesis were seen at 60 mg/kg/day and prostatic atrophy was seen at 40 and 60 mg/kg/day.

4.7 Effects on Ability to Drive and Use Machines

As with other antipsychotics, patients should be cautioned about operating hazardous machinery, including motor vehicles, until they are reasonably certain that Aripiprazole Lupin tablets do not affect them adversely.

4.8 Undesirable Effects

Aripiprazole has been evaluated for safety in 13,543 patients who participated in multiple-dose clinical trials in Schizophrenia (including schizo-affective disorder), Bipolar Disorder, Major Depressive Disorder, Dementia of the Alzheimer's type, Parkinson's disease, and alcoholism, and who had approximately 7,619 patient-years of exposure to oral aripiprazole. A total of 3,390 patients were treated with oral aripiprazole for at least 180 days and 1,933 patients treated with oral aripiprazole had at least 1 year of exposure.

The conditions and duration of treatment with aripiprazole (monotherapy and adjunctive therapy with or mood stabilizers) included (in overlapping categories) double-blind, comparative and noncomparative

open-label studies, inpatient and outpatient studies, fixed- and flexible-dose studies, and short- and longer- term exposure.

Adverse events during exposure were obtained by collecting voluntarily reported adverse events, as well as results of physical examinations, vital signs, weights, laboratory analyses, and ECG. Adverse experiences were recorded by clinical investigators using terminology of their own choosing. In the tables and tabulations that follow, MedDRA dictionary terminology has been used initially to classify reported adverse events into a smaller number of standardized event categories, in order to provide a meaningful estimate of the proportion of individuals experiencing adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatment uses and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the adverse event incidence in the population studied.

Oral Administration

Adult Patients with Schizophrenia

Adverse Events Associated with Discontinuation of Treatment in Short-Term, Placebo- Controlled Trials of Patients with Schizophrenia

Based on a pool of five placebo-controlled trials (four 4-week and one 6-week) in which aripiprazole was administered to acutely relapsed patients with schizophrenia in doses ranging from 2 to 30 mg/day, there was no difference in the incidence of discontinuation due to adverse events between aripiprazole-treated (7%) and placebo-treated (9%) patients. The types of adverse events that led to discontinuation were similar between the aripiprazole and placebo- treated patients.

Adult Patients with Bipolar Mania

Monotherapy

The following findings are based on a pool of 3-week, placebo-controlled, Bipolar mania trials in which oral aripiprazole was administered at doses of 15 mg/day or 30 mg/day.

Adverse Reactions Associated with Discontinuation of Treatment

Overall, in patients with Bipolar Mania, there was little difference in the incidence of discontinuation due to adverse reactions between aripiprazole-treated (11%) and placebo-treated (10%) patients. The types of adverse reactions that led to discontinuation were similar between aripiprazole-treated and placebo-treated patients.

Commonly Observed Adverse Reactions

Commonly observed adverse reactions associated with the use of aripiprazole in patients with Bipolar Mania (incidence of 5% or greater and aripiprazole incidence at least twice that for placebo) are shown in the following Table:

Table 1: Commonly Observed Adverse Reactions in Short-Term, Placebo-Controlled Trials of Adult Patents with Bipolar Mania Treated with Oral aripiprazole Monotherapy

Preferred Term	Percentage of Patients Reporting Reaction	
	Aripiprazole (n=917)	Placebo (n=753)
Akathisia	13	4
Sedation	8	3
Restlessness	6	3
Tremor	6	3
Extrapyramidal Disorder	5	2

Less Common Adverse Reactions in Adults

Adverse Events Occurring at an Incidence of at Least 2% Among Aripirazole-Treated Patients in Short-Term Placebo-Controlled Trials

Table 2 enumerates the pooled incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during acute therapy (up to 6 weeks in Schizophrenia and up to 3 weeks in Bipolar Mania) including only those events that occurred in at least 2% of patients treated with aripiprazole (doses ≥2 mg/day) and for which the incidence in patients treated with aripiprazole was greater than the incidence in patients treated with placebo in the combined dataset.

Table 2: Adverse Reactions in Short-Term, Placebo-Controlled Trials in Adult Patients Treated with Oral Aripiprazole

System Organ Class Preferred Term	Percentage of Patients Reporting Reaction[a]	
	Aripiprazole (n=1,843)	Placebo (n=1,166)
Eye Disorders		
Blurred Vision	3	1
Gastrointestinal Disorders		
Nausea	15	11
Constipation	11	7
Vomiting	11	6
Dyspepsia	9	7
Dry Mouth	5	4
Toothache	4	3
Abdominal Discomfort	3	2
Stomach Discomfort	3	2
General Disorders and Administration Site Conditions		
Fatigue	6	4
Pain	3	2
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal Stiffness	4	3
Pain in Extremity	4	2

System Organ Class Preferred Term	Percentage of Patients Reporting Reaction[a]	
	Aripiprazole (n=1,843)	Placebo (n=1,166)
Myalgia	2	1
Muscle Spasm	2	1
Nervous System Disorders		
Headache	27	23
Dizziness	10	7
Akathisia	10	4
Sedation	7	4
Extrapyradimal Disorder	5	3
Tremor	5	3
Somnolence	5	3
Psychiatric Disorders		
Agitation	19	17
Insomnia	18	13
Anxiety	17	13
Restlessness	5	3
Respiratory, Thoracic, and Mediastinal Disorders		
Pharyngolaryngeal Pain	3	2
Cough	3	2

[a]Adverse reactions reported by at least 2% of patients treated with oral aripiprazole, except adverse reactions which had an incidence equal to or less than placebo.

An examination of population subgroups did not reveal any clear evidence of differential adverse reaction incidence on the basis of age, gender, or race.

Adult Patients with Adjunctive Therapy with Bipolar Mania

The following findings are based on a placebo-controlled trial of adult patients with Bipolar Disorder in which aripirazole was administered at doses of 15 mg/day or 30 mg/day as adjunctive therapy with lithium or valporate.

Adverse Reactions Associated with Discontinuation of Treatment

In a study of patients who were already tolerating either lithium or valporate as monotherapy, discontinuation rates due to adverse reactions were 12% for patients treated with adjunctive aripiprazole compared with 6% for patients treated with adjunctive placebo. The most common adverse drug reactions associated with discontinuation in the adjunctive aripiprazole-treated compared to placebo-treated patients were akathisia (5% and 1%, respectively) and tremor (2% and 1%, respectively).

Commonly Observed Adverse Reactions

The commonly observed adverse reactions associated with adjunctive aripiprazole and lithium or valporate in patients with Bipolar mania (incidence of 5% or greater and incidence at least twice that for adjunctive placebo) were: akathisia, insomnia, and extrapyramidal disorder.

Less Common Adverse Reactions in Adults with Adjunctive Therapy in Bipolar Mania

Table 3 enumerates the incidence, rounded to the nearest percent, of adverse reactions that occurred during acute treatment (up to 6 weeks), including only those reactions that occurred in 2% or more of

patients treated with adjunctive aripiprazole (doses of 15 mg/day or 30 mg/day) and lithium or valporate and for which the incidence in patients treated with this combination was greater than the incidence in patients treated with placebo plus lithium or valporate.

Table 3: Adverse Reactions in a Short-Term, Placebo-Controlled Trial of Adjunctive Therapy in Patients with Bipolar Disorder

System Organ Class Preferred Term	Percentage of Patients Reporting Reaction[a]	
	Aripiprazole + Lithium or Valporate (n=253)	Placebo + Lithium or Valporate (n=130)
Gastrointestinal Disorders		
Nausea	8	5
Vomiting	4	0
Salivary hypersecretion	4	2
Dry Mouth	2	1
Infections and Infestations		
Nasopharyngitis	3	2
Investigations		
Weight increased	2	1
Nervous System Disorders		
Akathisia	19	5
Tremor	9	6
Extrapyradimal Disorder	5	1
Dizziness	4	1
Sedation	4	2
Psychiatric Disorders		
Insomnia	8	4
Anxiety	4	1
Restlessness	2	1

[a] Adverse reactions reported by at least 2% of patients treated with oral aripiprazole, except adverse reactions which had an incidence equal to or less than placebo

Dose-Related Adverse Events in Short-Term, Placebo-Controlled Trials in Schizophrenia
Dose response relationships for the incidence of treatment-emergent adverse events were evaluated from four trials comparing fixed doses (2, 10, 15, 20, and 30 mg/day) of aripiprazole tablets to placebo. This analysis, stratified by study, indicated that the only adverse event to have a possible dose response relationship, and then most prominent only with 30 mg, was somnolence (including sedation) [placebo, 7.1%; 10 mg, 8.5%, 15 mg, 8.7 %; 20 mg, 7.5%; 30 mg, 12.6%].

Adverse Events Occurring in Long-Term Controlled Trials
The adverse events reported in a 26-week, double-blind trial comparing aripiprazole tablets and placebo in patients with schizophrenia were generally consistent with those reported in the short- term, placebo-controlled trials, except for a higher incidence of tremor [8% (12/153) for aripiprazole vs. 2% (3/153) for placebo]. In this study, the majority of the cases of tremor were of mild intensity (8/12 mild and 4/12 moderate), occurred early in therapy (9/12 ≤49 days), and were of limited duration (7/12 ≤10 days). Tremor infrequently led to discontinuation (<1%) of aripiprazole. In addition, in a long-term (52-week),

active-controlled study, the incidence of tremor for aripiprazole was 5% (40/859). A similar profile was observed in a long-term study in Bipolar Disorder.

Weight Gain
In placebo-controlled trials, there was a slight difference in mean weight change between aripiprazole and placebo patients (+0.7 kg vs –0.05 kg, respectively, in short-term studies; p≤0.01, and –1.3 kg vs –0.9 kg, respectively, in 26 week study; p= n.s.) and also a difference in the proportion of patients meeting the significant weight gain criterion of ≥7% of body weight (aripiprazole 8% compared to placebo 3% in short-term studies p≤0.01: and aripiprazole compared to placebo 4% in long-term studies: p=n.s.).

In 3-week trials in adults with Mania with monotherapy aripiprazole, the mean weight gain for aripiprazole and placebo patients was 0.1kg versus 0.0kg, respectively. The proportion of patients meeting a weight gain criterion of ≥7% of body weight was aripiprazole (2%) compared to placebo (3%). In the 6-week trial in Mania with aripiprazole as adjunctive therapy with either lithium or valporate, the mean weight gain for aripiprazole and placebo patients was 0.6 kg versus 0.2 kg, respectively. The proportion of patients meeting a weight gain criterion of ≥7% of body weight with adjunctive aripiprazole was 3% compared to adjunctive placebo 4%.

In long-term, double-blind, active-comparator trials in schizophrenia, aripiprazole was associated with a higher incidence of significant weight gain (≥7% above baseline) compared with haloperidol (20% vs 13%,, respectively; p≤0.01; 1.1 kg vs 0.4 kg , respectively; p=n.s.) but a lower incidence of significant weight gain compared to olanzapine (aripiprazole 13% vs olanzapine 33%; p<0.001; -0.9 kg vs 3.4 kg; p<0.001 in a double-blind study).

Weight change results (see Table 4) from long-term, double-blind, controlled trials in schizophrenia showed that patients with high body mass index (BMI) (>27) were less likely to have significant weight gain on aripiprazole than those with low BMI (<23).

Table 4: Weight Change Results Categorised by BMI at Baseline in Double-Blind, Controlled Trials in Schizophrenia

Study		BMI <23	BMI 23-27	BMI >27
52-week Haloperidol Controlled	Mean Change from Baseline (kg)	2.6	1.4	-1.2
	% Patients with ≥7% increase of body weight relative to baseline	30%	19%	8%
26-week Olanzapine Controlled	Mean Change from Baseline (kg)	1.2	-0.4	-1.4
	% Patients with ≥7% increase of body weight relative to baseline	21%	7%	11%
26-week Placebo Controlled	Mean Change from Baseline (kg)	-0.5	-1.3	-2.1
	% Patients with ≥7% increase of body weight relative to baseline	7%	5%	6%

Extrapyramidal Symptoms
In the short-term, placebo-controlled trials of schizophrenia in adults, the incidence of reported EPS-related events excluding events related to akathisia for aripiprazole-treated patients was 13% vs. 12 % for placebo. The incidence of akathisia-related events for aripiprazole-treated patients was 8% vs 5% for placebo-treated patients.

In the short-term, placebo-controlled trials in Bipolar Mania in adults, the incidence of reported EPS-related events, excluding events related to akathisia, for monotherapy aripiprazole-treated patients was

16% versus 8% for placebo and the incidence of akathisia-related events for monotherapy aripiprazole-treated patients was 13% versus 4% for placebo. In the 6-week, placebo-controlled trial in Bipolar Mania for adjunctive therapy with lithium or valporate, the incidence of reported EPS-related events, excluding events related to akathisia for adjunctive aripiprazole-treated patients was 15% versus 8% for adjunctive placebo and the incidence of akathisia-related events for adjunctive aripiprazole-treated patients was 19% versus 5% for adjunctive placebo.

Objectively collected data from those trials on the Simpson Angus Rating Scale (for EPS), the Barnes Akathisia Scale (for akathisia), and the Assessments of Involuntary Movement Scales (for dyskinesias) did not show a difference between aripiprazole and placebo, with the exception of the Barnes Akathisia Scale (aripiprazole, 0.08; placebo, -0.05).

In the adult Bipolar Mania trials with monotherapy aripiprazole, The Simpson Angus Rating Scale and the Barnes Akathisia Scale showed a significant difference between aripiprazole and placebo (aripiprazole, 0.50; placebo, -0.01 and aripiprazole, 0.21; placebo, -0.05). Changes in the Assessment of Involuntary Movement Scales were similar for the aripiprazole and placebo groups. In the Bipolar Mania trials with aripiprazole as adjunctive therapy with either lithium or valporate, The Simpson Angus Rating Scale and the Barnes Akathisia Scale showed a significant difference between adjunctive aripiprazole and adjunctive placebo (aripiprazole, 0.73; placebo, 0.07 and aripiprazole, 0.30; placebo, 0.11). Changes in the Assessment of Involuntray Movement Scales were similar for adjunctive aripiprazole and adjunctive placebo.

In a long-term, double-blind, haloperidol-controlled study in schizophrenia, the incidence of haloperidol-treated patients showing at least one EPS-related adverse event, including dystonia, was significantly greater than that of the aripiprazole group (57% vs 26%; $p<0.001$). In a long- term, double-blind, olanzapine-controlled study, the incidence of olanzapine-treated patients showing at least one EPS-related adverse event was comparable to aripiprazole -treated patients (15% vs 15%, respectively; p= n.s.).

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 drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

ECG Changes
Between group comparisons for pooled, acute, placebo-controlled trials in patients with schizophrenia or Bipolar Mania, revealed no significant differences between oral aripiprazole and placebo in the proportion of patients experiencing potentially important changes in ECG parameters. In fact, within the dose range of 10 to 30 mg/day, aripiprazole tended to slightly shorten the QTc interval. Aripiprazole was associated with a median increase in heart rate of two beats per minute compared to no increase among placebo patients.

In a 26-week, placebo-controlled trial in schizophrenia, there were no significant differences between aripiprazole and placebo in the proportion of patients experiencing potentially important changes in ECG parameters.

Laboratory Test Abnormalities
A between group comparison for acute, 3 to 6-week, placebo-controlled trials in adults revealed no medically important differences between the aripiprazole and placebo groups in the proportions of patients experiencing potentially clinically significant changes in routine serum chemistry, haematology,

or urinalysis parameters. Similarly, there were no aripiprazole/placebo differences in the incidence of discontinuations for changes in serum chemistry, haematology, or urinalysis in adult patients.

In a long-term (26-week), placebo-controlled trial, there were no statistically significant differences between the aripiprazole and placebo patients in the mean change from baseline in fasting glucose, triglyceride, LDL, and total cholesterol measurements.

Adverse Reactions Observed During the Premarketing Evaluation of oral aripiprazole
The following is a list of MedRA terms that reflect adverse reactions reported by adult patients treated with oral aripirazole at multiple doses ≥ 2 mg/day during any phase of a trial within a database of 13,543 adult patients. The listing does not show adverse events mentioned in Table 2, 3 and 4 or in other sections of this prescribing information. It is important to emphasise that although the events reported occurred with treatment, they are not necessarily caused by it. The adverse reactions are classified by system organ class and are according to the following definitions: common adverse reactions are those occurring in at least 1/100 patients; uncommon adverse reactions are those occurring in at least 1/1000, but less than 1/100 patients; rare adverse reactions are those occurring in less than 1/1000 patients.

Blood and Lymphatic System Disorders:
uncommon: leukopenia, neutropenia, thrombocytopenia
rare - eosinophilia, lymphadenopathy.

Cardiac Disorders:
Uncommon - bradycardia, palpitations, cardiopulmonary failure, myocardial infarction, cardio-respiratory arrest, atrioventricular block, extrasystoles, sinus tachycardia, atrial fibrillation, angina pectoris, myocardial ischaemia;
rare - atrial flutter, supraventricular tachycardia, ventricular tachycardia.

Ear and Labyrinth Disorders:
rare - ear canal erythema, hypoacusis, vertigo positional, tinnitus.

Endocrine Disorders:
rare - early menarche.

Eye Disorders:
uncommon - dry eye, photophobia, diplopia, eyelid oedema, photopsia;
rare - eye redness, chromotopsia, conjunctivitis, eye disorder, eye movement disorder, gaze palsy, lacrimation increased.

Gastrointestinal Disorders:
uncommon - diarrhoea, gastritis, dysphagia, gastroesophageal reflux disease, swollen tongue, oesophagitis, hypoaesthesia oral;
rare - abdominal distension, abnormal faeces, eructation, faeces discoloured, constipation, gastrointestinal disorder, gastrointestinal pain, glossitis, lip dry, parotid gland enlargement, pruritus ani, tongue discolouration, pancreatitis.

General Disorders and Administration Site Conditions:
common - asthenia, peripheral oedema, irritability, chest pain;
uncommon - face oedema, angiodema, gait disturbance, adverse event, chills, discomfort, feeling abnormal, mobility decreased;
rare - difficulty in walking, facial pain, , swelling, malaise, thirst, chest discomfort, cyst, energy increased, feeling cold, generalised oedema, local swelling, oedema, tenderness, xerosis, hypothermia.

Hepatobiliary Disorders:

rare **-** hepatitis, jaundice.

Immune System Disorders:
rare **-** decreased immune responsiveness, hypersensitivity.

Infections and Infestations:
rare **-** sinusitis, urinary tract infection, body tinea, gastroenteritis viral, herpes simplex, localized infection, lower respiratory tract infection, oral candidiasis, parotitis, gastroenteritis.

Injury, Poisoning, and Procedural Complications:
common **-** fall;
uncommon **-** self mutilation;
rare **-** heat stroke, injury, muscle strain, clavicle fracture, femoral neck fracture, hip fracture, humerus fracture, mouth injury, open wound.

Investigations:
common **-** weight decreased, creatinine phosphokinase increased;
uncommon **-** weight increased, blood creatinine increased, heart rate increased, blood glucose increased, pyrexia, blood prolactin increased, blood urea increased, electrocardiogram QT prolonged, blood bilirubin increased, hepatic enzyme increased;
rare **-** electrocardiogram abnormal, urine output increased, blood creatine phosphokinase abnormal, orthostatic hypotension, blood urine present, electrocardiogram PR prolongation, electrocardiogram T wave inversion, eosinophil count increased, head lag abnormal, heart rate irregular, physical examination, urine ketone body present, white blood cell count increased, blood lactate dehydrogenase increased, glycosalted haemoglobin increased, gamma-glutamyl transferase increased.

Metabolism and Nutrition Disorders:
uncommon **-** hyperlipidaemia, anorexia, diabetes mellitus (including blood insulin increased, carbohydrate tolerance decreased, diabetes mellitus non-insulin-dependent, glucose tolerance impaired, glycosuria, glucose urine, glucose urine present), hyperglycaemia, hypokalaemia, hypoglycaemia, polydipsia, increased appetite, dehydration, hyponatraemia;
rare **-** diabetic ketoacidosis, hyperuricaemia.

Musculoskeletal and Connective Tissue Disorders:
Uncommon **–** muscle rigidity, musculoskeletal rigidity, muscle tightness, muscle spasms, muscular weakness, mobility decreased;
rare **-** bone pain, nuchal rigidity, sensation of heaviness, flank pain, jaw disorder, kyphosis, osteoarthritis, rhabdomyolysis.

Neoplasms Benign, Malignant and Unspecified (Including Cysts and Polyps):
rare **-** oral neoplasm, skin papilloma.

Nervous System Disorders:
common **–** coordination abnormal;
uncommon **-** memory impairment, cerebrovascular accident, hypokinesia, hypotonia, myoclonus, hypertonia, akinesia, bradykinesia, drooling, cogwheel rigidity, dystonia, disturbance in attention, dizziness postural, dysarthria, paraesthesia, parkinsonism, psychomotor hyperactivity, hypoaesthesia, speech disorder, tardive dyskinesia;
rare **-** burning sensation, convulsion, depressed level of consciousness, dysgeusia, akinaesthesia, ataxia, bradykinesia, coma, dysphasia, facial palsy, judgement impaired, loss of consciousness, migraine, neuroleptic malignant syndrome, paraesthesia circumoral, sleep phase rhythm disturbance, Grand Mal convulsion, choreoathetosis, unresponsive to verbal stimuli.

Psychiatric Disorders:
common – suicidal ideation;
uncommon – aggression, loss of libido, suicide attempt, hostility, libido increased, anger, anorgasmia, delirium, intentional self-injury, completed suicide, tic, homicidal ideation, depression, confusional state, nightmare, mania, abnormal dreams, hallucination auditory, nervousness, hallucination, apathy, thinking abnormal, bruxism,
rare - catatonia, sleepwalking, bradyphrenia, delirium, depressed mood, disorientation, euphoric mood, logorrhea, mental status changes, mood altered, panic attack, sleep disorder, blunted affect, cognitive deterioration, delusional perception, insomnia, eating disorder, emotional distress, impulsive behaviour, asthenia, mood swings, psychomotor retardation, somatoform disorder.

Renal and Urinary Disorders:
uncommon - nocturia, polyuria, pollakiuria, incontinence, urinary retention;
rare - proteinuria, bladder discomfort, chromaturia, enuresis, micturition urgency, oliguria, urethral discharge, urinary hesitation.

Reproductive System and Breast Disorders:
uncommon - erectile dysfunction, amenorrhea[f], breast pain, menstruation irregular[f];
rare - genital pruritus female[f], vulvovaginal discomfort, pelvic pain, breast discharge, sexual dysfunction, gynaecomastia, priapism.

Respiratory, Thoracic and Mediastinal Disorders:
common – nasal congestion, dyspnea, pneumonia aspiration;
uncommon - hiccups, epistaxis;
rare - dry throat, rhinorrhoea, sinus congestion, hoarseness, nasal dryness, painful respiration, paranasal sinus hypersecretion.

Skin and Subcutaneous Tissue Disorders:
common – rash (including erythematous, exfoliative, generalised, macular, maculopapular, popular rash, acneiform, allergic, contact, exfoliative, seborrheic dermatitis, neurodermatitis, and drug eruption), hyperhydrosis;
uncommon - pruritus, photosensitivity reaction, alopecia, urticaria;
rare - decubitus ulcer, face oedema, pemphigus, psoriasis, dry skin.

Social Circumstances:
rare - smoker.

Vascular Disorders:
common – hypertension; uncommon – hypotension, hot flush, rare - flushing, hyperaemia.
[f](female) indicates incidence based on gender total

Post-marketing Experience

The following adverse reactions have been identified during post-approval use of aripiprazole. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to establish a causal relationship to drug exposure: rare occurrences of allergic reaction (anaphylactic reaction, angiodema, laryngospasm, pruritis/urticaria, or oropharyngeal spasm), and blood glucose fluctuation. Very rare occurrences of increased AST, increased ALT and hiccups have been reported.

Endocrine Disorders:
Very Rare - Diabetic hyperosmolar coma.

Psychiatric Disorders

Uncommon - Hypersexuality
Unknown - Pathological gambling, impulse-control disorders, obsessive-compulsive disorders, eating disorders

Nervous system disorders:
Very Rare - Restless legs syndrome

Eye Disorders:
Not known - oculogyric crisis

Vascular disorders:
Very Rare - Syncope.

Skin and subcutaneous tissue disorders:
Very Rare - Drug reaction with eosinophilia and systemic symptoms (DRESS)

Investigations:
Uncommon - Blood prolactin decreased

Reporting of Suspected Adverse Effects

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/}

4.9 Overdose

Human Experience
In clinical studies, and post-marketing experience, accidental or intentional acute overdosage of aripiprazole alone was identified in adult patients with estimated doses up to 1260 mg with no fatalities. The potentially medically important signs and symptoms observed in adult patients who overdosed with aripiprazole alone at doses up to 1260 mg included lethargy, blood pressure increased, somnolence, tachycardia and vomiting. In addition, reports of accidental overdose with aripiprazole alone (up to 195 mg) in children have been received. The potentially medically serious signs and symptoms reported include somnolence, and transient loss of consciousness. In the patients who were evaluated in hospital settings, there were no reported observations indicating a clinically significant adverse change in vital signs, laboratory assessments, or ECG.

Management of Overdosage
No specific information is available on the treatment of overdose with aripiprazole. The possibility of multiple drug involvement should be considered. Therefore, cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. Otherwise, management of overdose should concentrate on supportive therapy, maintaining an adequate airway, oxygenation and ventilation, and management of symptoms. Close medical supervision and monitoring should continue until the patient recovers.

Charcoal: In the event of an overdose of aripiprazole, an early charcoal administration may be useful in partially preventing the absorption of aripiprazole. In a single-dose study in which 15 mg of aripiprazole was administered to fully compliant, fully conscious, healthy, male volunteers and followed by activated charcoal (50 g), administered one hour after aripiprazole, aripiprazole AUC and C_{max} was decreased by 51 and 41%, respectively, compared to historic controls, suggesting that charcoal may be effective for overdose management.

Haemodialysis: Although there is no information on the effect of haemodialysis in treating an overdose with aripiprazole, haemodialysis is unlikely to be useful in overdose management, since aripiprazole is not eliminated unchanged by the kidneys and is highly bound to plasma proteins.

The Poisons Information Centre, telephone number 0800 764 766 in New Zealand, should be contacted for advice on management.

{For risk assessment and advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766)}.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

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

The mechanism of action of aripiprazole, as well as other drugs having efficacy in schizophrenia and bipolar disorder, is unknown. However, it has been proposed that the efficacy of aripiprazole is mediated through a combination of partial agonist activity at dopamine D2 and serotonin 5HT1A receptors and antagonist activity at serotonin 5HT2A receptors.

Aripiprazole exhibited higher affinity binding in vitro for dopamine D2 and D3, serotonin 5HT1A and 5HT2A receptors (Ki values of 0.3, 0.8, 1.7, and 3.4 nM, respectively), than for dopamine D4, serotonin 5HT2C and 5HT7, alpha1-adrenergic and histamine H1 receptors (Ki values of 44, 15, 39, 57, and 61 nM, respectively) and the serotonin reuptake site (Ki value of 98 nM). Aripiprazole exhibited no appreciable affinity for muscarinic receptors (IC50 >1000 nM).

The predominant metabolite in human plasma, dehydro-aripiprazole has been shown to have a similar affinity for dopamine D2 and D3 receptors (Ki values 0.4 and 0.5nM, respectively) as the parent compound and a much lower affinity for the other receptor subtypes.

Aripiprazole exhibited antagonist properties in animal models of dopaminergic hyperactivity and agonist properties in animal models of dopaminergic hypoactivity.

Interaction with receptors other than dopamine and serotonin subtypes may explain some of the other clinical effects of aripiprazole.

Clinical Trials

Schizophrenia

The efficacy of aripiprazole in the treatment of schizophrenia was evaluated in six short-term (4- and 6-week), placebo-controlled trials of inpatients, four of which also included an active control group consisting of either risperidone (one trial) or haloperidol (three trials). Studies were not powered to allow for a comparison of aripiprazole and the active comparators. Efficacy was also documented in two long-term trials, one of 52 weeks duration, which compared aripiprazole to haloperidol and one of 26 weeks duration, which compared aripiprazole to placebo. Patients in these trials met DSM-III/IV criteria for schizophrenia or schizo-affective disorder.

Several instruments were used for assessing psychiatric signs and symptoms. The Positive and Negative Syndrome Scale (PANSS) and Brief Psychiatric Rating Scale (BPRS) are both multi- item inventories of general psychopathology used to evaluate the effects of drug treatment in schizophrenia. The BPRS

Psychosis Cluster (Core Score), a subset of the BPRS that can also be derived from the PANSS, is used to assess actively psychotic patients. The Clinical Global Impression (CGI) assessment reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient.

Four short-term, fixed-dose trials were well controlled and powered to statistically demonstrate the efficacy of aripiprazole over placebo. The results of these trials are described below.

Trial 1: In a 4-week, placebo-controlled trial (n=414) involving administration of 2 fixed doses of aripiprazole (15 or 30 mg/day) and haloperidol (10 mg/day) in acutely relapsed patients with a DSM-IV diagnosis of schizophrenia or schizo-affective disorder, aripiprazole 15 mg/day was superior to placebo with clinically meaningful changes in PANSS total, PANSS positive and negative subscales, CGI-severity, CGI-improvement, and PANSS-derived BPRS-core scores. The 30-mg dose was superior to placebo for all parameters except PANSS negative subscale.

Trial 2: In a 4-week, placebo-controlled trial (n=404) involving administration of 2 fixed doses of aripiprazole (20 or 30 mg/day) and risperidone (6 mg/day) in acutely relapsed patients with a DSM-IV diagnosis of schizophrenia or schizo-affective disorder, both doses of aripiprazole were superior to placebo with clinically meaningful changes in the PANSS total, PANSS positive and negative subscales, CGI-severity, CGI-improvement and PANSS-derived BPRS-core scores.

Trial 3: In a 6-week, placebo-controlled trial (n=420) involving administration of 3 fixed doses of aripiprazole (10, 15, or 20 mg/day) in acutely relapsed patients with a DSM-IV diagnosis of schizophrenia, all aripiprazole dose groups were superior to placebo with clinically meaningful changes in the PANSS total score, the PANSS positive and negative subscales, the CGI severity and improvement scales, and the PANSS-derived BPRS core score.

Trial 4: In a 6-week trial (n=367) comparing three fixed doses of aripiprazole (2, 5 or 10 mg/day) to placebo, in acutely relapsed patients with a DSM-IV diagnosis of schizophrenia, the 10-mg dose of aripiprazole was superior to placebo in the PANSS total score, the primary outcome measure of the study. In addition, the 10 mg dose was also superior to placebo in the PANSS positive subscale and the CGI severity score. Although the 5-mg dose of aripiprazole did not reach significance in the PANSS total score or the PANSS positive subscale, it was superior to placebo in the negative subscale and the CGI severity scale. The 2-mg dose did not reach significance in any of these outcome measures.

Two initial placebo-controlled trials were conducted to explore the efficacy of aripiprazole. The first one (Trial 5) was a placebo-controlled, 4-week ascending dose trial of aripiprazole (5 to 30 mg/day) in 103 patients diagnosed with schizophrenia according to the DSM-III-R criteria with acute schizophrenic relapse and a history of response to antipsychotic drugs. In this trial, aripiprazole differentiated from placebo in the PANSS total score, the PANSS positive subscale, and the CGI severity scale. The second one (Trial 6) was a placebo-controlled, 4-week, fixed- dose trial of aripiprazole (2, 10, or 30 mg/day) in 272 patients diagnosed with schizophrenia according to the DSM-IV criteria with acute schizophrenic relapse and a history of response to antipsychotic drugs. Statistical significance was reached only for the 30-mg dose on the PANSS total score, the PANSS positive subscale, and the CGI severity and improvement scales.

Thus, the efficacy of 10-mg, 15-mg, 20-mg and 30-mg was established in two studies for each dose. Among these doses there was no evidence that the higher dose groups offered any advantage over the lowest dose group. Broad efficacy was established across a variety of endpoints with an onset of action as early as Week 1 for positive symptoms at doses of 15 mg and higher.

Table 5: summarizes the results across all six trials

	PANSS Total Score	PANSS Positive Subscale Score	PANSS Negative Subscale Score	PANSS-Derived BPRS Core Score	CGI-Severity Score	CGI Improvement Score
Trial/Treatment	**Mean Change**	**Mean Change**	**Mean Change**	**Mean Change**	**Mean Change**	**Mean Change**
Trial 1						
Placebo	-2.9	-0.6	-1.2	-1.1	-0.1	4.3
Ari 15 mg	-15.5**	-4.2**	-3.6**	-3.1**	-0.6**	3.5**
Ari 30 mg	-11.4**	-3.8**	-2.3	-3.0**	-0.4**	3.8*
Trial 2						
Placebo	-5.0	-1.8	-0.8	-1.7	-0.2	4.0
Ari 20 mg	-14.5**	-4.9**	-3.4**	-3.5**	-0.5*	3.4**
Ari 30 mg	-13.9**	-3.9*	-3.4**	-3.3*	-0.6**	3.3**
Trial 3						
Placebo	-2.3	-1.1	0.1	-1.4	-0.2	4.0
Ari 10 mg	-15.0**	-5.0**	-3.5**	-3.9**	-0.7**	3.3**
Ari 15 mg	-11.7**	-3.8**	-2.6**	-2.9*	-0.5*	3.4**
Ari 20 mg	-14.4**	-4.5**	-3.3**	-3.6**	-0.6**	3.3**
Trial 4						
Placebo	-5.3	-2.3	-1.3	-2.3	-0.3	3.6
Ari 2 mg	-8.2	-2.4	-2.0	-2.3	-0.3	3.6
Ari 5 mg	-10.6	-3.4	-2.9*	-3.2	-0.6*	3.2
Ari 10 mg	-11.3*	-4.2*	-2.7	-3.4	-0.6*	3.2
Trial 5						
Placebo	-1.5	-0.1	-0.9	-2.4	0.0	4.0
Ari 5-30 mg	-13.5**	-3.0*	-3.6	-8.6*	-0.6**	3.5*
Trial 6						
Placebo	-3.0	-0.97	-1.31	-1.48	-2.8	3.9
Ari 2 mg	-8.0	-1.96	-2.05	-1.95	-0.30	3.7
Ari 10 mg	-8.6	-2.10	-2.48	-1.79	-0.30	3.5
Ari 30 mg	-13.7**	-3.89*	-3.11	-2.97	-0.60*	3.1**

** ($P \leq 0.01$), *($0.01 < P \leq 0.05$) significantly different from placebo.
NOTE: Results in boxes indicate the protocol-specified primary efficacy measures.
Ari = aripiprazole

A 52-week, haloperidol-controlled, long-term, maintenance trial (n=1294) was conducted in patients with acute relapse of chronic schizophrenia. In this trial involving the administration of aripiprazole 30 mg/day and haloperidol 10 mg/day, with a one-time option to decrease aripiprazole to 20 mg/day and haloperidol to 7 mg/day, aripiprazole was at least comparable to haloperidol in time-to-failure to maintain response in responders. Based on patients who responded at any time during the 52-week study (610/853, 72% in the aripiprazole group and 298/430, 69% in the haloperidol group), there was a 12% lower risk of subsequent failure with aripiprazole relative to haloperidol (relative risk: 0.881, 95% CI: 0.645 - 1.204). Aripiprazole was comparable to haloperidol in time-to-failure to maintain response in

all randomized patients. Patients in the aripiprazole group had a 14% lower risk of failure compared with the haloperidol group (relative risk: 0.858, 95% CI: 0.721, 1.021). Aripiprazole was statistically superior to haloperidol in the analysis of the proportion of patients on treatment and in response at Weeks 8, 26, and 52 (pre- specified key time points). At Week 52, 40% of aripiprazole patients were still on-study and in response compared to 27% of haloperidol patients (p<0.001). Aripiprazole-treated patients had a statistically significant lower risk (31%) of discontinuations due to lack of efficacy or adverse event relative to haloperidol treated patients (relative risk 0.692; 95% CI: 0.573 - 0.837). There were no significant differences between aripiprazole and haloperidol groups in terms of change from baseline PANSS total scores, PANSS positive subscores, CGI-severity or improvement scores. aripiprazole did result in a significantly greater improvement in the PANSS negative subscores at weeks 26 & 52 and the MADRS total score at Weeks 8, 26, and 52. [Mean change PANSS negative subscale score (week 26: p=0.029; 95% CI: -1.52, -0.08) (week 52: p=0.011; 95% CI: -1.73, -0.23). Mean change MADRS total score (week 8: p=0.027; 95% CI: -1.74, -0.11) (week 26:p=0.22; 95% CI:-1.95, -0.15) (week 52: p= 0.031; 95% CI: -1.97, -0.09).]

To further demonstrate the maintenance effects of aripiprazole, a double-blind study was conducted in chronic, symptomatically stable schizophrenic patients (n=310) randomised to aripiprazole 15 mg or placebo and followed for 26 weeks. Patients were observed for "impending psychotic relapse", defined as CGI-improvement score ≥5 (minimally worse) or scores ≥5 (moderately severe) on the hostility or uncooperativeness items of the PANSS on two consecutive days or ≥20% increase in the PANSS Total Score. Patients in the placebo group experienced a higher relapse rate and/or relapsed sooner than those in the aripiprazole group. From 4 weeks onwards there were noticeably more relapses in the placebo group than the aripiprazole group. Kaplan Meier estimates showed that the estimated probability of not experiencing relapse prior to week 26 was 39% in the placebo group versus 63% in the aripiprazole group [relative risk aripiprazole: placebo = 0.50 (95% CI=0.35, 0.71, p≤0.01)]. The number of relapses was significantly lower in the aripiprazole group compared to placebo (34% vs 57%, RR=0.59, 95% CI: 0.45, 0.75, p≤0.01).

No trials have been conducted in patients with first episode schizophrenia or treatment-resistant schizophrenia. Thus, efficacy in these groups of patients has not been established.

Bipolar Mania
Monotherapy
Adults
The efficacy of aripiprazole in the treatment of acute manic episodes was established in four 3- week, placebo-controlled trials in hospitalized patients who met the DSM-IV criteria for Bipolar I Disorder with manic or mixed episodes. These studies included patients with or without psychotic features and two of the studies also included patients with or without a rapid-cycling course.

The primary instrument used for assessing manic symptoms was the Young Mania Rating Scale (Y-MRS), an 11-item clinician-rated scale traditionally used to assess the degree of manic symptomatology (irritbility, disruptive/aggressive behaviour, sleep, elevated mood, speech, increased activity, sexual interest, language/thought disorder, thought content, appearance, and insight) in a range from 0 (no manic features) to 60 (maximum score). A key secondary instrument included the Clinical Global Impression – Bipolar (CGI-BP) Scale.

In the four positive 3 week, placebo-controlled trials (n=268; n=248; n= 480; n= 485) which evaluated aripiprazole in a range of 15 mg to 30 mg, once daily (with a starting dose of 15 mg/day in two studies and 30 mg/day in two studies). Aripiprazole was superior to placebo in the reduction of Y-MRS total score and CGI-BP Severity of Illness score (mania). In the two studies with a starting dose of 15 mg/day, 48% and 44% of patients were on 15 mg/day at endpoint. In the two studies with a starting dose of 30 mg/day, 86% and 85% of patients were on 30 mg/day at endpoint.

A trial was conducted in patients with DSM-IV criteria for Bipolar I Disorder with a recent manic or mixed episode who had been stabilized on open-label aripiprazole and who had maintained a clinical response for at least 6 weeks. The first phase of this trial was an open-label stabilisation period in which inpatients and outpatients were clinically stabilized and then maintained on open- label aripiprazole (15 mg/day or 30 mg/day, with a starting dose of 30 mg/day) for at least 6 consecutive weeks. One hundred sixty-one outpatients were then randomized in a double-blind fashion, to either the same dose of aripiprazole they were on the end of stabilization and maintenance period or placebo and were then monitored for manic or depressive relapse. During the randomization phase, aripiprazole was superior to placebo on time to the number of combined affective relapses (manic plus depressive), the primary outcome measure for this study. The majority of these relapses were due to manic rather than depressive symptoms. There is insufficient data to know whether aripiprazole is effective in delaying the time to occurrence of depression in patients with Bipolar I Disorder.

An examination of population subgroups did not reveal any clear evidence of differential responsiveness on the basis of age and gender, however, there were insufficient numbers of patients in each of the ethnic groups to adequately assess inter-group differences.

Adjunctive Therapy
The efficacy of adjunctive aripiprazole with concomitant lithium or valporate in the treatment of manic or mixed episodes was established in a 6-week, placebo-controlled study (n=384) with a 2-week lead-in mood stabilizer monotherapy phase in adult patients who met DSM-IV criteria for Bipolar I Disorder. This study included patients with manic or mixed episodes and with or without psychotic features.

Patients were initiated on open-label lithium (0.6 mEq/l to 1.0 mEq/l) or valporate (50 µg/mL to 125 µg/mL) at therapeutic serum levels, and remained on stable doses for 2 weeks. At the end of 2 weeks, patients demonstrating inadequate response (Y-MRS total score ≥ 16 and ≤25% improvement on the Y-MRS total score) to lithium or valporate were randomized to receive either aripiprazole (15 mg/day or an increase to 30 mg/day as early as day 7) or placebo as adjunctive therapy with open-label lithium or valporate. In the 6-week placebo-controlled phase, adjunctive aripiprazole starting at 15 mg/day with concomitant lithium or valporate (in a therapeutic range of 0.6 mEq/l to 1.0 mEq/l or 50 µg/mL to 125 µg/mL, respectively) was superior to lithium or valporate with adjunctive placebo in the reduction of the Y-MRS total score and CGI-BP Severity of Illness score (mania). Seventy-one percent of the patients co-administered valproate and 62% of the patients co-administered lithium were on 15 mg/day at the 6-week endpoint.

5.2 Pharmacokinetic Properties

Absorption
Aripiprazole is well absorbed after oral administration of Aripiprazole Lupin tablets, with peak plasma concentrations occurring within 3-5 hours after dosing. The absolute oral bioavailability of the tablet formulation of Aripiprazole Lupin tablets is 87%. Aripiprazole Lupin tablets can be administered without regard to meals. Following administration of a 15 mg Aripiprazole Lupin tablet with a standard high-fat meal, the C_{max} of aripiprazole and its active metabolite, dehydro-aripiprazole, increased by 11%. The AUC of aripiprazole was increased by 18% and that of the active metabolite by 14%. Food delayed T_{max} by 3 hours for aripiprazole and 12 hours for the active metabolite. Aripiprazole accumulation is predictable from single dose pharmacokinetics. At steady state, the pharmacokinetics of aripiprazole are dose-proportional. There is no diurnal variation in the disposition of aripiprazole and its active metabolite, dehydro-aripiprazole.

Distribution
Aripiprazole is widely distributed throughout the body with an apparent volume of distribution of 4.9l/kg. At therapeutic concentrations, aripiprazole is highly bound (88–97% to >99%, as determined by polydimethylsiloxane-glass bead and equilibrium dialysis assays, respectively) to serum proteins,

primarily albumin, in vitro. Aripiprazole did not alter the pharmacokinetics and pharmacodynamics of highly protein-bound warfarin, suggesting that protein displacement of
warfarin did not occur.

Metabolism

Aripiprazole undergoes minimal pre-systemic metabolism. Aripiprazole is extensively metabolized by the liver primarily by three biotransformation pathways: dehydrogenation, hydroxylation, and N-dealkylation. Based on in vitro studies, CYP3A4 and CYP2D6 enzymes are primarily responsible for dehydrogenation and hydroxylation of aripiprazole, while N-dealkylation is primarily catalyzed by CYP3A4. Aripiprazole is the predominant drug moiety in systemic circulation. At steady state, dehydro-aripiprazole, the active metabolite, represented about 39% of aripiprazole AUC in plasma. Approximately 8% of Caucasians lack the capacity to metabolize CYP2D6 substrates and are classified as poor metabolizers (PM), whereas the rest are extensive metabolizers (EM). PMs have about an 80% increase in aripiprazole exposure and about a 30% decrease in exposure to the active metabolite compared to EMs, resulting in about a 60% higher exposure to the total active moieties from a given dose of aripiprazole compared to EMs. Subjects were entered into clinical studies without knowledge of their metabolizer status and, therefore, the safety profile reflects experience in both EMs and PMs.

Excretion

Following a single, oral dose of [14C]-labelled aripiprazole, approximately 27% and 60% of the administered radioactivity was recovered in the urine and faeces, respectively. Less than 1% of unchanged aripiprazole was excreted in the urine and approximately 18% of the oral dose was recovered unchanged in the faeces. The total body clearance of aripiprazole is 0.7mL/min/kg, which is primarily hepatic.

In a bioavailability study comparing fasted and fed subjects at a dose of 15 mg, the elimination half-life of aripiprazole from human plasma was found to be 75 hours mean, range 32–146 hours, n=58, in fasted subjects and 84 hours mean, range 32-157 hours, n=57 in subjects taking a high- fat meal immediately before drug administration. Steady-state concentrations are attained within 14 days of dosing. The plasma elimination half-life of the chief metabolite, dehydro-aripiprazole, from human plasma was found to be approx. 100 hours.

Elderly

There were no differences in the pharmacokinetics of aripiprazole between healthy elderly and younger adult subjects nor was there any detectable effect of age in a population pharmacokinetic analysis in schizophrenic patients. In formal single-dose pharmacokinetic studies (with aripiprazole given in a single dose of 15 mg), aripiprazole clearance was 20% lower in elderly (≥65 years) subjects compared to younger adult subjects (18-64 years). There was no detectable age effect, however, in the population pharmacokinetic analysis in schizophrenia patients. Also, the pharmacokinetics of aripiprazole after multiple doses in elderly patients appeared similar to that observed in young healthy subjects. No dosage adjustment is recommended for elderly patients. (See **Section 4.4 Special Warnings and Precautions for Use - Increased Mortality in Elderly Patients with Dementia- Related Psychosis and Use in the Elderly**)

Gender

There were no differences in the pharmacokinetics of aripiprazole between healthy male and female subjects nor was there any detectable effect of gender in a population pharmacokinetic analysis in schizophrenic patients. C_{max} and AUC of aripiprazole and its active metabolite, dehydro-aripiprazole, are 30 to 40% higher in women than in men, and correspondingly, the apparent oral clearance of aripiprazole is lower in women. These differences, however, are largely explained by differences in body weight (25%) between men and women. No dosage adjustment is recommended based on gender.

Race

Population pharmacokinetic evaluation has revealed no evidence of clinically significant race- related differences in the pharmacokinetics of aripiprazole.

Smoking

Population pharmacokinetic evaluation has revealed no evidence of clinically significant effects of smoking on the pharmacokinetics of aripiprazole. Based on studies utilizing human liver enzymes in vitro, aripiprazole is not a substrate for CYP1A2 and also does not undergo direct glucuronidation. Smoking should, therefore, not have an effect on the pharmacokinetics of aripiprazole. Consistent with these in vitro results, population pharmacokinetic evaluation did not reveal any significant pharmacokinetic differences between smokers and non-smokers. No dosage adjustment is recommended based on smoking status.

Renal Impairment

The pharmacokinetic characteristics of aripiprazole and dehydro-aripiprazole were found to be similar in patients with severe renal disease compared to young healthy subjects. In patients with severe renal impairment (creatinine clearance <30 mL/min), C_{max} of aripiprazole (given in a single dose of 15 mg) and dehydro-aripiprazole increased by 36% and 53%, respectively, but AUC was 15% lower for aripiprazole and 7% higher for dehydro-aripiprazole. Renal excretion of both unchanged aripiprazole and dehydro-aripiprazole is less than 1% of the dose. No dosage adjustment is required in subjects with renal impairment.

Hepatic Impairment

A study in 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. In a single-dose study (15 mg of aripiprazole) in subjects with varying degrees of liver cirrhosis (Child-Pugh Classes A, B, and C), the AUC of aripiprazole, compared to healthy subjects, increased 31% in mild HI, increased 8% in moderate HI, and decreased 20% in severe HI. None of these differences would require dose adjustment.

5.3 Preclinical Safety Data

Carcinogenicity and Mutagenicity

Carcinogenicity: Lifetime carcinogenicity studies were conducted in ICR mice and in Sprague- Dawley (SD) and Fischer (F344) rats. Aripiprazole was administered for 2 years in the diet at doses of 1, 3, 10, and 30 mg/kg/day to ICR mice and 1, 3, and 10 mg/kg/day to F344 rats (0.2 to 5 and 0.3 to 3 times the maximum recommended human dose [MRHD] based on mg/m^2, respectively). SD rats were dosed orally by gavage for 2 years at 10, 20, 40, and 60 mg/kg/day (3 to 18 times the MRHD based on mg/m^2). There was no evidence of tumorigenesis in male mice or rats. In female mice, the incidences of pituitary gland adenomas and mammary gland adenocarcinomas and adenoacanthomas were increased at dietary doses of 3 to 30 mg/kg/day (0.1 to 0.9 times MRHD based on AUC and 0.5 to 5 times the MRHD based on mg/m^2). In female rats, the incidence of mammary gland fibroadenomas was increased at a dietary dose of 10 mg/kg/day (<0.1 times MRHD based on AUC and 3 times the MRHD based on mg/m^2); and the incidences of adrenocortical carcinomas and combined adrenocortical adenomas/carcinomas were increased at an oral gavage dose of 60 mg/kg/day (10 times the MRHD based on AUC and 18 times MRHD based on mg/m^2). In male rats, the incidence of benign and combined benign/malignant phaeochromocytomas were also increased at an oral gavage dose of 60 mg/kg/day (10 times the MRHD based on AUC and 18 times the MRHD based on mg/m^2).

Proliferative changes in the pituitary and mammary gland of rodents have been observed following chronic administration of other antipsychotic agents and are considered prolactin- mediated. Serum prolactin was not measured in the aripiprazole carcinogenicity studies. At the doses associated with

mammary gland and pituitary tumours, hyperprolactinaemia was observed in female mice in a 13-week dietary study but not in female rats in 4- and 13-week dietary studies. Serum prolactin was increased in female rats, and decreased in male rats, after 5 and 13 weeks of oral gavage dosing at 60 mg/kg/day. The relationship between tumourigenic findings with aripiprazole and prolactin is unclear and the relevance for human risk of prolactin-mediated tumours is unknown. The adrenocortical response in female rats is considered a consequence of increased adrenocortical cell proliferation secondary to chronic drug-related adrenocortical cytotoxicity. The no-effect-dose (40 mg/kg/day) was 7 – 12 times the MRHD based on AUC and mg/m^2.

Mutagenicity: Aripiprazole was tested in a standard range of assays for gene mutation, chromosomal damage, and DNA damage and repair. Aripiprazole was non-genotoxic in the in vitro bacterial reverse-mutation assay, the in vitro forward gene mutation assay in mouse lymphoma cells, in vitro bacterial DNA repair assay, and the unscheduled DNA synthesis assay in rat hepatocytes. However, aripiprazole and its minor metabolite 2,3-DCPP were clastogenic in the in vitro chromosomal aberration assay in Chinese hamster lung (CHL) cells in both the presence and absence of metabolic activation. A positive response for aripiprazole in 1 of 6 in vivo mouse micronucleus tests was attributed to drug-induced hypothermia.

Animal Toxicology

Choleliths (gallsand and/or gallstones) were observed in the bile of monkeys given aripiprazole orally for 4 – 52 weeks at doses of 25 –125 mg/kg/day (1 – 3 times the MRHD based on plasma AUC and 15 –76 times the MRHD based on mg/m^2) and were attributed to precipitation of sulphate conjugates of hydroxy metabolites, which exceeded their solubility limits in bile. Human biliary concentrations of these sulphate conjugates after repeated daily administration of the MRHD are substantially lower (0.2 – 14% of their in vitro solubility limits).

Bilateral retinal degeneration was observed in albino rats given oral aripiprazole for 6 months at a dose of 60 mg/kg/day and 2 years at doses of 40 – 60 mg/kg/day. These doses were 7 – 13 times the MRHD based on AUC and 12 – 18 times the MRHD based on mg/m^2. The mechanism and clinical relevance of this finding is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

The inactive ingredients in the tablets are: lactose, maize starch, microcrystalline cellulose, hydroxypropylcellulose, and magnesium stearate.

6.2 Incompatibilities

None are known.

6.3 Shelf Life

3 years (36 months).

6.4 Special Precautions for Storage

Store below 30°C

6.5 Nature and Contents of Container

Al/Al blister packs containing 30 tablets

6.6 Special Precautions for Disposal

No special precautions required

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

Lupin NZ Limited
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9 DATE OF FIRST APPROVAL

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10 DATE OF REVISION OF THE TEXT

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SUMMARY TABLE OF CHANGES

Section Changed	Summary of New Information
All	Editorial and formatting changes Brand name changed to Aripiprazole Lupin
8	Sponsor details updated