

Paliperidone (Invega) for schizophrenia

(pally-PER-ee-dohne)

Summary

- Paliperidone is the major active metabolite of risperidone. The clinical response to paliperidone is likely to be similar to that of risperidone, but there are no comparative data.
- The prolonged-release formulation of paliperidone is an alternative to other atypical antipsychotics, including risperidone, for people with schizophrenia.
- There is no published evidence to suggest that paliperidone is more effective than risperidone or other atypical antipsychotics. Efficacy data from clinical trials comparing paliperidone with olanzapine have not yet been published.
- Paliperidone appears to have adverse effects similar to those of risperidone. However, its long-term safety profile is yet to be established.
- Start with 6 mg once daily. If necessary, adjust up or down by 3 mg. Allow an interval of at least 5 days between each dose increase (dose range 3–12 mg once daily).

PBS listing

Authority required (streamlined)

Schizophrenia.

Reason for PBS listing

The Pharmaceutical Benefits Advisory Committee recommended paliperidone for listing on a cost-minimisation basis — that is, similar efficacy and cost — compared with olanzapine for the treatment of schizophrenia.¹

Place in therapy

9-Hydroxyrisperidone (paliperidone) is the major active metabolite of risperidone.^{2,3} Paliperidone has been formulated as a prolonged-release tablet.⁴ It is an atypical (or 'second generation') antipsychotic used for treating schizophrenia.

Paliperidone is an option for people with schizophrenia who cannot use other atypical antipsychotics because of intolerance, poor response or drug interactions with other concomitant therapies. There is no published

evidence to suggest that paliperidone is more effective than risperidone or any other atypical antipsychotic.

Clozapine is the drug of choice for treatment-resistant schizophrenia. The efficacy of paliperidone for this condition is not established.^{5,6}

Paliperidone is the major active metabolite of risperidone

Risperidone is mainly metabolised in the liver to 9-hydroxyrisperidone (paliperidone): the major active metabolite responsible for most of risperidone's effects.² After giving risperidone, steady-state blood levels of 9-hydroxyrisperidone (paliperidone) are about 22-fold higher than those of risperidone^{7,8}: hence the clinical responses to paliperidone and risperidone are likely to be similar (there are no direct comparative data to verify this).

Risperidone reaches peak plasma concentrations within 1–2 hours after oral dosing and has an elimination half-life of 3–17 hours.² In contrast, paliperidone reaches peak plasma concentrations about 24 hours after oral dosing and has an elimination half-life of about 23 hours.⁴

The prolonged-release formulation of paliperidone may be a useful alternative to risperidone for some people with schizophrenia

Paliperidone has been formulated as a prolonged-release tablet.⁴ It may be a useful alternative to risperidone for some people, including those who cannot use risperidone because of mild-moderate hepatic impairment or drug interactions due to hepatic metabolism (see Safety issues). The prolonged-release formulation uses osmotic pressure to release paliperidone at a controlled rate over 24 hours, reducing fluctuations in plasma concentrations.⁴ This allows once-daily dosing and may reduce the impact of missed doses. However, these potential advantages — compared with risperidone or other atypical antipsychotics — need to be confirmed in clinical practice.

Some people may have difficulty swallowing the prolonged-release tablet because it must be swallowed whole and not broken, chewed or crushed (unlike the scored tablet and orally disintegrating tablet [quicklet] formulations available for risperidone).^{2,9} The rigid tablet casing is excreted in the faeces (which may cause unnecessary concern for some people).^{4,9}

There is no published evidence to suggest that paliperidone is more effective than other atypical antipsychotics in the treatment of schizophrenia

Few clinical trials compare paliperidone directly with other antipsychotics, which makes it difficult to draw conclusions about its relative efficacy for schizophrenia. Paliperidone has been compared with olanzapine in clinical trials¹⁰ but efficacy data have not yet been published (refer to *NPS News 51: What's 'atypical' about the newer antipsychotics?*¹¹ for more information about other atypical antipsychotics for the treatment of schizophrenia).

The efficacy of paliperidone has been assessed in the treatment of acute schizophrenia in three dose–response trials (n = 1665).^{12–14} Paliperidone 3–15 mg once daily, improved symptoms of acute schizophrenia more than placebo after 6 weeks. The trials included olanzapine 10 mg once daily as an active control but were not powered to allow a direct comparison with paliperidone.

A further trial (n = 207) assessed the efficacy of paliperidone in preventing recurrence of schizophrenic symptoms.¹⁵ People with schizophrenic symptoms

controlled by paliperidone (3–15 mg once daily; starting dose 9 mg once daily) were randomised to continue paliperidone or switch to placebo. Not surprisingly, there were more episodes of symptom recurrence in the placebo group (from whom effective treatment had been withdrawn).

Safety issues

Paliperidone's adverse-effect profile appears to be similar to that of risperidone.^{2,4} However, its full adverse-effect profile will only be established after more widespread and long-term use in a broader patient population.

Common adverse effects reported for paliperidone in clinical trials affected the nervous system (e.g. headache, akathisia, extrapyramidal symptoms), gastrointestinal system (e.g. nausea) and cardiovascular system (e.g. tachycardia). Paliperidone is associated with a dose-dependent increased risk of extrapyramidal symptoms, weight gain, hyperprolactinaemia and cardiovascular adverse effects (e.g. orthostatic hypotension). Experience with risperidone shows that it causes hyperglycaemia in some people.⁹ At this stage, there are no data showing changes in glucose or lipid parameters with paliperidone use. However, these data are limited to pre-registration clinical trials, which focus on efficacy and are limited in their ability to detect rare or long-term adverse effects.^{4,16} Refer to the Invega product information for more information about adverse effects.⁴

Paliperidone may be useful for people with mild–moderate hepatic impairment because, unlike risperidone, it is mainly excreted unchanged by the kidneys. However, as with risperidone, people with renal impairment have an increased risk of adverse effects (see Dosing issues, below).

Paliperidone is not expected to have clinically important pharmacokinetic interactions with cytochrome P450 2D6 inhibitors, so it may be an alternative to risperidone* for people taking medicines known to inhibit this enzyme.^{4,9}

Report suspected adverse reactions to the Adverse Drug Reactions Advisory Committee (ADRAC) online (www.tgasime.health.gov.au) or by using the 'Blue Card' distributed with Australian Prescriber. For information about reporting adverse reactions, see the Therapeutic Goods Administration website (www.tga.gov.au).

* Risperidone is metabolised in the liver (mainly by cytochrome P450 2D6) so the risk of adverse effects may increase if risperidone is coadministered with inhibitors of this enzyme.⁹

Dosing issues

Start with 6 mg once daily. If necessary, adjust up or down by 3 mg. Allow an interval of at least 5 days between each dose increase (dose range 3–12 mg once daily). Paliperidone should be taken in the morning and at the same time in relation to food.⁴

No dose adjustment is required in mild–moderate hepatic impairment. For people with renal impairment⁴:

- start with 3 mg once daily if creatinine clearance is 50–80 mL/minute (adjust if necessary, in 3 mg increments; allow an interval of at least 5 days between each dose increase)
- give no more than 3 mg once daily if creatinine clearance is 30–50 mL/minute
- start with 3 mg once *every other day* for people with creatinine clearance 10–30 mL/minute (adjust if necessary, to 3 mg once daily).

Information for patients

Advise patients:

- that paliperidone must be taken every morning at the same time in relation to food
- to swallow the tablet whole and not to break, chew or crush it
- that the tablet casing is excreted in the faeces (this is sometimes an unnecessary cause for concern).

Advise patients and carers of both common adverse effects (see Safety issues) and rare but significant adverse effects, and to report any symptoms of these, including:

- twitching of the tongue, face, mouth or jaw
- significant rise or fall in body temperature
- stiff muscles, fast breathing, abnormal sweating or decreased mental alertness.

Suggest or provide the Invega consumer medicine information (CMI) leaflet.

Counsel patients with schizophrenia to avoid alcohol, tobacco and illicit substances (e.g. cannabis). Even intermittent use can worsen schizophrenic symptoms.

References

1. Pharmaceutical Benefits Advisory Committee. November 2007 positive recommendations. Canberra: Australian Government Department of Health and Ageing, 2007. [http://www.health.gov.au/internet/main/publishing.nsf/Content/A008C4F78F359BF2CA2573A800032DBF/\\$File/11-07%20PBAC%20positive%20decisions%20for%20website.pdf](http://www.health.gov.au/internet/main/publishing.nsf/Content/A008C4F78F359BF2CA2573A800032DBF/$File/11-07%20PBAC%20positive%20decisions%20for%20website.pdf) (accessed 16 January 2008).
2. Janssen Cilag Pty Ltd. Risperdal product information. 20 March 2007.
3. Sweetman S, ed. Martindale: The Complete Drug Reference Updated Periodically (Thomson Micromedex). London: Pharmaceutical Press, 2006.
4. Janssen Cilag Pty Ltd. Invega product information. 12 December 2007.
5. Psychotropic Writing Group. Therapeutic Guidelines: Psychotropic. Version 5 Updated November 2007 [eTG complete CD-ROM]. Melbourne: Therapeutic Guidelines Ltd, 2003.
6. National Institute for Clinical Excellence (NICE). NICE Technology Appraisal Guidance - No 43. Guidance on the use of newer (atypical) antipsychotic drugs for the treatment of schizophrenia. London: NICE, 2002. <http://guidance.nice.org.uk/> (accessed 26 November 2007).
7. Aravagiri M, et al. Therapeutic Drug Monitoring 2003;25:657–64.
8. Aravagiri M, et al. Pharmacopsychiatry 1998;31:102–9.
9. Australian Medicines Handbook 2008.
10. Pharmaceutical Benefits Advisory Committee. Public summary document: paliperidone prolonged-release tablets, 3mg, 6mg, 9mg, 12mg. Canberra: Australian Government Department of Health and Ageing, 2008. <http://www.health.gov.au/internet/main/publishing.nsf/Content/pbac-psd-paliperidone-nov07> (accessed 29 February 2008).
11. National Prescribing Service. What's 'atypical' about the newer antipsychotics? NPS News 51. Sydney: National Prescribing Service, 2007. http://nps.org.au/site.php?content=/html/news.php&news=/resources/NPS_News/news51 (accessed 26 November 2007).
12. Kane J, et al. Schizophr Res 2007;90:147–61.
13. Davidson M, et al. Schizophr Res 2007;93:117–30.
14. Marder SR, et al. Biol Psychiatry 2007;62:1363–70.
15. Kramer M, et al. J Clin Psychopharmacol 2007;27:6–14.
16. European Medicines Evaluation Agency. Invega European Public Assessment Report. London: EMEA, 2007. <http://www.emea.europa.eu/humandocs/Humans/EPAR/invega/invega.htm> (accessed 26 November 2007).

Updated April 2008: Deleted amiodarone as an example of a cytochrome P450 2D6 inhibitor that could be co-administered with paliperidone (see Safety issues) because amiodarone prolongs the QT interval. Use caution when prescribing paliperidone (or risperidone) to people taking drugs known to prolong the QT interval.^{2,4}

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The information contained in this material is derived from a critical analysis of a wide range of authoritative evidence. Any treatment decisions based on this information should be made in the context of the clinical circumstances of each patient.