

# New drugs

## Lurasidone

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### Approved indication: schizophrenia

**Latuda (Dainippon Sumitomo Pharma)**

**20 mg, 40 mg and 80 mg tablets**

**Australian Medicines Handbook section 18.2**

There are over 15 antipsychotics approved for schizophrenia in Australia. Lurasidone is the most recent addition to this drug class. As with other antipsychotics, lurasidone blocks dopaminergic transmission in the brain via the dopamine D<sub>2</sub> receptor. It also antagonises serotonin 5HT<sub>7</sub> and 5HT<sub>2A</sub> receptors and is a partial agonist of 5HT<sub>1A</sub>. Lurasidone does not appear to affect muscarinic and histamine receptors.

The efficacy of lurasidone for acute schizophrenia has been assessed in several short-term, placebo-controlled trials.<sup>1-5</sup> After six weeks of treatment, once-daily doses of 40 mg, 80 mg, 120 mg and 160 mg significantly lowered signs and symptoms of

schizophrenia, measured on psychiatric rating scales (see Table).<sup>1-5</sup> However, efficacy was not consistently shown for each dose and a dose-response relationship was not evident in the trials. For example, in a study of lurasidone 40 mg, 80 mg and 120 mg, only the 80 mg dose had a statistically significant effect over placebo.<sup>4</sup> Discontinuation rates were very high in some of the trials (28-65%).<sup>1-5</sup> Lack of efficacy and withdrawal of consent were the most common reasons for stopping treatment.

One of the placebo-controlled trials<sup>1</sup> was extended to assess the long-term efficacy of lurasidone (40-160 mg/day) compared to quetiapine (200-800 mg/day) in 292 people.<sup>6</sup> Flexible dosing was allowed. At 12 months, the estimated probability of relapse was 23.7% in people receiving lurasidone compared with 33.6% in those receiving quetiapine. Discontinuation rates were high (48% for lurasidone, 61% for quetiapine).<sup>6</sup>

Another longer term comparative study enrolled patients with stable schizophrenia. After 12 months, 20% of people (82/410) receiving lurasidone had relapsed compared with 16% (32/198) receiving risperidone.<sup>7</sup>

**Table Efficacy of lurasidone in acute schizophrenia in short-term, placebo-controlled trials**

Trial	Number of patients	Daily treatments	Outcome <sup>‡</sup> after 6 weeks of treatment
Loebel <sup>1</sup>	488	lurasidone 80, 160 mg placebo (quetiapine 600 mg) <sup>§</sup>	lurasidone 80 mg and 160 mg (p<0.001) and quetiapine (p<0.001) significantly better than placebo on PANSS
Meltzer <sup>2</sup>	478	lurasidone 40, 120 mg placebo (olanzapine 15 mg) <sup>§</sup>	lurasidone 40 mg (p<0.001) and 120 mg (p=0.011) and olanzapine (p<0.001) significantly better than placebo on PANSS
Nakamura <sup>3</sup>	180	lurasidone 80 mg placebo	lurasidone 80 mg significantly better than placebo on BPRSd (p=0.012)
Nasrallah <sup>4</sup>	500	lurasidone 40, 80, 120 mg placebo	only lurasidone 80 mg significantly better than placebo on PANSS (p<0.05)
Ogasa <sup>5</sup>	149	lurasidone 40, 120 mg placebo	lurasidone 40 mg (p=0.018) and 120 mg (p=0.004) significantly better than placebo on BPRSd

PANSS Positive and Negative Syndrome Scale

BPRSd Brief Psychiatric Rating Scale derived from PANSS scale

<sup>‡</sup> Mean change from baseline score on schizophrenia rating scale

<sup>§</sup> Olanzapine and quetiapine were included as active reference treatments which were compared to placebo but not to lurasidone.



Some of the views expressed in the following notes on newly approved products should be regarded as preliminary, as there may be limited published data at the time of publication, and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. Before new drugs are prescribed, the Committee believes it is important that more detailed information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

## NEW DRUGS

The most common adverse events in the short-term trials were somnolence (17% of patients), extrapyramidal symptoms (14%), akathisia (13%), insomnia (10%) and nausea (10%). Tachycardia, blurred vision, abdominal pain, diarrhoea, decreased appetite, rash, pruritus, hypertension and elevated creatine kinase also occurred in 1–10% of people. Prolactin elevations were more frequent with lurasidone than with placebo (2.8% vs 1%). QT prolongation did not seem to be a problem in the trials.

In the six-week trials, weight gain was modest with lurasidone compared with placebo (mean change of 0.43 kg vs -0.02 kg). In the longer term comparative studies, people taking lurasidone were less likely to have gained weight than those taking quetiapine<sup>6</sup> and risperidone.<sup>7</sup>

As with other antipsychotics, lurasidone can cause neuroleptic malignant syndrome, tardive dyskinesia and orthostatic hypotension. It should be used with care in patients at risk of hypotension or seizures. Lurasidone should not be used in elderly patients with dementia-related psychosis because of an increased risk of death with antipsychotics.

Lurasidone should be started at 40 mg once daily, taken with food. In the trials no additional benefit was seen with the 120 mg dose. The recommended starting dose in moderate to severe renal impairment is 20 mg. Lurasidone should not be used in people with severe hepatic impairment and the recommended starting dose is 20 mg in those with moderate impairment.

Peak concentrations are reached 1–3 hours after taking an oral dose and steady-state concentrations are reached within seven days. The drug's elimination half-life is 18 hours and most of the dose is excreted in the faeces.

Concomitant use of strong cytochrome P450 (CYP) 3A4 inhibitors (ketoconazole, clarithromycin, ritonavir) and inducers (rifampicin, St John's wort, phenytoin) is contraindicated as lurasidone is metabolised by CYP3A4. The lurasidone dose should be halved in people taking moderate inhibitors (diltiazem). Patients should avoid grapefruit juice as it may increase lurasidone exposure.

Lurasidone is a category B1 drug in pregnancy. In animal studies, no fetal toxicities were observed. However, exposure during the third trimester in pregnant women increased the risk of extrapyramidal and withdrawal symptoms in newborns. Some babies had to be managed in the intensive care unit.

Breastfeeding is not recommended with lurasidone as it has been found to be excreted in the milk of lactating rats.

In general, lurasidone was better than placebo in patients with acute schizophrenia. However, efficacy was not consistent at all doses and a dose–response relationship could not be shown. It is unclear how lurasidone will compare to other drugs in the class.

Transparency score not allocated

## REFERENCES \*†

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The Transparency score (T) is explained in 'New drugs: transparency', *Aust Prescr* 2014;37:27.

\* At the time the comment was prepared, information about this drug was available on the website of the Food and Drug Administration in the USA ([www.fda.gov](http://www.fda.gov)).

† At the time the comment was prepared, a scientific discussion about this drug was available on the website of the European Medicines Agency ([www.ema.europa.eu](http://www.ema.europa.eu)).