AUSTRALIAN PI – ARDIX® LURASIDONE (LURASIDONE HYDROCHLORIDE)

NAME OF THE MEDICINE

Lurasidone hydrochloride

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ARDIX LURASIDONE tablet contains 40 mg or 80 mg of lurasidone hydrochloride.

Lurasidone hydrochloride (HCl) is chemically identified as (3a*R*,4*S*,7*R*,7a*S*)-2-{(1*R*,2*R*)-2-[4-(1,2-benzisothiazol-3-yl)piperazin-1-ylmethyl]cyclohexylmethyl}hexahydro-4,7-methano-2*H*-isoindole-1,3-dione hydrochloride. Lurasidone is an atypical antipsychotic belonging to the chemical class of benzisothiazol derivatives. It has antagonist activity on the dopamine 2 (D2) and serotonin (5-HT)-2A receptors. Lurasidone HCl (active entity) is a white to off-white powder. It is very slightly soluble in water, practically insoluble or insoluble in 0.1 N HCl, slightly soluble in ethanol, sparingly soluble in methanol, practically insoluble or insoluble in toluene very slightly soluble in acetone and has a pKa of 7.6.

ARDIX LURASIDONE tablets contain 40 mg (equivalent to 37.24 mg lurasidone) or 80 mg (equivalent to 74.49 mg lurasidone).

For the full list of excipients, see section 6.1.

PHARMACEUTICAL FORM

Film-coated tablet.

ARDIX LURASIDONE 40 mg: White to off-white, round, strength specific one-sided debossing “L40”.

ARDIX LURASIDONE 80 mg: Pale green, oval, strength specific one-sided debossing “L80”.

CLINICAL PARTICULARS

THERAPEUTIC INDICATIONS

ARDIX LURASIDONE is indicated for the treatment of schizophrenia in adults and adolescents (aged 13 to 17 years).

DOSE AND METHOD OF ADMINISTRATION

ARDIX LURASIDONE film-coated tablets are intended for oral administration only.

The efficacy of ARDIX LURASIDONE has been established at doses of 40, 80, 120 and 160 mg/day. The recommended starting dose is 40 mg once daily. Initial dose titration is not required. Patients should be treated with the lowest effective dose that provides optimal clinical response and tolerability, which is expected to be 40 mg or 80 mg once daily for most patients. Dose increase should be based on physician judgement and observed clinical response. In the six week controlled trials, there was no suggestion of added benefit with the 120 mg/day dose compared to 40 and 80 mg/day. In the pooled analyses, added benefit occurred at 160 mg/day compared to lower doses.

Doses above 80 mg may be considered for certain patients based on individual clinical judgment. The maximum recommended dose is 160 mg/day. ARDIX LURASIDONE should be taken with food.

Children and adolescents

The recommended starting dose of lurasidone in adolescent patients 13 to 17 years of age with schizophrenia is 40 mg/day. The maximum recommended dose in adolescent patients is 80 mg/day. Lurasidone was studied in adolescent patients 13 to 17 years of age with schizophrenia at daily doses of 40 mg and 80 mg. The safety and efficacy of ARDIX LURASIDONE in children aged less than 13 years have not been established (see section 4.4).

Due to difficulties associated with diagnosing schizophrenia in adolescents, diagnosis of schizophrenia in adolescents should be made by practitioners experienced in the diagnosis and management of adolescent psychiatric disorders.

The effectiveness of ARDIX LURASIDONE has not been established in controlled studies for treatment duration of more than 6 weeks in adolescents. Therefore, if ARDIX LURASIDONE is to be used for more than 6 weeks, the treating physician should periodically re-evaluate the long-term use of ARDIX LURASIDONE for the individual patient.

Patients with renal impairment

There are limited clinical data in patients with renal impairment. No dose adjustment for ARDIX LURASIDONE is required in patients with mild (CrCL: 50 to 80 mL/min) renal impairment.

In patients with moderate (CrCl: 30 to < 50 mL/min) or severe (CrCL: < 30 mL/min) renal impairment, the recommended starting dose is 20 mg[§] and the maximum dose should not exceed 80 mg once daily. As the 20 mg tablet is not available in Australia, ARDIX LURASIDONE should not be started in patients with moderate or severe renal impairment.

Patients with hepatic impairment

There are limited clinical data in patients with hepatic impairment.

No dose adjustment for ARDIX LURASIDONE is required in patients with mild hepatic impairment.

Dose adjustment is recommended in patients with moderate (Child-Pugh Class B) hepatic impairment. The recommended starting dose is 20 mg. The dose in patients with moderate hepatic impairment should not exceed 80 mg. As the 20 mg tablet is not available in Australia, ARDIX LURASIDONE should not be started in patients with moderate (Child-Pugh Class B) hepatic impairment.

ARDIX LURASIDONE is not recommended in patients with severe (Child-Pugh Class C) hepatic impairment.

[§] The 20 mg tablet is not currently available in Australia

Elderly Patients

No dose adjustment is necessary in elderly patients. Clinical studies of ARDIX LURASIDONE in the treatment of schizophrenia did not include sufficient numbers of patients aged 65 and older to determine whether or not they respond differently from younger patients. In elderly patients with psychosis (65 to 85), ARDIX LURASIDONE concentrations (20 mg/day) were similar to those in young subjects.

Dosing recommendations for older patients with normal renal function (CrCl ≥ 80 mL/min) are the same as for adults with normal renal function. However, as older patients may have diminished renal function, dose adjustments may be required according to their renal function status (see section 4.2). Renal function and cardiovascular status should be assessed prior to commencing treatment with ARDIX LURASIDONE.

Dose adjustment due to interactions

If ARDIX LURASIDONE is being prescribed and a moderate CYP3A4 inhibitor (e.g. diltiazem) is added to therapy, the ARDIX LURASIDONE dose should be reduced to half of the original dose level.

Similarly, if a moderate CYP3A4 inhibitor is being prescribed and ARDIX LURASIDONE is added to the therapy, the recommended starting dose of ARDIX LURASIDONE is 20 mg per day[**], and the maximum dose of ARDIX LURASIDONE is 80 mg per day. As the 20 mg tablet is not available in Australia, ARDIX LURASIDONE should not be used in combination with moderate CYP3A4 inhibitors.

ARDIX LURASIDONE is contraindicated for use in combination with strong CYP3A4 inhibitors (e.g. ketoconazole, clarithromycin, ritonavir, and voriconazole) and strong CYP3A4 inducers (e.g. rifampin, St. John's wort, phenytoin, and carbamazepine).

Grapefruit and grapefruit juice should be avoided in patients taking ARDIX LURASIDONE, as these may inhibit CYP3A4 and alter ARDIX LURASIDONE concentrations.

Switching between antipsychotic medicinal products

Due to different pharmacodynamic and pharmacokinetic profiles among antipsychotic medicinal products, supervision by a clinician is needed when switching to another antipsychotic product is considered medically appropriate.

Abuse

ARDIX LURASIDONE has not been systematically studied in humans for its potential for abuse or physical dependence or its ability to induce tolerance. While clinical studies with ARDIX LURASIDONE did not reveal any tendency for drug-seeking behaviour, these observations were not systematic and it is not possible to predict the extent to which a CNS-active drug will be misused, diverted and/or abused once it is marketed. Patients should be evaluated carefully for a history of drug abuse, and such patients should be observed carefully for signs of ARDIX LURASIDONE misuse or abuse (e.g. development of tolerance, drug-seeking behaviour, increases in dose).

[**] The 20 mg tablet is not currently available in Australia

CONTRAINDICATIONS

ARDIX LURASIDONE (lurasidone HCl) is contraindicated in any patient with a known hypersensitivity to lurasidone HCl or any components in the formulation.

ARDIX LURASIDONE is contraindicated with strong CYP3A4 inhibitors (e.g. ketoconazole, clarithromycin, ritonavir, and voriconazole) and strong CYP3A4 inducers (e.g. rifampin, St. John's wort, phenytoin, and carbamazepine) (see section 4.4).

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

In placebo-controlled trials with similar atypical antipsychotics in elderly subjects with dementia-related psychosis, there was a higher incidence of fatalities, compared to placebo-treated subjects. Elderly patients with dementia-related psychosis treated with atypical antipsychotics are at an increased risk of death compared to placebo. A meta-analysis of seventeen placebo controlled trials with dementia-related behavioural disorders showed a risk of death in the drug-treated patients of approximately 1.6 to 1.7 times that seen in placebo-treated patients. The clinical trials included in the meta-analysis were undertaken with olanzapine, aripiprazole, risperidone and quetiapine. Over the course of these trials averaging about 10 weeks in duration, the rate of death in drug-treated patients was about 4.5 %, compared to a rate of approximately 2.6 % in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g. heart failure, sudden death) or infectious (e.g. pneumonia) in nature. ARDIX LURASIDONE is not approved for the treatment of elderly patients with dementia-related psychosis or behavioural disorders.

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

In placebo-controlled trials with risperidone, aripiprazole, and olanzapine in elderly subjects with dementia, there was a higher incidence of cerebrovascular adverse reactions (cerebrovascular accidents and transient ischemic attacks), including fatalities, compared to placebo-treated subjects. ARDIX LURASIDONE is not approved for the treatment of patients with dementia-related psychosis.

Neuroleptic Malignant Syndrome

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS), characterised by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated serum creatine phosphokinase levels, has been reported in association with administration of antipsychotic medicines, including ARDIX LURASIDONE. Additional signs may include 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 medicines, including ARDIX LURASIDONE, must be discontinued.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. If reintroduced, the patient should be carefully monitored, since recurrences of NMS have been reported.

Seizures

As with other antipsychotic medicines, ARDIX LURASIDONE should be used cautiously in patients with a history of seizures or with conditions that lower the seizure threshold, e.g. Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in patients 65 years or older.

Suicide

The possibility of a suicide attempt is inherent in psychotic illness and close supervision of high-risk patients should accompany treatment with an antipsychotic medicine. Prescriptions for ARDIX LURASIDONE should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

Weight Gain

Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

Pooled data from short-term, placebo-controlled schizophrenia studies are presented in Table 1. The mean weight gain was 0.43 kg for ARDIX LURASIDONE-treated patients compared to -0.02 kg for placebo-treated patients. The proportion of patients with a ≥ 7 % increase in body weight (at Endpoint) was 4.8 % for ARDIX LURASIDONE-treated patients versus 3.3 % for placebo-treated patients.

Table 1: Mean Change in Weight (kg) from Baseline in Schizophrenia Studies

		ARDIX LURASIDONE				
	Placebo (n=696)	**20 mg/day (n=71)**	**40 mg/day (n=484)**	**80 mg/day (n=526)**	**120 mg/day (n=291)**	**160 mg/day (n=114)**
All Patients	-0.02	-0.15	+0.22	+0.54	+0.68	+0.60

In long-term controlled studies, for patients who had normal BMI status at baseline (18.5 to < 25.0), the rate of clinically significant weight gain (≥ 7 % increase in BMI) at month 12 was 12.4 %, 34.5 % and 5.6 % and to study endpoint (LOCF) was 9.6 %, 17.7 % and 8.3 % of the ARDIX LURASIDONE, risperidone and quetiapine XR groups, respectively. For those who were overweight at baseline (BMI 25.0 to < 30.0), the rate of clinically significant weight gain at study endpoint was 6.3 %, 14.1 % and 9.5 %, in patients given ARDIX LURASIDONE, risperidone and quetiapine XR, respectively.

Orthostatic Hypotension, Syncope and Cardiovascular Disease

ARDIX LURASIDONE may cause orthostatic hypotension, perhaps due to its α1-adrenergic receptor antagonism. ARDIX LURASIDONE should be used with caution in patients with known cardiovascular disease (e.g. heart failure, history of myocardial infarction, ischemia, or conduction abnormalities), cerebrovascular disease, or conditions that predispose the patient to hypotension (e.g. dehydration, hypovolemia, and treatment with antihypertensive medications). Monitoring of orthostatic vital signs should be considered in patients who are vulnerable to hypotension.

Caution should be exercised when ARDIX LURASIDONE is prescribed in patients with known cardiovascular disease or family history of QT prolongation, hypokalaemia, and in concomitant use with other medicinal products thought to prolong the QT interval. ARDIX LURASIDONE 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 trials. Due to the risk of orthostatic hypotension with ARDIX LURASIDONE, caution should be observed in patients with known cardiovascular disease.

Electrocardiogram (ECG) measurements were taken at various time points during the ARDIX LURASIDONE clinical trial program. No post-baseline QT prolongations exceeding 500 msec were reported in patients treated with ARDIX LURASIDONE. Within a subset of patients defined as having an increased cardiac risk, no potentially important changes in ECG parameters were observed. No cases of torsade de pointes or other severe cardiac arrhythmias were observed in the pre-marketing clinical program.

The effects of ARDIX LURASIDONE on the QT/QTc interval were evaluated in a dedicated QT study involving 87 clinically stable patients with schizophrenia or schizoaffective disorder, who were treated with ARDIX LURASIDONE doses of 120 mg daily, 600 mg daily, or ziprasidone 160 mg daily. Holter monitor-derived electrocardiographic assessments were obtained over an eight hour period at baseline and steady state. The maximum mean (upper 1-sided, 95 % CI) increases of baseline-adjusted QTc intervals based on individual correction method (QTcI) were 0.36 (1.40) ms for ARDIX LURASIDONE 120 mg and 1.69 (6.51) ms for ARDIX LURASIDONE 600 mg. No patients treated with ARDIX LURASIDONE experienced QTc increases > 60 msec from baseline, nor did any patient experience a QTc of > 500 msec.

Tardive Dyskinesia

Tardive dyskinesia is a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements that can develop in patients treated with antipsychotic medicines, including lurasidone. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic medicines differ in their potential to cause tardive dyskinesia is unknown.

The risk of development of tardive dyskinesia may be reduced by using the lowest effective dose. ARDIX LURASIDONE should not be continued in patients who have not responded to treatment. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to antipsychotic medicines, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on ARDIX LURASIDONE, discontinuation of ARDIX LURASIDONE should be considered.

Venous thromboembolism

Cases of venous thromboembolism (VTE) have been reported with antipsychotic medicinal products. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with ARDIX LURASIDONE and preventive measures undertaken.

Hyperprolactinemia

As with other medicines that antagonize dopamine D_2 receptors, ARDIX LURASIDONE elevates prolactin levels. Hyperprolactinemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotrophin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds. Long-standing hyperprolactinemia, when associated with hypogonadism, may lead to decreased bone density in both female and male patients. Premenopausal women who develop secondary amenorrhoea of greater than six months duration should receive appropriate preventative therapy to avoid hypooestrogenic bone loss.

In short-term, placebo-controlled schizophrenia studies, the median change from baseline to endpoint in prolactin levels for ARDIX LURASIDONE-treated patients was +0.4 ng/mL and was -1.9 ng/mL in the placebo-treated patients. The median change from baseline to endpoint for males was +0.5 ng/mL and for females was -0.2 ng/mL. Median changes for prolactin by dose are shown in Table 2.

Table 2: Median Change in Prolactin (ng/mL) from Baseline in Adult Schizophrenia Studies

		ARDIX LURASIDONE				
	Placebo	**20 mg/day**	**40 mg/day**	**80 mg/day**	**120 mg/day**	**160 mg/day**
All Patients	-1.9 (n=672)	-1.1 (n=70)	-1.4 (n=476)	-0.2 (n=495)	+3.3 (n=284)	+3.3 (n=115)
Females	-5.1 (n=200)	-0.7 (n=19)	-4.0 (n=149)	-0.2 (n=150)	+6.7 (n=70)	+7.1 (n=36)
Males	-1.3 (n=472)	-1.2 (n=51)	-0.7 (n=327)	-0.2 (n=345)	+3.1 (n=214)	+2.4 (n=79)

The proportion of patients with prolactin elevations ≥ 5× upper limit of normal (ULN) was 2.8 % for ARDIX LURASIDONE-treated patients versus 1.0 % for placebo-treated patients. The proportion of female patients with prolactin elevations ≥ 5x ULN was 5.7 % for ARDIX LURASIDONE-treated patients versus 2.0 % for placebo-treated female patients. The proportion of male patients with prolactin elevations ≥ 5x ULN was 1.6 % versus 0.6 % for placebo-treated male patients.

Leukopenia, Neutropenia and Agranulocytosis

Leukopenia/neutropenia has been reported during treatment with antipsychotic agents. Agranulocytosis (including fatal cases) has been reported with other agents in the class.

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 pre-existing low WBC or a history of drug-induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and ARDIX LURASIDONE should be discontinued at the first sign of decline in WBC, in the absence of other causative factors.

Patients with 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 ARDIX LURASIDONE and have their WBC followed until recovery.

Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. Pooled data from short-term, placebo-controlled schizophrenia studies are presented in Table 3.

Table 3: Change in Fasting Glucose in Adult Schizophrenia Studies

		ARDIX LURASIDONE				
	Placebo	**20 mg/day**	**40 mg/day**	**80 mg/day**	**120 mg/day**	**160 mg/day**
Mean Change from Baseline (mg/dL)						
	n=680	**n=71**	**n=478**	**n=508**	**n=283**	**n=113**
Serum Glucose	-0.0	-0.6	+2.6	-0.4	+2.5	+2.5
Proportion of Patients with Shifts to ≥ 126 mg/dL						
Serum Glucose (≥ 126 mg/dL)	8.3 % (52/628)	11.7 % (7/60)	12.7 % (57/449)	6.8 % (32/472)	10.0 % (26/260)	5.6 % (6/108)

Dyslipidemia

Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics. Pooled data from short-term, placebo-controlled schizophrenia studies are presented in Table 4.

Table 4: Change in Fasting Lipids in Adult Schizophrenia Studies

	ARDIX LURASIDONE					
	Placebo	**20 mg/day**	**40 mg/day**	**80 mg/day**	**120 mg/day**	**160 mg/day**
Mean Change from Baseline (mg/dL)						
	n=660	**n=71**	**n=466**	**n=499**	**n=268**	**n=115**
Total Cholesterol	-5.8	-12.3	-5.7	-6.2	-3.8	-6.9
Triglycerides	-13.4	-29.1	-5.1	-13.0	-3.1	-10.6
Proportion of Patients with Shifts						
Total Cholesterol (≥ 240 mg/dL)	5.3 % (30/571)	13.8 % (8/58)	6.2% (25/402)	5.3% (23/434)	3.8 % (9/238)	4.0 % (4/101)
Triglycerides (≥ 200 mg/dL)	10.1 % (53/526)	14.3 % (7/49)	10.8 % (41/379)	6.3 % (25/400)	10.5 % (22/209)	7.0 % (7/100)

In long term controlled studies the rate of markedly abnormal metabolic parameters was similar between ARDIX LURASIDONE, risperidone and quetiapine XR. For patients given any dose of ARDIX LURASIDONE the rate of shift from normal to high total cholesterol was 2.2 % and triglycerides was 6.2 %.

Body Temperature Regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing ARDIX LURASIDONE for patients who will be experiencing conditions that 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.

Dysphagia

Oesophageal dysmotility and aspiration have been associated with the use antipsychotic medicines. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. ARDIX LURASIDONE and other antipsychotic medicines should be used cautiously in patients at risk for aspiration pneumonia.

Sleep apnoea

Sleep apnoea and related disorders have been reported in patients treated with antipsychotic medicines, with or without prior history of sleep apnoea, and with or without concomitant weight-gain. In patients who have a history of or are at risk for sleep apnoea, or who are concomitantly using central nervous system depressants, antipsychotic medicines including lurasidone should be used with caution.

Use in the elderly

Clinical studies with ARDIX LURASIDONE did not include sufficient numbers of patients aged 65 and older to determine whether or not they respond differently from younger patients. In elderly patients with psychosis (65 to 85), ARDIX LURASIDONE concentrations (20 mg/day) were similar to

those in young subjects. It is unknown whether dose adjustment is necessary on the basis of age alone.

Elderly patients with schizophrenia may have reduced renal function and co-existing cardiovascular disease. In these patients, the starting dose should be reduced (see section 4.2).

Elderly patients with dementia-related psychosis treated with ARDIX LURASIDONE are at an increased risk of death compared to placebo. ARDIX LURASIDONE is not approved for the treatment of patients with dementia-related psychosis.

Paediatric use

The safety and efficacy of ARDIX LURASIDONE has been established in adolescents aged 13 to 17 years. The safety and efficacy of ARDIX LURASIDONE in children aged less than 13 years have not yet been established. ARDIX LURASIDONE is not recommended in children aged less than 13 years.

INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Given the primary central nervous system effects of lurasidone (see section 4.8), ARDIX LURASIDONE should be used with caution in combination with other centrally acting medicines and alcohol.

Effects on ARDIX LURASIDONE

Based on in vitro studies, lurasidone is not a substrate of CYP1A1, CYP1A2, CYP2A6, CYP4A11, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP2E1 enzymes. This suggests that an interaction of lurasidone with medicines that are inhibitors or inducers of these enzymes is unlikely.

Grapefruit and grapefruit juice inhibits CYP3A4 and may increase the serum levels of ARDIX LURASIDONE. It should not be taken with ARDIX LURASIDONE.

Lurasidone is predominantly metabolized by CYP3A4; interaction of ARDIX LURASIDONE with strong and moderate inhibitors or inducers of this enzyme has been observed (Table 5). ARDIX LURASIDONE should not be used in combination with strong inhibitors or inducers of this enzyme.

Table 5: Summary of Effect of Coadministered Medicines on Exposure to ARDIX LURASIDONE in Healthy Adult Subjects or Adult Patients with Schizophrenia

Coadministered Medicine	**Dose Schedule**		**Effect on ARDIX LURASIDONE Pharmacokinetics**		**Recommendation**
	Coadministered Medicine	**ARDIX LURASIDONE**	**C_{max}**	**AUC**	
Ketoconazole (strong CYP3A4 inhibitor)	400 mg/day for 7 days	10 mg single dose	6.8-fold increase	9.3-fold increase	Should not be coadministered with ARDIX LURASIDONE (contraindicated)

Diltiazem (moderate CYP3A4 inhibitor)	240 mg/day for 5 days	20 mg single dose	2.1-fold increase	2.2-fold increase	Recommended starting dose is 20 mg[††]; ARDIX LURASIDONE dose should not exceed 80 mg/day (see section 4.2).
Rifampin (strong CYP3A4 inducer)	600 mg/day for 8 days	40 mg single dose	85 % decrease	82-83 % decrease	Should not be coadministered with ARDIX LURASIDONE (contraindicated)
Lithium	600 mg BID for 8 days	120 mg/day for 8 days	92 %[a]	107 %[a]	No ARDIX LURASIDONE dose adjustment required.

[a]Ratio of geometric least squares means (lurasidone + lithium/lurasidone)

Effects on Coadministered Medicines

Digoxin (P-gp substrate):

Coadministration of ARDIX LURASIDONE (120 mg/day) at steady state with a single dose of digoxin (0.25 mg) increased C_{max} and $AUC_{(0-24)}$ for digoxin by approximately 9 % and 13 %, respectively relative to digoxin alone. Digoxin dose adjustment is not required when coadministered with ARDIX LURASIDONE.

Lithium:

Coadministration of ARDIX LURASIDONE (120 mg/day) and lithium (1200 mg/day) at steady state resulted in comparable mean lithium C_{max} values on Day 4 (0.65 mmol/L) and Day 8 (0.75 mmol/L) and maintenance of the therapeutic range for lithium (0.6 to 1.2 mmol/L). No adjustment of lithium dose is required when coadministered with ARDIX LURASIDONE.

Midazolam (CYP3A4 substrate):

Coadministration of ARDIX LURASIDONE (120 mg/day) at steady state with a single dose of 5 mg midazolam increased midazolam C_{max} and $AUC_{(0-24)}$ by approximately 21 % and 44 %, respectively relative to midazolam alone. Midazolam dose adjustment is not required when coadministered with ARDIX LURASIDONE.

Oral Contraceptive (estrogen/progesterone):

Coadministration of ARDIX LURASIDONE (40 mg/day) at steady state with an oral contraceptive (OC) containing ethinyl estradiol and norelgestimate resulted in equivalent $AUC_{(0-24)}$ and C_{max} of ethinyl estradiol and norelgestromin relative to OC administration alone. Also, sex hormone binding globulin levels were not meaningfully affected by coadministration of ARDIX LURASIDONE and OC. Dose adjustment of OC dose is not required when coadministered with ARDIX LURASIDONE.

[††] The 20 mg tablet is not currently available in Australia

FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There was no effect on mating performance or fertility in male rats treated with lurasidone prior to and during mating at oral doses up to 150 mg/kg/day, corresponding to about 9 times the maximum recommended human dose (MRHD) based on body surface area.

In female rats given lurasidone prior to and during mating and in early pregnancy, oestrus was prolonged and mating was delayed at oral doses of 1.5-150 mg/kg/day (0.1-9 times the MRHD based on body surface area); the no-effect dose was 0.1 mg/kg/day. At the 150 mg/kg/day dose, reductions were observed in the proportion of females mating, fertility and the number of corpora lutea, implantations and live fetuses per dam. These changes were reversed after a 14-day treatment-free period. The no-effect dose for reduced fertility was 15 mg/kg/day (approximately the MRHD based on body surface area).

Use in pregnancy

Australian Pregnancy Categorisation: B1.

There are no adequate and well-controlled studies in pregnant women. Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during treatment with ARDIX LURASIDONE. ARDIX LURASIDONE should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

Human Data

Neonates exposed to antipsychotic medicines during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been 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 intensive care unit support and prolonged hospitalization.

Animal Data

No teratogenic or other adverse effects on fetuses were observed in studies in which lurasidone was administered during the period of organogenesis to rats and rabbits at respective oral doses up to 25 and 50 mg/kg/day, corresponding to 1.5 and 5 times, respectively, the MRHD based on body surface area. No effects on delivery or pup development were observed in rats given lurasidone from early gestation to weaning at oral doses up to 10 mg/kg/day (about half the MRHD based on body surface area).

Use in lactation

Lurasidone and/or other metabolites were excreted in milk of rats during lactation and the same would be expected for human milk. Women receiving ARDIX LURASIDONE should not breastfeed.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

ARDIX LURASIDONE, like other antipsychotics, has the potential to impair judgment, thinking or motor skills. Patients should not operate hazardous machinery, including motor vehicles, until they are reasonably certain that therapy with ARDIX LURASIDONE does not affect them adversely.

ADVERSE EFFECTS (UNDESIRABLE 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.

The following findings are derived from a clinical study database for ARDIX LURASIDONE consisting of 2,905 patients with schizophrenia exposed to one or more doses with a total experience of 985.3 patient-years. Of these patients, 1,508 participated in short-term, placebo-controlled schizophrenia studies with doses of 20 mg, 40 mg, 80 mg, 120 mg or 160 mg once daily. A total of 769 ARDIX LURASIDONE-treated patients had at least 24 weeks and 371 ARDIX LURASIDONE-treated patients had at least 52 weeks of exposure.

The most common adverse events (incidence ≥ 5 % and at least twice the rate of placebo) in patients treated with ARDIX LURASIDONE were somnolence, akathisia, nausea and parkinsonism.

Adverse events reported with the use of ARDIX LURASIDONE (incidence of 2 % or greater, rounded to the nearest percent and ARDIX LURASIDONE incidence greater than placebo) that occurred during acute therapy (up to 6-weeks in patients with schizophrenia) are shown in Table 6.

Table 6: Adverse Events in 2 % or More of ARDIX LURASIDONE-Treated Adult Patients and That Occurred at Greater Incidence than in the Placebo-Treated Adult Patients in Short-term Schizophrenia Studies

	Percentages of Patients Reporting Event						
		ARDIX LURASIDONE					
Body System or Organ Class	**Placebo (N=708) (%)**	**20 mg/day (N=71) (%)**	**40 mg/day (N=487) (%)**	**80 mg/day (N=538) (%)**	**120 mg/day (N=291) (%)**	**160 mg/day (N=121) (%)**	**All (N=1,508) (%)**
Gastrointestinal Disorders							
Nausea	5	11	10	9	13	7	10
Vomiting	6	7	6	9	9	7	8
Dyspepsia	5	11	6	5	8	6	6
Salivary hypersecretion	<1	1	1	2	4	2	2
Musculoskeletal and Connective Tissue Disorders							
Back Pain	2	0	4	3	4	0	3
Nervous System Disorders							
Akathisia	3	6	11	12	22	7	13

	Percentages of Patients Reporting Event						
		ARDIX LURASIDONE					
Body System or Organ Class	**Placebo (N=708) (%)**	**20 mg/day (N=71) (%)**	**40 mg/day (N=487) (%)**	**80 mg/day (N=538) (%)**	**120 mg/day (N=291) (%)**	**160 mg/day (N=121) (%)**	**All (N=1,508) (%)**
Gastrointestinal Disorders							
Nausea	5	11	10	9	13	7	10
Vomiting	6	7	6	9	9	7	8
Dyspepsia	5	11	6	5	8	6	6
Salivary hypersecretion	<1	1	1	2	4	2	2
Musculoskeletal and Connective Tissue Disorders							
Extrapyramidal disorder*	6	6	11	12	22	13	14
Dizziness	2	6	4	4	5	6	4
Somnolence**	7	15	16	15	26	8	17
Psychiatric Disorders							
Insomnia	8	8	10	11	9	7	10
Agitation	4	10	7	3	6	5	5
Anxiety	4	3	6	4	7	3	5
Restlessness	1	1	3	1	3	2	2

Note: Figures rounded to the nearest integer

* Extrapyramidal symptoms includes adverse event terms: bradykinesia, cogwheel rigidity, drooling, dystonia, extrapyramidal disorder, hypokinesia, muscle rigidity, oculogyric crisis, oromandibular dystonia, parkinsonism, psychomotor retardation, tongue spasm, torticollis, tremor, and trismus

** Somnolence includes adverse event terms: hypersomnia, hypersomnolence, sedation, and somnolence

Dose-Related Adverse Events

Akathisia and extrapyramidal symptoms were dose-related in adults with schizophrenia. The frequency of akathisia increased with dose up to 120 mg/day (5.6% for ARDIX LURASIDONE 20 mg, 10.7% for ARDIX LURASIDONE 40 mg, 12.3 % for ARDIX LURASIDONE 80 mg, and 22.0 % for ARDIX LURASIDONE 120 mg). Akathisia was reported by 7.4 % (9/121) of adult patients receiving 160 mg/day. Akathisia occurred in 3.0 % of adult subjects receiving placebo. The frequency of extrapyramidal symptoms increased with dose up to 120 mg/day (5.6 % for ARDIX LURASIDONE 20 mg, 11.5 % for ARDIX LURASIDONE 40 mg, 11.9 % for ARDIX LURASIDONE 80 mg, and 22.0 % for ARDIX LURASIDONE 120 mg).

Due to the observed dose-related adverse effects, the recommended starting dose of ARDIX LURASIDONE in adults (40 or 80 mg/day) should be utilized for initial treatment based on clinical evaluation. Dose increases should be based on physician judgment and observed clinical response.

Extrapyramidal Symptoms

In the short-term, placebo-controlled schizophrenia studies, for ARDIX LURASIDONE-treated adult patients, the incidence of reported events related to extrapyramidal symptoms (EPS), excluding akathisia and restlessness, was 13.5 % versus 5.8 % for placebo-treated patients. The incidence of akathisia for ARDIX LURASIDONE-treated adult patients was 12.9 % versus 3.0 % for placebo-treated adult patients. Incidence of EPS by dose is provided in Table 7.

Table 7: Incidence of EPS Compared to Placebo in Adult Schizophrenia Studies

Adverse Event Term	Placebo (N=708) (%)	ARDIX LURASIDONE				
		20 mg/day (N=71) (%)	40 mg/day (N=487) (%)	80 mg/day (N=538) (%)	120 mg/day (N=291) (%)	160 mg/day (N=121) (%)
All EPS events	**9**	**10**	**21**	**23**	**39**	**20**
All EPS events, excluding Akathisia/ Restlessness	**6**	**6**	**11**	**12**	**22**	**13**
Akathisia	3	6	11	12	22	7
Dystonia*	< 1	0	4	5	7	2
Parkinsonism**	5	6	9	8	17	11
Restlessness	1	1	3	1	3	2

Note: Figures rounded to the nearest integer

* Dystonia includes adverse event terms: dystonia, oculogyric crisis, oromandibular dystonia, tongue spasm, torticollis, and trismus

** Parkinsonism includes adverse event terms: bradykinesia, cogwheel rigidity, drooling, extrapyramidal disorder, hypokinesia, muscle rigidity, parkinsonism, psychomotor retardation, and tremor

Other Adverse Reactions Observed During the Premarketing Evaluation of ARDIX LURASIDONE

Following is a list of other adverse reactions and laboratory investigations reported by adult patients treated with ARDIX LURASIDONE at multiple doses of ≥ 20 mg once daily during any phase of a study within the database of 3,202 patients. The reactions listed are those that could be of clinical relevance, as well as reactions that are plausibly drug-related on pharmacologic or other grounds. Reactions listed in Table 6 or those that appear elsewhere in the ADVERSE EFFECTS section are not included. Although the reactions reported occurred during treatment with ARDIX LURASIDONE, they were not necessarily caused by it.

The following adverse reactions are classified by system organ class and are according to the following definitions: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100), rare (≥ 1/10,000 to < 1/1000), very rare (<1 /10,000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Blood and Lymphatic System Disorders:	***uncommon:*** anaemia; ***rare:*** leukopenia, neutropenia
Cardiac Disorders:	***common:*** tachycardia*;* ***uncommon:*** angina pectoris, bradycardia; ***rare:*** AV block 1st degree
Ear and Labyrinth Disorders:	***uncommon:*** vertigo
Eye Disorders:	***common:*** vision blurred
Gastrointestinal Disorders:	***common:*** abdominal pain, diarrhoea*;* ***uncommon:*** dysphagia, gastritis
General Disorders and Administrative Site Conditions:	***rare:*** sudden death
Investigations:	***common:*** creatinine phosphokinase increased
Metabolism and Nutritional System Disorders:	***common:*** decreased appetite; ***uncommon:*** hyponatremia
Musculoskeletal and Connective Tissue Disorders:	***rare:*** rhabdomyolysis
Nervous System Disorders:	***uncommon*****:** dysarthria*:*, cerebrovascular accident, syncope, tardive dyskinesia; ***rare:*** neuroleptic malignant syndrome, seizure
Psychiatric Disorders:	***uncommon*****:** abnormal dreams, panic attack, sleep disorder*;* ***rare:*** suicidal behaviour
Renal and Urinary Disorders:	***uncommon:*** dysuria; ***rare:*** renal failure
Reproductive System and Breast Disorders:	***uncommon:*** amenorrhea, dysmenorrhoea, erectile dysfunction ***rare:*** breast pain, galactorrhoea, breast enlargement
Skin and Subcutaneous Tissue Disorders:	***common:*** rash, pruritus; ***rare:*** angioedema
Vascular Disorders:	***common:*** hypertension; ***uncommon*****:** orthostatic hypotension

Paediatric population

The following findings are based on the short-term, placebo-controlled pre-marketing study for schizophrenia in which lurasidone was administered at daily doses ranging from 40 to 80 mg (n=326). The most common adverse events reported (incidence ≥ 5 % and at least twice the rate of placebo) in patients treated with lurasidone were somnolence, nausea, akathisia, and vomiting.

Adverse events reported with the use of lurasidone (incidence of 2 % or greater, rounded to the nearest percent and lurasidone incidence greater than placebo) that occurred during acute therapy (up to 6-weeks in adolescent patients with schizophrenia) are shown in Table 8.

Table 8: Adverse Events in 2% or More of Lurasidone-Treated Adolescent Patients That Occurred at Greater Incidence than in the Placebo-Treated Adolescent Patients in the Short-term Schizophrenia Study

Body System or Organ Class Dictionary-derived Term	Percentage of Patients Reporting Reaction			
	Placebo (N=112)	Lurasidone 40 mg (N=110)	Lurasidone 80 mg (N=104)	All Lurasidone (N=214)
Gastrointestinal Disorders				
Nausea	3	13	14	14
Vomiting	2	8	7	8
Diarrhoea	< 1	3	5	4
Dry mouth	0	2	3	2
Infections and Infestations				
Viral Infection	< 1	3	2	2
Nervous System Disorders				
Somnolence*	7	16	14	15
Akathisia	2	9	9	9
Dizziness	< 1	5	5	5

* Somnolence includes adverse event terms: hypersomnia, sedation, and somnolence

Note: Figures rounded to the nearest integer

Clinical Laboratory Changes

Serum Creatinine: In short-term, placebo-controlled trials in adults, the mean change from Baseline in serum creatinine was +0.05 mg/dL for ARDIX LURASIDONE-treated patients compared to +0.02 mg/dL for placebo-treated patients. A creatinine shift from normal to high occurred in 3.0 % (43/1,453) of ARDIX LURASIDONE-treated patients and 1.6 % (11/681) on placebo (Table 9). The threshold for high creatinine value varied from > 0.79 to > 1.3 mg/dL based on the centralized laboratory definition for each study.

Table 9: Adult Serum Creatinine Shifts from Normal at Baseline to High at Study End-Point

Laboratory Parameter	Placebo (N=708)	ARDIX LURASIDONE				
		20 mg/day (N=71)	40 mg/day (N=487)	80 mg/day (N=538)	120 mg/day (N=291)	160 mg/day (N=121)
Serum Creatinine Elevated	2 %	1 %	2 %	2 %	5 %	7 %

Table 10: Serum Creatinine Shifts from Normal at Baseline to High at Study End-Point in Adolescent Schizophrenia Study

Laboratory Parameter	Placebo (N=103)	ARDIX LURASIDONE 40 mg/day (N=97	ARDIX LURASIDONE 80 mg/day (N=97)
Serum Creatinine Elevated	3 %	7 %	7 %

Adverse reactions Observed Post-marketing

As these reactions are reported voluntarily from a population of uncertain size, the incidence rate of these adverse reactions cannot be estimated (frequency unknown).

The following adverse reactions, classified by system organ class and frequency, have been identified with ARDIX LURASIDONE in the post-marketing period:

Immune System Disorders:	***frequency unknown:*** hypersensitivity (hypersensitivity may include symptoms such as throat swelling, tongue swelling, urticaria, or symptoms of angioedema. Hypersensitivity may also include symptoms of severe cutaneous reactions such as dermatitis bullous, rash maculopapular, rash pustular, skin eruption and skin exfoliation).
Metabolism and Nutritional System Disorders	***frequency unknown:*** hyponatraemia

The following adverse reactions, classified by system organ class and frequency, have been identified with atypical antipsychotic medicines including ARDIX LURASIDONE in the post-marketing period:

Psychiatric Disorders	***frequency unknown:*** Somnambulism (sleepwalking) and related behaviours including sleep-related eating disorder

OVERDOSE

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

There is no specific antidote to lurasidone, therefore, appropriate supportive measures should be instituted and close medical supervision and monitoring should continue until the patient recovers.

Cardiovascular monitoring should commence immediately, including continuous electrocardiographic monitoring for possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide, and quinidine carry a theoretical hazard of additive QT-prolonging effects when administered in patients with an acute overdose of ARDIX LURASIDONE. Similarly the alpha-blocking properties of bretylium might be additive to those of ARDIX LURASIDONE, resulting in problematic hypotension.

Hypotension and circulatory collapse should be treated with appropriate measures. Adrenaline and dopamine should not be used or other sympathomimetics with beta agonist activity, since beta stimulation may worsen hypotension in the setting of ARDIX LURASIDONE-induced alpha blockade. In case of severe extrapyramidal symptoms, anticholinergic medication should be administered.

Administration of activated charcoal together with a laxative should be considered.

The possibility of obtundation, seizures, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis.

PHARMACOLOGICAL PROPERTIES

PHARMACODYNAMIC PROPERTIES

Mechanism of action

The mechanism of action of lurasidone, as with other medicines having efficacy in schizophrenia, is not fully understood. However, based on its receptor pharmacology, it is believed that the efficacy of ARDIX LURASIDONE is mediated mainly through antagonist activity at dopamine D_2 and 5-hydroxytryptamine (5-HT, serotonin) 5-HT_{2A} receptors.

In vitro receptor binding studies revealed that ARDIX LURASIDONE binds with high affinity at human D_2 receptors (Ki=0.994 nM) and 5-HT_{2A} (Ki=0.47 nM) and 5-HT_7 (Ki=0.495 nM) receptors, with moderate affinity at human $\alpha 2_C$ adrenergic receptors (Ki=10.8 nM), D_3 receptors (Ki=15.7 nM) and 5-HT_{1A} (Ki=6.38 nM) receptors, and with weak affinity at human $D_{4.4}$ (Ki=29.7 nM) and α_{2A} (Ki = 40.7 nM) and α_{1A} (Ki = 35.7 nM) adrenergic receptors. ARDIX LURASIDONE exhibits little or no affinity for human histamine H_1 and muscarinic M_1 receptors (IC_{50} >1,000 nM). ARDIX LURASIDONE is a partial agonist at 5-HT_{1A} receptors but is believed to act as an antagonist at all the other receptors.

ARDIX LURASIDONE doses ranging from 10 to 80 mg administered to healthy subjects produced a dose-dependent reduction in the binding of 11C-raclopride, a D_2/D_3 receptor ligand, in the caudate, putamen and ventral striatum detected by positron emission tomography.

After single administration at doses of 20 and 40 mg in a quantitative electroencephalographic evaluation, ARDIX LURASIDONE decreased the threshold of flicker discrimination in the flicker test without affecting GFP value in any frequency band in electroencephalography.

Clinical trials

The efficacy of ARDIX LURASIDONE in the treatment of adults with schizophrenia was established in five short-term (6-week), placebo-controlled, studies in adult patients (mean age of 38.4 years, range 18-72) who met DSM-IV criteria for schizophrenia. An active control arm (olanzapine or quetiapine XR) was included in two studies to assess assay sensitivity.

Several instruments were used for assessing psychiatric signs and symptoms in these studies:

1. Positive and Negative Syndrome Scale (PANSS), is a multi-item inventory of general psychopathology used to evaluate the effects of drug treatment in schizophrenia. PANSS total scores may range from 30 to 210.
2. Brief Psychiatric Rating Scale derived (BPRSd), derived from the PANSS, is a multi-item inventory primarily focusing on positive symptoms of schizophrenia, whereas the PANSS includes a wider range of positive, negative and other symptoms of schizophrenia. BPRSd scores may range from 18 to 126.
3. The Clinical Global Impression severity scale (CGI-S) is a validated clinician-rated scale that measures the subject's current illness state on a 1 to 7-point scale.

The endpoint associated with each instrument is change from baseline in the total score to the end of Week 6. These changes are then compared to placebo changes for the ARDIX LURASIDONE and control groups.

The results of the studies follow (Table 11):

1. In a 6-week, placebo-controlled trial (N=145) involving two fixed doses of ARDIX LURASIDONE (40 or 120 mg/day), both doses of ARDIX LURASIDONE at Endpoint were superior to placebo on the BPRSd total score, and the CGI-S.
2. In a 6-week, placebo-controlled trial (N=180) involving a fixed dose of ARDIX LURASIDONE (80 mg/day), ARDIX LURASIDONE at Endpoint was superior to placebo on the BPRSd total score, and the CGI-S.
3. In a 6-week, placebo and active-controlled trial (N=473) involving two fixed doses of ARDIX LURASIDONE (40 or 120 mg/day) and an active control (olanzapine), both ARDIX LURASIDONE doses and the active control at Endpoint were superior to placebo on the PANSS total score, and the CGI-S.
4. In a 6-week, placebo-controlled trial (N=489) involving three fixed doses of ARDIX LURASIDONE (40, 80 or 120 mg/day), only the 80 mg/day dose of ARDIX LURASIDONE at Endpoint was superior to placebo on the PANSS total score, and the CGI-S.
5. In a 6-week, placebo and active-controlled trial (N=482) involving two fixed doses of ARDIX LURASIDONE (80 or 160 mg/day) and an active control (quetiapine XR), both ARDIX LURASIDONE doses and the active control at Endpoint were superior to placebo on the PANSS total score, and the CGI-S.

Table 11: Summary of Results for Primary Efficacy Endpoints

Study Number	Primary Endpoint	LS Mean (SE)[a] Difference from Placebo in Change from Baseline					
		ARDIX LURASIDONE				Olanzapine	Quetiapine XR
		40 mg/day	80 mg/day	120 mg/day	160 mg/day	15 mg/day	600 mg/day
1	BPRSd	-5.6* (2.1)	-	-6.7* (2.2)	-	-	-
2	BPRSd	-	-4.7* (1.8)	-	-	-	-
3	PANSS	-9.7* (2.9)	-	-7.5* (3.0)	-	-12.6# (2.8)	-
4	PANSS	-2.1 (2.5)	-6.4* (2.5)	-3.5 (2.5)	-	-	-
5	PANSS	-	-11.9* (2.6)	-	-16.2* (2.5)	-	-17.5# (2.6)

BPRSd: Brief Psychiatric Rating Scale derived; PANSS: Positive and Negative Syndrome Scale

*adjusted p-value ≤0.05

non-adjusted p-value ≤0.05

[a] Least Squares Mean (Standard Error)

Examination of population subgroups based on age (there were few patients over 65), gender and race did not reveal any clear evidence of differential responsiveness.

An analysis of adult patients with a ≥ 30 % reduction from baseline PANSS score (clinical response analysis) was performed in three of these studies. The placebo response rate was around 35 % across the studies and the response rates for ARDIX LURASIDONE 40 mg, 80 mg and 120 mg were all

around
50 %, giving a 15 % difference in response rates from placebo and a NNT of 6.7 for one patient to achieve a clinically significant improvement. One study assessed efficacy of the 160 mg dose and 120 patients were given this dose. The response rate for 160 mg ARDIX LURASIDONE was 63 %, a NNT of approximately 3.6. There was limited evidence of dose response for doses between 40 mg and 80 mg.

Adolescents

The efficacy of lurasidone in the treatment of schizophrenia in adolescent patients (13 to 17 years of age) was evaluated in one 6-week, placebo-controlled study of patients (N=327) who met DSM-IV criteria for schizophrenia [D1050301]. Both the 80 mg and 40 mg doses of lurasidone demonstrated superiority over placebo on the PANSS total score after 6 weeks of double-blind treatment (Table 12).

Table 12: Summary of Results for Primary Efficacy Endpoints

Primary Endpoint	LS Mean (SE)[a] Difference from Placebo in Change from Baseline	
	Lurasidone 40 mg/day	Lurasidone 80 mg/day
PANSS	-8.0 (2.21)*	-7.7 (2.22)*

PANSS: Positive and Negative Syndrome Scale
* adjusted p-value ≤0.001
# non-adjusted p-value ≤0.05
a Least Squares Mean (Standard Error)

Maintenance of Effect

A double-blind study compared flexibly dosed ARDIX LURASIDONE (40 to 160 mg daily) with flexibly dosed quetiapine XR (200 to 600 mg daily) for up to 12 months in adult patients with schizophrenia who had shown a clinical response to ARDIX LURASIDONE in a short-term study. The mean daily dose of ARDIX LURASIDONE was 125.5 mg and of quetiapine XR was 629.6 mg. Relapses were reported in 21 % of subjects given ARDIX LURASIDONE and in 27 % given quetiapine XR. The probability of relapse by month 12 was 23.7 % and 33.6 % for ARDIX LURASIDONE and quetiapine, respectively. The relapse hazard ratio of ARDIX LURASIDONE versus quetiapine XR was 0.728 (95 % CI: 0.41, 1.29).

PHARMACOKINETIC PROPERTIES

The activity of ARDIX LURASIDONE is primarily due to the parent drug. The pharmacokinetics of ARDIX LURASIDONE is dose-proportional within a total daily dose range of 20 mg to 160 mg. Steady-state concentrations of lurasidone are reached within 7 days of starting lurasidone. Following administration of 40 mg the mean (%CV) elimination half-life was 18 (7) hours.

Absorption

ARDIX LURASIDONE is absorbed and reaches peak serum concentrations in approximately 1-3 hours. It is estimated that 9-19 % of an administered dose is absorbed. In a food effect study, ARDIX LURASIDONE mean Cmax and AUC were about 3-times and 2-times, respectively, when administered with food compared to the levels observed under fasting conditions. ARDIX LURASIDONE exposure was not affected as meal size was increased from 350 to 1000 calories and was independent of meal fat content (see section 4.2).

Distribution

Following administration of 40 mg of ARDIX LURASIDONE, the mean (%CV) apparent volume of distribution was 6173 (17.2) L. Lurasidone is highly bound (~99 %) to serum proteins.

Metabolism

ARDIX LURASIDONE is metabolised mainly via CYP3A4. The major biotransformation pathways are oxidative N-dealkylation, hydroxylation of norbornane ring, and S-oxidation. ARDIX LURASIDONE is metabolised into two non-major active metabolites (ID-14283 and ID-14326) and two major non-active metabolites (ID-20219 and ID-20220). ARDIX LURASIDONE and its metabolites ID-14283, ID-14326, ID-20219 and ID-20220 correspond to approximately 11.4, 4.1, 0.4, 24 and 11 % respectively, of serum radioactivity respectively. ARDIX LURASIDONE is a single isomer form, which does not appear to undergo conversion to other enantiomers on metabolism.

Excretion

Total excretion of radioactivity in urine and faeces combined was approximately 89 %, with about 80 % recovered in faeces and 9 % recovered in urine, after a single dose of [^{14}C]-labeled ARDIX LURASIDONE. Following administration of 40 mg the mean (%CV) apparent clearance was 3,902 (18.0) mL/min.

Special Populations

Renal Impairment

After administration of a single dose of 40 mg ARDIX LURASIDONE to 27 patients with mild (n=9; CrCL: 50 to 80 mL/min), moderate (n=9; CrCL: 30 to < 50 mL/min) and severe (n=9; CrCL: < 30 mL/min) renal impairment, mean Cmax increased by 1.4-, 1.9- and 1.5-fold, respectively, and mean AUC(0-∞) increased by 1.5-, 1.9- and 2.0-fold, respectively, compared to healthy matched subjects (n=9).

Hepatic Impairment

The exposure to lurasidone is increased in patients with Child-Pugh Class A and B hepatic impairment with mean Cmax increased by 1.3- and 1.2-fold, respectively and mean AUC(0-∞) increased by 1.5- and 1.7-fold, respectively compared to healthy matched subjects. The pharmacokinetics of ARDIX LURASIDONE has not been adequately established in patients with severe hepatic impairment and ARDIX LURASIDONE is not recommended in these patients.

Elderly

Limited data have been collected in patients ≥ 65 years. Of the data collected, similar exposure was obtained compared with subjects < 65 years.

Paediatrics

The pharmacokinetics of lurasidone, in paediatric patients 6-17 years of age was similar to those in adults. There were no clinically relevant differences between genders in the pharmacokinetics of lurasidone in patients with schizophrenia.

PRECLINICAL SAFETY DATA

Genotoxicity

Lurasidone was not genotoxic in the bacterial reverse mutation (Ames) test, the in vitro chromosomal aberration test in Chinese hamster lung cells, or the in vivo mouse bone marrow micronucleus test.

Carcinogenicity

Lurasidone was administered orally for 24 months at doses of 30, 100, 300, or 650 (the high dose was reduced from 1,200 in males) mg/kg/day to ICR mice and 3, 12, or 36 (high dose reduced from 50) mg/kg/day to Sprague-Dawley rats.

In the mouse study, there were increased incidences of malignant mammary gland tumours and pituitary gland adenomas in females at all doses; the lowest dose tested produced plasma levels (AUC in females) approximately equal to those in humans receiving the maximum recommended human dose (MRHD) of 160 mg/day. No increases in tumours were seen in male mice up to the highest dose tested, which produced plasma levels (AUC) 14 times those in humans receiving the MRHD.

In rats, an increased incidence of mammary gland carcinomas was seen in females at the two higher doses; the no-effect dose of 3 mg/kg produced plasma levels (AUC) 0.4 times those in humans receiving the MRHD. No increases in tumours were seen in male rats up to the highest dose tested, which produced plasma levels (AUC) 6 times those in human receiving the MRHD.

Proliferative and/or neoplastic changes in the mammary and pituitary glands of rodents have been observed following chronic administration of antipsychotic medicines and are considered to be prolactin mediated. The relevance of this increased incidence of prolactin-mediated pituitary or mammary gland tumours in rodents in terms of human risk is unknown.

To date, neither clinical studies nor epidemiological studies have shown an association between chronic administration of these medicines and mammary tumorigenesis. However, since tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent *in vitro*, ARDIX LURASIDONE should be used cautiously in patients with previously detected breast cancer or in patients with pituitary tumours.

PHARMACEUTICAL PARTICULARS

LIST OF EXCIPIENTS

Tablet core:
- Croscarmellose sodium
- Hypromellose
- Magnesium stearate
- Mannitol
- Pregelatinised maize starch

Film-coating (40 mg tablets):
- Carnauba wax

- Opadry complete film coating system 03F48969 white

Film-coating (80 mg tablets):
- Carnauba wax
- Opadry complete film coating system 03F48969 white
- Indigo carmine
- Iron oxide yellow

INCOMPATIBILITIES

See section 4.5 - *Interactions with other medicines and other forms of interactions*.

SHELF LIFE

4 years

SPECIAL PRECAUTIONS FOR STORAGE

Store below 30 °C

NATURE AND CONTENTS OF CONTAINER

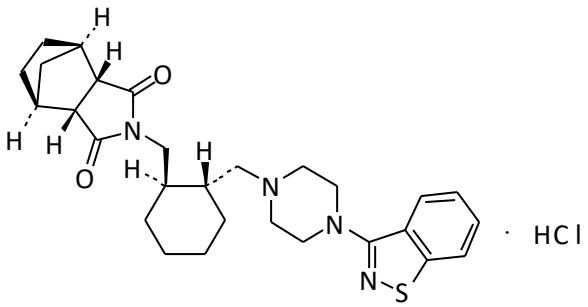
ARDIX LURASIDONE tablets are supplied in Aluminium/Aluminium blisters in cartons of 30 tablets.

SPECIAL PRECAUTIONS FOR DISPOSAL

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

PHYSICOCHEMICAL PROPERTIES

Chemical structure



CAS number

367514-88-3

MEDICINE SCHEDULE (POISONS STANDARD)

S4 - Prescription only medicine

SPONSOR

Servier Laboratories (Aust.) Pty. Ltd.
Level 4, Building 9
588A Swan Street
Burnley, 3121, Victoria

DATE OF FIRST APPROVAL

19 December 2019

DATE OF REVISION

03 August 2023

Summary table of changes

Section Changed	Summary of new information
n/a	Deletion of black triangle text and symbol