AUSTRALIAN PRODUCT INFORMATION – ABILIFY™ (ARIPIPRAZOLE) TABLETS

1 NAME OF THE MEDICINE

Aripiprazole

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet of Abilify contains aripiprazole as the active ingredient. Abilify is available in 2 mg , 5 mg, 10 mg, 15 mg , 20 mg , and 30 mg tablets.

Abilify tablets contain lactose monohydrate. For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Abilify (aripiprazole) is available as:

2 mg green, unscored, modified rectangular, shallow convex, bevel-edged, tablets, marked on one side with “A-006” and “2”;

5 mg blue, unscored, modified rectangular, shallow convex, bevel-edged, tablets, marked on one side with “A-007” and “5”;

10 mg pink, unscored, modified rectangular, shallow convex, bevel-edged, tablets, marked on one side with “A-008” and “10”;

15 mg yellow, unscored, round, shallow convex, bevel-edged, tablets, marked on one side with “A-009” and “15”;

20 mg white to pale yellowish white, unscored, round, shallow convex, bevel-edged, tablets, marked on one side with “A-010” and “20”;

30 mg pink, unscored, round, shallow convex, bevel-edged, tablets, marked on one side with “A-011” and “30”.

Not all presentations may be available in Australia.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Abilify is indicated for the treatment of schizophrenia including maintenance of clinical improvement during continuation therapy.

Acute treatment of manic or mixed episodes associated with Bipolar I Disorder in adults as monotherapy and in combination with lithium or valproate;

Maintenance treatment of manic or mixed episodes in Bipolar I Disorder in adults as monotherapy.

4.2 DOSE AND METHOD OF ADMINISTRATION

Recommended Dosage

Schizophrenia

Adults

The recommended starting dose for Abilify tablets is 10 or 15 mg/day administered orally 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 to 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 to 15 mg.

The maintenance dose for Abilify tablets is 15 mg/day.

Bipolar I Disorder

Acute Treatment

Adults

The recommended starting and target dose of Abilify tablets is 15 mg as monotherapy or as combination therapy with lithium or valproate 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

Patients responding to aripiprazole for an acute or mixed episode may be continued on monotherapy aripiprazole at 15 mg or 30 mg daily for a further 9 weeks. Maintenance of effect has not been demonstrated beyond 26 weeks (see Section 5.1 Pharmacological Properties - Clinical Trials).

Patients given aripiprazole for an acute manic or mixed episode may be continued on monotherapy at the same dose. Adjustments of daily dosage, including dose reductions should be considered on the basis of clinical status.

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).

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 Abilify concomitantly with potential CYP3A4 inhibitors: When concomitant administration of a potent CYP3A4 inhibitor such as ketoconazole, itraconazole, clarithromycin and HIV protease inhibitors with Abilify occurs, the Abilify dose should be decreased. When the CYP3A4 inhibitor is withdrawn from the combination therapy, the Abilify dose should then be increased.

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

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

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

Smoking

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

Switching from Other Antipsychotics

Data was prospectively and systematically collected to address the safety of switching from other antipsychotics to Abilify (30 mg/day). These data indicate that any of the following methods can be used safely for switching patients to Abilify from another antipsychotic monotherapy:

- immediate discontinuation of the patient's current antipsychotic regimen and immediate initiation of Abilify;
- immediate initiation of Abilify while tapering off the current antipsychotic regimen over a 2-week period; upward titration of Abilify 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

Abilify is contraindicated in patients who are hypersensitive to aripiprazole or any of the excipients (see 6.1 List of excipients).

For specific information about the contraindications of mood stabilisers refer to the Contraindications section of the prescribing information for these products when combination with lithium or valproate 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 Abilify 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 Abilify -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 Abilify treated patients and 1.7% (6/343) in the placebo group.

Abilify 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 I Disorder and close supervision of high-risk patients should accompany drug therapy. Prescriptions for

Abilify should be written for the smallest quantity consistent with good patient management, in order to reduce the risk of overdose.

Sleep apnoea

Sleep apnoea and related disorders have been reported in patients treated with aripiprazole, with or without prior history of sleep apnoea.

Aripiprazole should be used with caution in patients who have sleep apnoea or risk factors for developing sleep apnoea, which include overweight/obesity, males, and concomitant use of central nervous system depressants.

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 Abilify, 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 Abilify. 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 Abilify must be discontinued.

Seizure

In short-term, placebo-controlled trials, seizures occurred in 0.1% (3/2467) of adult patients treated with aripiprazole.

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

Falls

Somnolence, postural hypotension, motor and sensory instability have been reported with the use of antipsychotics, including aripiprazole, which may lead to falls, and consequently, other

fall-related injuries. Caution should be taken when treating patients with diseases, conditions, or who are taking medications that could exacerbate these effects.

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 risperidone, aripiprazole, and olanzapine in 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 to 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 and diabetes mellitus, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, have been reported in patients with atypical antipsychotics including Abilify. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increase background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycaemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycaemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycaemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g. obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycaemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

In patients with significant treatment-emergent hyperglycaemia, discontinuation of Abilify should be considered.

Cardiovascular Disorders

Potentially due to its α_1-adrenergic receptor antagonism, Abilify may be associated with orthostatic hypotension.

The incidence of orthostatic hypotension-associated events from short-term, placebo-controlled trials of adult patients on oral Abilify (n=2467) 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% (112/13543) of oral aripiprazole-treated patients during clinical trials.

As with other atypical antipsychotics, Abilify 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).

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 treatment with Abilify and preventive measures undertaken.

Body Temperature Regulation

Disruption of the body's ability to increase or reduce core body temperature has been attributed to antipsychotic agents, including Abilify. Appropriate care is advised when prescribing Abilify 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. Abilify 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 postmarketing experience, events of leukopenia/neutropenia have been reported temporally related to antipsychotic agents, including Abilify. Agranulocytosis has also been reported.

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC) and history of drug-induced leukopenia/neutropenia. Patients with a history of a clinically significant low WBC or drug-induced leukopenia/neutropenia should have their complete blood cell (CBC) monitored frequently during the first few months of therapy and discontinuation of Abilify 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 neutropenia 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 neutropenia (absolute neutrophil count < 1000/mm^3) should discontinue Abilify and have their WBC followed until recovery.

Potential for Cognitive and Motor Impairment

Abilify, 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=2467) treated with oral Abilify (11%, 6%). Somnolence (including sedation) led to discontinuation in 0.3% (8/2467) of adult patients on oral Abilify 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 Abilify 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))

Lactose

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency of glucose-galactose malabsorption should not take this medicine.

Use in Patients with Concomitant Illness

Clinical experience with Abilify in patients with certain concomitant systemic illnesses is limited. (See Section 5.2 Pharmacokinetic properties: Renal Impairment and Hepatic Impairment).

Abilify 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 to 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 Abilify in the treatment of patients with psychosis associated with dementia have not been established. Abilify is 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.)

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 section 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)

Use in the elderly

Placebo-controlled studies of Abilify 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 Abilify in clinical trials, 1073 (8%) were ≥65 years old and 799 (6%) were ≥75 years old. The majority (81%) of the 1073 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 Abilify in the treatment of patients with psychosis associated with Alzheimer's disease has not been established. Abilify is not indicated for the treatment of psychosis associated with Alzheimer's disease.

Of the 749 patients treated with aripiprazole injection in clinical trials, 99 (13%) were ≥65 years old and 78 (10%) were ≥75 years old. Almost all of the use in the elderly was in clinical trials for an indication for which registration has not been requested. Placebo-controlled studies of aripiprazole injection in patients with agitation associated with schizophrenia did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

There was no effect of age on the pharmacokinetics of a single, 15 mg dose of Abilify. 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.

Paediatric use

The safety and efficacy of Abilify in patients less than 18 years of age have not been established.

Effects on laboratory tests

A between group comparison for acute, 3 to 6-week, placebo-controlled trials in adults revealed no medically important differences between the Abilify 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 Abilify/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.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

CNS Drugs (including Alcohol)

Given the primary CNS effects of Abilify, caution should be used when Abilify is taken in combination with other centrally acting drugs and alcohol.

Patients should be advised to avoid alcohol while taking Abilify.

Coadministration 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 to 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 to 125 μg/mL for at least 14 days, with 30 mg Abilify 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.

When aripiprazole was administered concomitantly with either valproate, lithium or lamotrigine, there was no clinically important change in valproate, lithium or lamotrigine concentrations.

Antihypertensive Agents

Due to its α_1-adrenergic receptor antagonist activity, Abilify has the potential to enhance the effect of certain antihypertensive agents.

Medicines which cause QT prolongation or electrolyte imbalance

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

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, strong inhibitors of CYP2D6 (***quinidine***) and 3A4 (***ketoconazole***) decreased oral clearance of aripiprazole by 52% and 38%, respectively. Other strong 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 Medications)

No data are available for use of Abilify 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.

Dose reduction of Abilify should be applied with concomitant administration of potent CYP3A4 inhibitors such as itraconazole, clarithromycin and HIV protease inhibitors, as similar effects to that seen in the clinical studies with ketoconazole may be expected. Dose reduction of Abilify should be applied with concomitant administration of potent CYP2D6 inhibitors such as fluoxetine and paroxetine as similar effects to that seen in the clinical studies with

quinidine may be expected (**see** Section 4.2 Dose and method of administration: Concomitant Medications).

In a clinical study in patients with schizophrenia or schizo-affective disorder, co-administration of ***carbamazepine*** (200 mg twice daily), a strong 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 strong 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. Other potent inducers of CYP3A4 include, but are not limited to, St Johns Wort, phenytoin, rifampicin, efavirenz, and nevirapine. 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 Abilify concomitantly with potential 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 Abilify 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* (IC_{50} values 2.4 to 25 μM). Neither aripiprazole nor dehydro-aripiprazole inhibited CYP1A2 -mediated metabolism *in vitro* (IC_{50} value >50 to 66 μM).

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

Famotidine

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

Food

Abilify can be administered without regard to meals. Following administration of a 15 mg Abilify 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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on 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. Disturbances of spermatogenesis were seen at 60 mg/kg/day and prostatic atrophy was seen at 40 and 60 mg/kg/day.

Use in pregnancy – Pregnancy Category C

Congenital anomalies have been reported; however, a causal relationship with aripiprazole could not be established. 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, undescended testes, and delayed skeletal ossification. There were no adverse effects on embryofoetal 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). Postnatally, 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.

Non-teratogenic class effect: Neonates exposed to antipsychotic drugs (including Abilify) 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.

Abilify 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.

Use in lactation

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 Abilify.

Use in Labor and Delivery

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

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 Abilify does not affect them adversely.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Abilify has been evaluated for safety in 13543 patients who participated in multiple-dose clinical trials in Schizophrenia (including schizo-affective disorder), Bipolar I Disorder, Major Depressive Disorder, Dementia of the Alzheimer's type, Parkinson's disease, and alcoholism, and who had approximately 7619 patient-years of exposure to oral aripiprazole and 749 patients with exposure to aripiprazole injection. A total of 3390 patients were treated with oral aripiprazole for at least 180 days and 1933 patients treated with oral aripiprazole had at least 1 year of exposure.

The conditions and duration of treatment with Abilify (monotherapy and in combination treatment with lithium or valproate) 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 Abilify 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 Abilify-treated (7%) and placebo-treated (9%) patients. The types of adverse events that led to discontinuation were similar between the Abilify and placebo-treated patients.

Adult Patients with Bipolar I Disorder

Monotherapy

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

Adverse Reactions Associated with Discontinuation of Treatment

Overall, in patients with Bipolar I Disorder, 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 I Disorder (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 Patients with Bipolar I Disorder Treated with Oral Abilify Monotherapy

	Percentage of Patients Reporting Reaction	
Preferred Term	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 Abilify-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), 2 or more of patients treated with Abilify (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 Abilify

	Percentage of patients Reporting Reaction[a]	
System Organ Class Preferred Term	Aripiprazole (n=1843)	Placebo (n=1166)
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		

	Percentage of patients Reporting Reaction[a]	
System Organ Class Preferred Term	Aripiprazole (n=1843)	Placebo (n=1166)
Fatigue	6	4
Pain	3	2
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal Stiffness	4	3
Pain in Extremity	4	2
Myalgia	2	1
Muscle Spasm	2	1
Nervous System Disorders		
Headache	27	23
Dizziness	10	7
Akathisia	10	4
Sedation	7	4
Extrapyramidal 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 I Disorder

The following findings are based on a placebo-controlled trial of adult patients with Bipolar I Disorder in which aripiprazole was administered at doses of 15 mg/day or 30 mg/day in combination with lithium or valproate.

Adverse Reactions Associated with Discontinuation of Treatment

In a study of patients who were already tolerating either lithium or valproate 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 valproate in patients with Bipolar I Disorder (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 I Disorder

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 15mg/day or 30mg/day) and lithium or valproate and for which the incidence in patients treated with this combination was greater than the incidence in patients treated with placebo plus lithium or valproate.

Table 3: Adverse Reactions in a Short-Term, Placebo-Controlled Trial of combination therapy with lithium or valproate in Patients with Bipolar I Disorder.

	Percentage of Patients Reporting Reaction [a]	
System Organ Class	**Aripiprazole + Lithium or Valproate**	**Placebo + Lithium or Valproate**
Preferred Term	**(n=253)**	**(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
Extrapyramidal 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 Abilify 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%; 10mg, 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 Abilify 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 Abilify 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 Abilify. In addition, in a long-term (52-week), active-controlled study, the incidence of tremor for Abilify was 5% (40/859). A similar profile was observed in a long-term study in Bipolar I Disorder.

Weight Gain

In placebo-controlled trials, there was a slight difference in mean weight change between Abilify 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 (Abilify 8% compared to placebo 3% in short-term studies; p≤0.01; and Abilify 6% compared to placebo 4% in long-term studies; p = n.s.).

In 3-week trials in adults with Bipolar I Disorder–with monotherapy aripiprazole, the mean weight gain for aripiprazole and placebo patients was 0.1 kg versus 0.0 kg, 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 Bipolar I Disorder-with aripiprazole as adjunctive therapy with either lithium or valproate, 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, Abilify 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 (Abilify 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 Abilify 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 to 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 I Disorder 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 I Disorder for combination therapy with lithium or valproate, the incidence of reported EPS-related events, excluding events related to akathisia for patients treated with aripiprazole in combination with lithium or valproate was 15% versus 8% for patients treated with aripiprazole and placebo and the incidence of akathisia-related events for patients treated with aripiprazole in combination with lithium or valproate was 19% versus 5% for patients treated with aripiprazole and 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 I Disorder 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 I Disorder trials with aripiprazole in combination with either lithium or valproate, The Simpson Angus Rating Scale and the Barnes Akathisia Scale showed a significant difference between adjunctive aripiprazole and combination therapy placebo (aripiprazole, 0.73; placebo, 0.07 and aripiprazole, 0.30; placebo, 0.11). Changes in the Assessment of Involuntary Movement Scales were similar for adjunctive aripiprazole and combination therapy 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 Abilify 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 Abilify-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, and/or spasmodic deviations of the eyes, most commonly upward. 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 I Disorder revealed no significant differences between oral Abilify 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. Abilify 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 Abilify and placebo in the proportion of patients experiencing potentially important changes in ECG parameters.

Adverse Reactions Observed During the Premarketing Evaluation of oral Abilify

The following is a list of MedRA terms that reflect adverse reactions reported by adult patients treated with oral aripiprazole at multiple doses ≥ 2mg/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 1, Table 2, Table 3 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, very rare are those occurring in less than 1/10,000 and unknown cannot be estimated from the available data.

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, angioedema, 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, glycosylated 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, sleep walking, 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[f], pelvic pain, breast discharge, sexual dysfunction, gynaecomastia, priapism.

Respiratory, Thoracic and Mediastinal Disorders: ***common*** - nasal congestion, dyspnoea, 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), hyperhidrosis; ***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

Postmarketing Experience

The following adverse reactions have been identified during post approval use of Abilify. 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: occurrences of allergic reaction (anaphylactic reaction, angioedema, laryngospasm, pruritus/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, somnambulism (sleepwalking) and related behaviours including sleep-related eating disorder.

Nervous system disorders
Very Rare: Restless legs syndrome

Eye Disorders:
Unknown - 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

Drug Abuse and Dependence

Abilify has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. In self-administration studies in rats and monkeys, Abilify 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 Abilify misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behaviour).

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Signs and Symptoms

In clinical studies, and postmarketing 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 Overdose

No specific information is available on the treatment of overdose with Abilify. Management of overdose should concentrate on supportive care, including close medical supervision and monitoring. Ensure an adequate airway, oxygenation and ventilation, and management of symptoms. Monitor cardiac rhythm and vital signs, and include continuous electrocardiographic monitoring to detect possible arrhythmias. Use supportive and symptomatic measures. Treatment should consist of general measures employed in the management of overdosage with any drug. Consider the possibility of multiple drug involvement. Following any confirmed or suspected overdose with aripiprazole, close medical supervision and monitoring should continue until the patient recovers.

There is no specific antidote to aripiprazole. Consider the half-life of aripiprazole when assessing treatment needs and recovery.

***Charcoal*:** In the event of an overdose of Abilify, 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 Abilify, 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 Abilify, 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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Aripiprazole is a novel antipsychotic agent with unique pharmacologic properties.

Mechanism of action

The mechanism of action of Abilify, as well as other drugs having efficacy in schizophrenia, is unknown. However, it has been proposed that the efficacy of Abilify is mediated through a combination of partial agonist activity at dopamine D_2 and serotonin $5HT_{1A}$ receptors and antagonist activity at serotonin $5HT_{2A}$ receptors.

Abilify activity is primarily due to the parent drug, aripiprazole

Aripiprazole exhibited higher affinity binding *in vitro* for dopamine D_2 and D_3, serotonin 5-HT1A and 5-HT2A receptors (K_i values of 0.3, 0.8, 1.7, and 3.4 nM, respectively), than for dopamine D_4, serotonin 5-HT2C and 5-HT7, α1-adrenergic and histamine H_1 receptors (K_i values of 44, 15, 39, 57, and 61 nM, respectively) and the serotonin reuptake site (K_i value of 98 nM). Aripiprazole exhibited no appreciable affinity for muscarinic receptors (IC_{50} >1000 nM).

The predominant metabolite in human plasma, dehydro-aripiprazole has been shown to have a similar affinity for dopamine D_2 and D_3 receptors (K_i values 0.4 and 0.5 nM, 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 Abilify.

Clinical trials

Schizophrenia

The efficacy of Abilify 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 Abilify and the active comparators. Efficacy was also documented in two long-term trials, one of 52 weeks duration, which compared Abilify to haloperidol and one of 26 weeks duration, which compared Abilify 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 Abilify 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 Abilify (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, Abilify 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 Abilify (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 Abilify 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 Abilify (10, 15, or 20 mg/day) in acutely relapsed patients with a DSM-IV diagnosis of schizophrenia, all Abilify 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 Abilify (2, 5 or 10 mg/day) to placebo, in acutely relapsed patients with a DSM-IV diagnosis of schizophrenia, the 10 mg dose of Abilify 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 Abilify did not reach significance in the PANSS total score or the PANSS positive subscale, it was superior to placebo in the PANSS 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 Abilify. The first one (Trial 5) was a placebo-controlled, 4-week ascending dose trial of Abilify (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, Abilify 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 Abilify (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.

Table 5: Key Efficacy Results in Short-Term, Placebo-Controlled Trials

	PANSS Total Score	PANSS Positive Subscale Score	PANSS Negative Subscale Score	PANSS-Derived BPRS Core Score	CGI-Severity Score	CGI Improve-ment 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 Abilify 30 mg/day and haloperidol 10mg/day, with a one time option to decrease Abilify to 20 mg/day and haloperidol to 7 mg/day, Abilify 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 Abilify group and 298/430, 69% in the haloperidol group), there was a 12% lower risk of subsequent failure with Abilify relative to haloperidol (relative risk: 0.881, 95% CI: 0.645 to 1.204). Abilify was comparable to haloperidol in time-to-failure to maintain response in all randomised patients. Patients in the Abilify group had a 14% lower risk of failure compared with the haloperidol group (relative risk: 0.858, 95% CI: 0.721, 1.021). Abilify was statistically superior to haloperidol in the analysis of the proportion of patients on treatment and in response at Weeks 8, 26, and 52 (prespecified key time points). At Week 52, 40% of Abilify patients were still on-study and in response compared to 27% of haloperidol patients ($p<0.001$). Abilify-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 to 0.837). There were no significant differences between Abilify and haloperidol groups in terms of change from baseline PANSS total scores, PANSS positive subscores, CGI-severity or improvement scores. Abilify 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 Abilify, a double-blind study was conducted in chronic, symptomatically stable schizophrenic patients (n=310) randomised to Abilify 15mg 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 Abilify group. From 4 weeks onwards there were noticeably more relapses in the placebo group than the Abilify 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 Abilify group [relative risk Abilify: placebo = 0.50 (95% CI=0.35, 0.71, $p\leq0.01$)]. The number of relapses was significantly lower in the Abilify group compared to placebo (34% vs 57%, RR=0.59, 95% CI: 0.45, 0.75, $p\leq0.01$).

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 I Disorder

Acute manic and mixed episodes

Adults

Monotherapy

The efficacy of Abilify in the treatment of acute manic episodes was established in four 3-week, placebo-controlled trials in hospitalised adult patients who met the DSM-IV criteria for Bipolar I Disorder with manic or mixed episodes. These studies included adult patients with or without psychotic features and two of the studies also included adult 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 (irritability, 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 Abilify 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). Abilify 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.

Combination therapy with lithium or valproate

The efficacy of adjunctive Abilify with concomitant lithium or valproate 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 stabiliser monotherapy phase in adult patients who met DSM-IV criteria for Bipolar 1 Disorder. This study included patients with manic or mixed episodes and with or without psychotic features.

Adult patients were initiated on open-label lithium (0.6 mEq/L to 1.0 mEq/L) or valproate (50µg/mL to 125µg/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 valproate were randomised 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 valproate. In the 6-week placebo-controlled phase, adjunctive Abilify starting at 15 mg/day with concomitant lithium or valproate (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 valproate 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 coadministered lithium were on 15 mg/day at the 6-week endpoint.

Maintenance of manic and mixed episodes

Monotherapy Maintenance of Effect

Two short term studies in adult patients with an acute manic or mixed episode included assessment of maintenance of effect to 12 weeks. Patients in the haloperidol active-comparator study commenced on placebo, haloperidol (5 mg daily with an option to increase up to 15 mg daily), or aripiprazole (15 mg daily with an option to increase up to 30 mg daily). At Week 3 patients initially randomised to placebo were switched to aripiprazole. There were 274 (56.5%) patients completed the 12-week double-blind phase of the study, 56.9% given aripiprazole, 57.6% given haloperidol and 54.9% who were initially randomised to placebo and then switched to aripiprazole. The placebo-aripiprazole patients were not included in the maintenance of effect analyses. The mean change from baseline in Y-MRS total scores at Week 12 for patients given 12 weeks of continuous aripiprazole was -17.16 compared with -17.84 for haloperidol. An increase in the proportion of patients with a reduction in Y-MRS total score of at least 50% from baseline (50% responder rates) for both aripiprazole and haloperidol was apparent between Weeks 3 and 12 (from 47.0% to 72.3% for aripiprazole and from 49.7% to 73.9% for haloperidol).

The other 12-week study included lithium as the active comparator. Adult patients in this study commenced on placebo, lithium (900 mg daily with an option to increase up to 1200 mg daily at Day 4 and 1500 mg daily at Day 7), or aripiprazole (15 mg daily with an option to increase to 30 mg daily). At Week 3 patients initially randomised to placebo were switched to aripiprazole. There were 143 (29.8%) patients who completed the 12-week double-blind phase of the study: 27.1% given aripiprazole, 33.8% given lithium, and 28.5% who were initially randomised to placebo and then switched blindly to aripiprazole. The placebo-aripiprazole patients were not included in the maintenance of effect analyses. The mean change from baseline in Y-MRS total scores at Week 12 for patients given 12 weeks of continuous aripiprazole was -14.41 compared with -12.71 for lithium. An increase in the proportion of patients with a reduction in Y-MRS total score of at least 50% from baseline (50% responder rates) for both aripiprazole and lithium was apparent between Weeks 3 and 12 (from 46.8% to 56.5% for aripiprazole and from 45.8% to 49.0% for lithium).

A placebo-controlled, randomised withdrawal study was conducted in adult patients who had experienced a recent acute manic or mixed episode. This study had an initial stabilisation phase where all patients received aripiprazole for 6 to 18 weeks. Patients continued in this phase until symptoms were stable for at least 6 weeks. They were then randomised to aripiprazole or placebo for a 26-week maintenance phase.

567 patients entered the stabilisation phase, of these 361 (64%) did not proceed further due mostly to adverse events (22%), lack of efficacy (12%) and withdrawal of consent (12%). Of the 206 patients who completed the stabilisation phase 161 were randomised to placebo (n=83) or aripiprazole (n=78). 94 (58%) of patients discontinued the maintenance phase, the most frequent reason for discontinuation was lack of efficacy (placebo 43%; aripiprazole 24%). The placebo group relapsed sooner than the aripiprazole group. In the maintenance phase the hazard ratio for recurrence for aripiprazole was 0.523 (95% CI: 0.300; 0.913; p =0.020).

There is insufficient data to know whether Abilify 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.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Aripiprazole is well absorbed after oral administration of Abilify, with peak plasma concentrations occurring within 3 to 5 hours after dosing. The absolute oral bioavailability of the tablet formulation of Abilify is 87%. Abilify can be administered without regard to meals. Following administration of a 15 mg Abilify 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 4.9 L/kg. At therapeutic concentrations, aripiprazole is highly bound (88 to 97% to > 99%, as determined by polydimethylsiloxane-glass bead and equilibrium dialysis assays, respectively) to serum proteins, binding 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 to 146 hours, n=58, in fasted subjects and 84 hours mean, range 32 to 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 to 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

Genotoxicity

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.

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, 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. Hyperprolactinaemia was observed in female mice in a 13-week dietary study at doses associated with mammary gland and pituitary tumours, but not in female rats in 4- and 13-week dietary studies at doses associated with mammary gland tumours. Hyperprolactinaemia was observed in female rats after 5 and 13 weeks of oral administration at doses up to that associated with adrenocortical tumours, but serum prolactin was decreased at this dose in male rats. The relationship between tumourigenic findings with aripiprazole and prolactin is unclear and the relevance for human risk of prolactin-mediated endocrine 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 exposure (plasma AUC) was about fold 7 clinical exposure at the MRHD.

Animal Toxicology

Choleliths (gallsand and/or gallstones) were observed in the bile of monkeys given aripiprazole orally for 4 to 52 weeks at doses of 25 to 125 mg/kg/day (1 to 3 times the MRHD based on plasma AUC and 15 to 76 times the MRHD based on mg/m2) and were attributed to precipitation of sulfate conjugates of hydroxy metabolites, which exceeded their solubility limits in bile. Human biliary concentrations of these sulfate conjugates after repeated daily administration of the MRHD are substantially lower (0.2 to 14% of their in vitro solubility limits).

Bilateral retinal degeneration was observed in albino rats given oral aripiprazole for 6 months or two years at exposures of 6 to 13 times the clinical exposure at the MRHD (based on plasma AUC). The exposure at the NOEL dose was 3 times that at the MRHD. A subsequent 18-month study reported this finding in albino but not pigmented rats, possibly due to lack of photoprotective ocular melanin in the albino rats, although it is unknown whether pigmentation prevented or merely delayed retinal degeneration in the pigmented rats. The clinical relevance of this finding is uncertain.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The inactive ingredients in the tablets are: lactose monohydrate, maize starch, microcrystalline cellulose, hyprolose, and magnesium stearate. The following colorants are also contained in the tablets: 2 mg tablets - indigo carmine aluminium lake and iron oxide yellow; 5 mg tablets - indigo carmine aluminium lake; 10 mg tablets - iron oxide red; 15 mg tablets – iron oxide yellow; 20 mg tablets – nil; 30 mg tablets – iron oxide red

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Abilify tablets are packed in aluminium blisters in cartons.

Not all pack sizes may be available in Australia.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

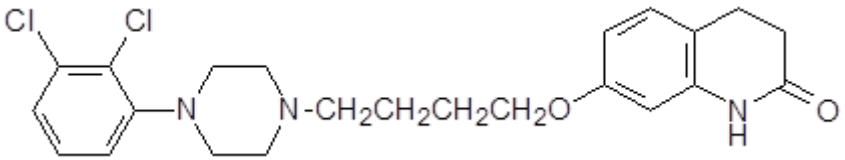
6.7 PHYSICOCHEMICAL PROPERTIES

Aripiprazole is a novel antipsychotic agent with a chemical structure that differs from current antipsychotic. Aripiprazole is insoluble in water with its equilibrium solubility being about 0.00001% w/v, its pKa was established in 20% aqueous ethanol pKa = 7.6 (20% ethanol, at 25°C). The partition coefficients (Po/w) of aripiprazole range from 3.4 at pH 2.0 to > 1000 at pH 6.0.

Chemical structure

Aripiprazole is 7-[4-[4-(2, 3-dichlorophenyl)-1-piperazinyl] butoxy]-3, 4- dihydrocarbostyril

The empirical formula is $C_{23}H_{27}Cl_2N_3O_2$ and its molecular weight is 448.39. The chemical structure is:



CAS number

129722-12-9

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 Prescription Medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

16 May 2003

10 DATE OF REVISION

25 September 2026

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.4, 4.5, 4.6, 4.9	Addition of Safety-related text relating to Falls, Cerebrovascular Adverse Events, and Management of Overdose as per Company Core Data Sheet.
4.4, 4.5, 4.6, 4.9, 5.1, 5.2, 5.3	Minor editorial changes.