**Lurasidone (Latuda) for schizophrenia**

**September 2014**

**DTG decision: Formulary Restricted**

The Drugs and Therapeutics Group has included lurasidone on the formulary as a restricted medicine. The decision was based on the limited efficacy and safety data, particularly in the longer term, limited comparative data, and cost. Its use is restricted to those patients who have experienced adverse metabolic side effects and where aripiprazole is not a suitable alternative treatment option.

Lurasidone appears to have a low propensity for metabolic adverse effects and weight gain (≥7%) and may offer advantage over other antipsychotics where this has caused a problem.

It is expensive in comparison with other generically available antipsychotics (and soon to be available generic aripiprazole). Primary care has traffic lighted lurasidone red, so any prescribing will remain in secondary care.

Clinicians wishing to prescribe lurasidone must make an entry in the patient’s notes which explains how the decision to use a restricted medicine meets the Trust’s restriction criteria.

For further information please see below.

What is it?

Lurasidone is a ‘second generation’ antipsychotic which is a full antagonist at dopamine D₂ and serotonin 5HT₂A receptors. It is licensed for the treatment of schizophrenia in adults aged 18 years or older.

How much does it cost?

Lurasidone has a flat based pricing structure – all strengths are £90.72 for a 28 day supply. This is comparable to the cost of 5mg, 10mg, and 15mg aripiprazole (£96.04 for 28 days). Aripiprazole 30mg is significantly more expensive (£192.08 for 28 days), however aripiprazole will soon lose its patent and cheaper generics will become available.

What is the dose?

The recommended starting dose of lurasidone (Latuda) in adults is 37mg once daily *with a meal*, swallowed whole to avoid the bitter taste. No initial dose titration is required. It is effective in a dose range of 37mg to 148mg (max daily dose) once daily. Dose increases should be based on physician judgment and observed clinical response.

*Special patient populations* (eg renally or hepatically impaired) – refer to SPC on eMC ([www.medicines.org.uk/emc](http://www.medicines.org.uk/emc)).

What size tablets are available?

Film coated tablets are available in three strengths: 18.5mg, 37mg, and 74mg.

What adverse effects does it cause?

As with all new drugs, lurasidone is a black triangle drug and all suspected adverse reactions should be reported to the MHRA via the [yellow card scheme](http://www.mhra.gov.uk/yellowcard).

<table>
<thead>
<tr>
<th>Very common (≥/10%)</th>
<th>Somnolence; akathisia (both dose-related)</th>
</tr>
</thead>
<tbody>
<tr>
<td>common (≥/1/100 to &lt;1/10)</td>
<td>weight gain**, insomnia, agitation, anxiety, dizziness, restlessness, Parkinsonism, dystonia, dyskinesia, nausea, vomiting, dyspepsia, hypersalivation, dry mouth, abdominal pain, musculoskeletal stiffness, raised creatine phosphokinase, raised creatinine, and fatigue</td>
</tr>
<tr>
<td>less common side effects (≥/1/1000 to &lt;1/100)</td>
<td>blurred vision, tachycardia, hyper- and hypo-tension, orthostatic hypotension, sweating, and hyperprolactinaemia.</td>
</tr>
<tr>
<td>Rare (≥/1/10000 to &lt;1/1000)</td>
<td>rhabdomyolysis and eosinophilia.</td>
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*(Other rare and very rare side effects may not yet have been determined.)*

**In studies, lurasidone appears to have a lower propensity to cause adverse metabolic side effects compared with olanzapine and quetiapine. NNH vs placebo for weight gain ≥7% from baseline was 4 for olanzapine and 9 for quetiapine XL in contrast to a NNH ranging from 43 to 150 for lurasidone (Citrome 2012).**
Are there any drug interactions?

Lurasidone is primarily metabolised by the CYP3A4 isoenzyme and is therefore liable to a number of interactions:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect</th>
</tr>
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<tbody>
<tr>
<td>Smoking</td>
<td>No effect.</td>
</tr>
<tr>
<td>Centrally acting medication and alcohol</td>
<td>Caution as potential for additive CNS effects</td>
</tr>
</tbody>
</table>
| QT prolonging drugs                       | Caution advised. (A dedicated QT study (n=87) indicated that lurasidone has a low risk for QT prolongation – there were no increases in QTc >60ms and no patient experienced a QTc >500ms.)*
| Grapefruit juice                          | Avoid due to potential rise in lurasidone concentration. (This has not been studied but there is a theoretical risk due to CYP3A4 inhibition) |
| Strong CYP3A4 inhibitors (eg: boceprevir, clarithromycin, cobicistat, indinavir, irtraconazole, ketoconazole, nefazodone, neflinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole) | Contraindicated                                  |
| Strong CYP3A4 inducers (eg carbamazepine, phenobarbital, phenytoin, rifampicin, St John’s Wort). | Contraindicated                                  |
| Mild to moderate CYP3A4 inhibitors (eg ditiazem, erythromycin, fluconazole, verapamil) and inducers (eg armodafinil, prednisone, bosentan, efavarlin, modafinil) | Caution. Tolerability and efficacy should be carefully monitored and the dose adjusted accordingly. |
| Digoxin, lithium or oral contraceptives    | No significant interactions.                     |

How should patients be switched from their current antipsychotic to lurasidone?

Switch strategies should be tailored to each individual and depend on a number of factors which include the reason for the switch (ie poor response or adverse effects), relapse risk, risks when unwell, physical status of the patient and risks relating to additive antipsychotic side effects. A cross taper is often appropriate but other strategies such as taper-in/taper-out or stop-start may be more appropriate depending on the individual circumstances.

An open label switching study (McEvoy 2012) in 244 clinically stable but symptomatic patients with schizophrenia or schizoaffective disorder who were receiving treatment with various antipsychotics (quetiapine 26%, risperidone 21%, aripiprazole 18%, olanzapine 10%, ziprasidone 11%, paliperidone 4%, iloperidone 1%, first generation 7%) were switched in one of three ways to lurasidone. All patients had their existing antipsychotic tapered to 50% of its dose by day 7 and then further tapered to zero by day 14. Patients were randomised to either lurasidone 40mg/day for 14 days, 80mg/day for 14 days or 40mg/day for 7 days followed by 80mg/day for 7 days. These dosing strategies were followed by 4 weeks of flexible dosing with 40 to 120mg/day. Time to treatment failure did not differ between groups and there were no clear differences in adverse effects occurring between the three dosing strategies. However when switching from olanzapine or quetiapine a greater incidence of insomnia (18.6% vs 9.7%) and vomiting (9.3% vs 5.8%) was noted, compared with all other antipsychotics which may be due to rebound effects as a result in the difference in affinity for H1 and cholinergic receptors.

If further advice about switching is required or for any other information on lurasidone please contact the Medicines Information Service on 01865 904365 or email: med.info@oxfordhealth.nhs.uk.

What is the evidence base?

NICE did not consider lurasidone appropriate for a technology appraisal. However a NICE Evidence Summary conducted in April 2013, which included only two studies (Meltzer 2011 (N= 478; 6 weeks) and Citrome 2012 (N=629; 12 months)), concluded that there was little evidence of clinically significant differences between lurasidone and the oral antipsychotics examined (olanzapine and risperidone). The overall rate of adverse effects was similar however the profile of adverse effects differed.

Five other 6-week RCTs have been conducted, four of which have been published (references upon request).

Longer term data

Published long term data is currently limited to the 12 month study by Citrome et al that has been included in the NICE Evidence Summary (no stat sig difference in relapse rates between lurasidone and risperidone) and a 12 month relapse prevention study (Loebel 2013) comparing lurasidone with quetiapine (lurasidone met non-inferiority criteria for relapse).