# New drugs

## Brexpiprazole

*Aust Prescr 2017;40:197–8*
https://doi.org/10.18773/austprescr.2017.064
*First published 15 August 2017*

**Approved indication: schizophrenia**

**Rexulti (Lundbeck)**
**0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg tablets**
**Australian Medicines Handbook section 18.2**

Brexpiprazole is a new antipsychotic for schizophrenia. It is structurally similar to aripiprazole and has a similar mechanism of action. It acts at many receptors. For example, it is a partial agonist at serotonin 5-$HT_{1A}$ and dopamine $D_2$ and $D_3$ receptors and an antagonist at the serotonin 5-$HT_{2A}$ and noradrenergic receptors.

Two six-week randomised, placebo-controlled trials investigated the safety and efficacy of brexpiprazole in 1310 patients with acute schizophrenia (see Table).[1,2] The primary outcome measure was improvement on the Positive and Negative Syndrome Scale (PANSS). This is a 30-item scale assessing positive (e.g. delusions, hallucinations), negative (e.g. emotional withdrawal) and general symptoms (e.g. anxiety, depression). In one trial, mean improvements in the PANSS scores after treatment were significantly higher with brexpiprazole 2 mg/day and 4 mg/day than with placebo.[1] However, in the other trial, only the 4 mg/day dose was significantly better than placebo.[2]

Another efficacy measure was response rate. This was defined as the proportion of patients with a ≥30% improvement in their PANSS score or Clinical Global Impression (CGI) score. In the trials, 46.1–49.7% of patients had responded to the 4 mg/day dose compared with 30.3–31.7% in the placebo groups (see Table).[1,2]

In another trial, flexible doses of open-label brexpiprazole (1–4 mg/day) and aripiprazole (10–20 mg/day) were compared in 97 patients with acute schizophrenia. After six weeks of treatment, mean changes in PANSS scores with brexpiprazole were comparable to aripiprazole (see Table).[3]

A longer term trial assessed brexpiprazole as a maintenance treatment for schizophrenia in patients who had been stabilised on brexpiprazole.[4] These patients were randomised to 52 weeks of brexpiprazole 1–4 mg/day (97 patients) or placebo (105 patients). The primary outcome was time between randomisation and exacerbation of psychotic symptoms or impending relapse. At the interim analysis, time to impending relapse was significantly delayed in the brexpiprazole group compared to the placebo group (hazard ratio 0.292, 95% confidence interval 0.156–0.548, p<0.0001) and the trial was terminated. As the trial was cut short, only 23 patients completed 52 weeks of treatment.[4]

Tolerance to brexpiprazole after short- and long-term exposure was assessed in a safety study.[5] In short-term studies of patients taking up to 6 mg/day brexpiprazole (n=1256), akathisia (5.8%) and gain in weight of more than 7% (4.7%) were more frequently reported with brexpiprazole than with placebo.[5] These effects appeared to be dose-related. Newly diagnosed metabolic syndrome was also more common with brexpiprazole than with placebo in the short-term trials (1.2% vs 0.8%), and was even higher in the longer term trials (3.1%). Of the patients who took the drug for a year or more, 5.6% gained at least 15 kg in weight.[5] Brexpiprazole did not increase the QT interval in the trials.

Brexpiprazole has not been tested during pregnancy. However, exposure to other antipsychotics during the third trimester increases the risk of extrapyramidal or withdrawal symptoms in neonates. In animal studies, brexpiprazole did not have teratogenic effects.

Brexpiprazole can be taken with or without food. The starting dose is 1 mg. This should be titrated to the recommended target dose of 2–4 mg over eight days depending on clinical response and tolerability. In people with moderate–severe hepatic or renal impairment, the maximum recommended daily dose is 3 mg.

After oral administration, peak plasma concentrations are reached within four hours. The terminal half-lives of brexpiprazole and its major metabolite are 86–91 hours. Approximately 25% of the dose is excreted in urine and 46% in faeces.

Brexpiprazole is mainly metabolised by cytochrome P450 (CYP) 3A4 and CYP2D6. Strong CYP3A4 inhibitors, such as ketoconazole, increase serum concentrations of brexpiprazole, while inducers (e.g. rifampicin) reduce concentrations so adjustment of the brexpiprazole dose is required with concomitant dosing. Dose reduction is recommended in patients who are poor CYP2D6 metabolisers.

The 4 mg/day dose of brexpiprazole seems to be effective for acute schizophrenia in short-term trials. Up to half of the patients responded to this dose.[1,2] In a longer term placebo-controlled trial, brexpiprazole reduced the risk of relapse in patients already established on brexpiprazole.[4] As with

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

*Table* **The efficacy of brexpiprazole for acute schizophrenia in six-week trials**

**Correll et al. 2015** [1]

| | Placebo | brexpiprazole/day | | |
|---|---|---|---|---|
| | | 0.25 mg | 2 mg | 4 mg |
| Number of patients | 184 | 90 | 182 | 180 |
| Mean baseline PANSS score | 95.9 | 93.4 | 95.9 | 94.9 |
| Mean improvement in PANSS score | 12.0 | 14.9 | 20.7* | 19.7* |
| Response rate† | 30.3% | 39.1% | 47.8% | 46.1% |

**Kane et al 2015** [2]

| | Placebo | brexpiprazole/day | | |
|---|---|---|---|---|
| | | 1 mg | 2 mg | 4 mg |
| Number of patients | 184 | 120 | 186 | 184 |
| Mean baseline PANSS score | 94.8 | 93.3 | 96.3 | 95.1 |
| Mean improvement in PANSS score | 13.5 | 16.9 | 16.6 | 20* |
| Response rate† | 31.7% | 43.6% | 38.6% | 49.7% |

**Citrome et al 2016** [3]

| | brexpiprazole 1–4 mg/day | aripiprazole 10–20 mg/day |
|---|---|---|
| Number of patients | 64 | 33 |
| Mean baseline PANSS score | 94.1 | 93.3 |
| Mean improvement in PANSS score | 22.9 | 19.4 |
| Response rate† | 60.9% | 48.5% |

PANSS Positive and Negative Syndrome Scale
* statistical significance over placebo
† proportion of patients with a ≥30% improvement in their PANSS score or Clinical Global Impression (CGI) score after 6 weeks treatment

other antipsychotics, akathisia and weight gain are common. Brexpiprazole has been approved as an adjunct treatment of major depression in the USA but not in Australia.

TT manufacturer provided additional useful information

## REFERENCES

1. Correll CU, Skuban A, Ouyang J, Hobart M, Pfister S, McQuade RD, et al. Efficacy and safety of brexpiprzole for the treatment of acute schizophrenia: a 6-week randomized, double-blind, placeo-controlled trial. Am J Psychiatry 2015;172:870-80. https://doi.org/10.1176/appi.ajp.2015.14101275
2. Kane JM, Skuban A, Ouyang J, Hobart M, Pfister S, McQuade RD, et al. A multicentre, randomised, double-blind, controlled phase 3 trial od fixed-dose brexpiprazole for the treatment of adults with acute schizophrenia. Schizophr Res 2015;164:127-35. https://doi.org/10.1016/j.schres.2015.01.038
3. Citrome L, Ota A, Nagamizu K, Perry P, Weiller E, Baker RA. The effect of brexpiprazole (OPC-34712) and aripiprazole in adult patients with acute schizophrenia: results from a randomized, exploratory study. Int Clin Psychopharmacol 2016;31:192-201. https://doi.org/10.1097/YIC.0000000000000123
4. Fleischhacker WW, Hobart M, Ouyang J, Forbes A, Pfister S, McQuade RD, et al. Efficacy and safety of brexpiprazole (OPC-34712) as maintenance treatment in adults with schizophrenia: a randomized, double-blind, placebo-controlled study. Int J Neuropsychopharmacol 2017;20:11-21. https://doi.org/10.1093/ijnp/pyw076
5. Kane JM, Skuban A, Hobart M, Ouyang J, Weiller E, Weiss C, et al. Overview of short- and long-term tolerability and safety of brexpiprazole in patients with schizophrenia. Schizophr Res 2016;174:93-8. https://doi.org/10.1016/j.schres.2016.04.013

The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, 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.