

Lurasidone (Latuda[®]) information sheet for GPs on its use in bipolar depression

Indication

Lurasidone is a lesser used antipsychotic, currently only licensed for the treatment of schizophrenia in adults. The CCG has approved its use for patients with schizophrenia, but not for its unlicensed use for bipolar depression, though there is good evidence to support its use and it has a different side-effect profile to other effective treatments. Only initiated by a consultant with approval of their clinical director, it will normally only be prescribed third or fourth-line, especially if the patient has an identified metabolic risk, e.g. diabetes. *Unlike its use in schizophrenia, when aripiprazole should have been tried first, aripiprazole is not effective in bipolar depression, so will not have been tried.*

Dosing and administration

Lurasidone is taken orally as a tablet after a meal or snack that contains a minimum of 350 calories. Studies have shown that if taken on an empty stomach, the amount of drug absorbed is reduced by around 50%. Lurasidone tablets are film-coated and should be swallowed whole in order to mask the bitter taste.

The dose range is 37mg to 148mg daily. 18.5mg, 37mg and 74mg tablets are available.

Missed doses: Patients on doses higher than 111mg daily that discontinue their treatment or miss doses for more than 3 days should be restarted at 111mg once daily and up-titrated to their optimal dose over a period based on tolerability and observed clinical response. For doses of 111mg daily or lower, patients can be restarted on their previous dose without the need for any titration.

The elderly: Dose recommendations for elderly patients with normal renal function are the same as for younger adults. There are limited data available to support the use of higher doses of lurasidone in the elderly and no data for the 148mg dose. Caution is required if treating elderly patients with higher doses. Lurasidone has not been studied in elderly patients with dementia and therefore should not be used.

Children & Adolescents: The product is not licensed for use in patients less than 18 years of age as efficacy and safety has not been established.

Renal impairment: No dosage adjustment is needed in patients with mild renal impairment. In moderate and severe renal impairment, the recommended starting dose is 18.5mg and the maximum dose should not exceed 74mg once daily.

Hepatic impairment: No dosage adjustment is needed patients with mild hepatic impairment. In moderate and severe hepatic impairment, the recommended starting dose is 18.5mg. In moderate impairment the maximum dose should not exceed 74mg once daily and in severe impairment should not exceed 37mg once daily.

Concomitant treatment with a potent CYP3A4 inducer or inhibitor: i.e. carbamazepine, phenytoin, rifampicin, St John's Wort, clarithromycin, telithromycin, ketoconazole, itraconazole, posaconazole, protease-inhibitors. Lurasidone is contraindicated.

Concomitant treatment with a moderate CYP3A4 inhibitor: eg. amiodarone, diltiazem, erythromycin, fluconazole, verapamil. Starting dose should be reduced to 18.5mg and the maximum dose should not exceed 74mg once daily. (List of drugs is not exhaustive).

Pregnancy and breast-feeding: There are limited data regarding the use of lurasidone during pregnancy. Therefore it should not be used unless the potential benefits are assessed as clearly outweighing the risks. It is not known whether lurasidone is excreted in human milk. Therefore it should not be used unless the potential benefits are assessed as clearly outweighing the risks.

Evidence summary

It has been demonstrated to show efficacy in two short-term and studies in bipolar depression one as monotherapy and the other as add on to lithium or valproate (Loebel et al., 2014a, 2014b) and one longer term study (Calabrese 2015) .

The first study (Loebel et al 2014a) patients (N= 168) were randomly assigned to receive double-blind treatment with lurasidone (20-60 mg/day [N=166] or 80-120 mg/day [N=169]) or placebo (N=170) for 6 weeks. Lurasidone treatment significantly reduced mean MADRS total scores at week 6 for both the 20-60 mg/day group (-15.4; effect size=0.51) and the 80-120 mg/day group (-15.4; effect size=0.51) compared with placebo (-10.7). Similarly, lurasidone treatment resulted in significantly greater endpoint reduction in CGI-BP depression severity scores for both the 20-60 mg/day group (-1.8; effect size=0.61) and the 80-120 mg/day group (-1.7; effect size=0.50) compared with placebo (-1.1). Both lurasidone groups also experienced significant improvements compared with placebo in anxiety symptoms and in patient-reported measures of quality of life and functional impairment. Monotherapy with lurasidone in the dosage range of 20-120 mg/day significantly reduced depressive symptoms in patients with bipolar I depression. Lurasidone was well tolerated, with few changes in weight or metabolic parameters.

The second study (Loebel et al 2014b) randomly assigned patients to receive 6 weeks of double-blind adjunctive treatment with lurasidone (N=183) or placebo (N=165), added to therapeutic levels of either lithium or valproate. Lurasidone treatment significantly reduced mean MADRS total score at week 6 compared with the placebo group (-17.1 versus -13.5; effect size=0.34). Similarly, lurasidone treatment resulted in significantly greater endpoint reduction in CGI-BP depression severity scores compared with placebo (-1.96 versus -1.51; effect size=0.36) as well as significantly greater improvement in anxiety symptoms and in patient-reported measures of quality of life and functional impairment. In patients with bipolar I depression, treatment with lurasidone adjunctive to lithium or valproate significantly improved depressive symptoms and was generally well tolerated

The third study evaluated the recurrence prevention efficacy of lurasidone for the maintenance treatment of bipolar I disorder, patients received up to 20 weeks of open-label lurasidone (20–80 mg/d) combined with lithium or valproate during an initial stabilization phase. A total of 496 patients met stabilization criteria and were randomized to 28 weeks of double-blind treatment with lurasidone (20–80 mg/d) or placebo, in combination with lithium or valproate. Treatment with lurasidone reduced the probability of recurrence of any mood episode by 29% (primary endpoint), however, the reduction did not achieve statistical significance. Probability of recurrence on lurasidone was significantly lower in patients with an index episode of depression (HR, 0.57; $P=0.039$), in patients with any index episode who were not rapid-cycling (HR, 0.69; $P=0.046$), and when recurrence was based on MADRS, YMRS, or CGI-BP-S severity criteria (HR, 0.53; $P=0.025$; sensitivity analysis). Long-term treatment with lurasidone combined with lithium or valproate was found to be safe and well-tolerated, with minimal effects on weight or metabolic parameters

Adverse effects

Discontinuation rates due to adverse events were similar in the 20-60 mg/day (6.6%), 80-120 mg/day (5.9%), and placebo (6.5%) groups. The most frequent adverse events associated with lurasidone were nausea, headache, akathisia, and somnolence. Minimal changes in weight, lipids, and measures of glycemic control were observed with lurasidone (Loebel et al 2014a).

Discontinuation rates due to adverse events were 6.0% and 7.9% in the lurasidone and placebo groups, respectively. Adverse events most frequently reported for lurasidone were nausea, somnolence, tremor, akathisia, and insomnia. Minimal changes in weight, lipids, and measures of glycemic control were observed during treatment with lurasidone. (Loebel et al 2014b)
Two adverse events occurred in the pre-randomization phase (Calabrese 2015) with a frequency $\geq 10\%$ (nausea and somnolence). In a comparison of the lurasidone and placebo groups, NNH values for all adverse events occurring in the double-blind phase were >20 , suggesting that lurasidone was well-tolerated during maintenance therapy. Over the open-label phase (up to 24 weeks), modest increases

were observed in body weight (mean, <1 kg). There was no difference between lurasidone and placebo at endpoint in body weight or BMI during the double-blind phase of treatment. Additionally, a similar proportion of patients in the lurasidone and placebo groups had a clinically significant ($\geq 7\%$) endpoint increase in weight (6.6% and 4.8%, respectively). Consistent with results from previous long-term studies in both schizophrenia and bipolar disorder there were no clinically meaningful, treatment-emergent differences between lurasidone and placebo in total cholesterol, HDL, LDL, triglycerides, glucose, or HbA1c. Consistent with the results of a comprehensive review of prolactin effects among pharmacologic treatments of bipolar disorder minimal changes in prolactin levels were observed during combined therapy with lurasidone and lithium or valproate.

References

1. Loebel A, Cucchiaro J, Silva R, et al. (2014a) Lurasidone monotherapy in the treatment of bipolar I depression: A randomized, double-blind, placebo-controlled study. *Am J Psychiatry* 171: 160–168.
2. Loebel A, Cucchiaro J, Silva R, et al. (2014b) Lurasidone as adjunctive therapy with lithium or valproate for the treatment of bipolar I depression: A randomized, double-blind, placebo-controlled study. *Am J Psychiatry* 171: 169–177.
3. Calabrese J, Pikelov A, Cucchiaro J, et al. (2015) Lurasidone adjunctive to lithium or divalproex for prevention of recurrence in patients with bipolar I disorder: Results of a 28-week, randomized, double-blind, placebo-controlled study. *Neuropsychopharmacology* 40: S479–480

Produced: January 2019

Next review due: January 2021