Rasagiline (Azilect) for Parkinson’s disease (Ra-SA-ji-leen)

**KEY POINTS**

Rasagiline, like selegiline, is an irreversible monoamine oxidase type-B (MAO-B) inhibitor
It inhibits the breakdown of dopamine in the brain and can be used as monotherapy or as an adjunct to levodopa.

Rasagiline (1 mg) is taken once a day
Rasagiline can be taken at any time of day. Increasing the dose does not increase the therapeutic effect but does increase the risk of adverse events.

Adjunctive therapy may increase levodopa-associated adverse events such as dyskinesia
Incidence of hallucination and hypersomnolence was similar to that for placebo or levodopa alone in trials. Impulse control disorders were not observed in trials.

There are no direct comparisons with dopamine agonists or selegiline, efficacy as adjunctive therapy may be similar to that of entacapone
Indirect comparisons as adjunctive therapy suggest less efficacy than dopamine agonists.

There is a risk of hypertensive crisis or serotonin toxicity if rasagiline is used concomitantly with certain medications
Use with other MAO inhibitors, dextromethorphan and certain opioid analgesics is contraindicated. Obtain specialist advice before combining with antidepressants.

Rasagiline is contraindicated in people with liver impairment
Rasagiline is metabolised in the liver by the enzyme CYP1A2. Potent inhibitors of CYP1A2 (e.g. ciprofloxacin, cimetidine or fluvoxamine) are contraindicated.

**PBS listing**

Authority required (Streamlined)
Parkinson’s disease.

May be prescribed by nurse practitioners (continuing therapy only)
Authorised nurse practitioners may prescribe continuing therapy of this medicine after it has been initiated by a medical practitioner. See the Pharmaceutical Benefits Scheme website for more information on nurse practitioner PBS prescribing.

What is it?
Rasagiline, like selegiline, is an irreversible monoamine oxidase type-B (MAO-B) inhibitor that inhibits degradation of dopamine. This increases dopamine activity in the brain and reduces motor symptoms of Parkinson’s disease. As an adjunct to levodopa, rasagiline also reduces ‘off time’ (phases with significant motor symptoms and no response to medication). MAO-B accounts for more than 80% of MAO activity in the brain, and rasagiline is highly selective for MAO-B over MAO-A at the approved dose of 1 mg/day. However, MAO-B selectivity can be lost if the dose is increased above the approved dose, increasing the risk of serotonin toxicity and hypertensive crisis. (See Dosing issues)
Who is it for?
Rasagiline is indicated for treating the symptoms of Parkinson's disease, either as monotherapy or as adjunctive therapy with levodopa. Participants in monotherapy trials had been diagnosed for approximately 4 months (ADAGIO trial) and 1 year (TEMPO trial) and did not have severe symptoms. Participants in adjunctive therapy trials had been diagnosed for about 10 years on average and experienced more severe motor symptoms as well as off-time and dyskinesia.

Rasagiline is contraindicated for people with hepatic impairment (i.e. Child-Pugh score Grade A [well-compensated disease] or worse).

Rasagiline may not be suitable for people already taking antidepressants; some classes and specific drugs are contraindicated and specialist advice should always be obtained (see section: Obtain specialist advice before combining rasagiline with antidepressants). Use of antidepressants in combination with dopamine agonists is less restricted. The suitability of rasagiline for people with severe depression, clinically significant or unstable vascular disease, congestive heart failure or cognitive impairment has not been investigated.

Where does it fit?
Parkinson's disease treatment must be individualised for each person; rasagiline is one treatment option. As with other treatment options, rasagiline does not cure the disease but can assist with management of symptoms.

Monotherapy
In early disease rasagiline may be used as monotherapy as an alternative to levodopa, dopamine agonists such as pramipexole, and the other MAO-B inhibitor selegiline. Rasagiline monotherapy is an option for people newly diagnosed with less severe Parkinson's disease.
It may also be suitable for people at increased risk of, or intolerant of, the side effects of dopamine agonists (see Table 1).

Although most people with Parkinson’s disease will ultimately require levodopa, people diagnosed under 70 years of age (including those with young-onset Parkinson’s disease) are at increased risk of developing levodopa-associated motor complications (off-time and dyskinesia) compared with people diagnosed after age 70. Using an MAO-B inhibitor such as rasagiline or a non-ergot-derived dopamine agonist such as pramipexole may offset the need for levodopa therapy and could delay the onset of motor complications. However, the clinical benefit of delaying the initiation of levodopa therapy has not been established.

**Adjunctive therapy**

In more advanced Parkinson’s disease, rasagiline may be used as adjunctive therapy with levodopa and is an alternative to non-ergot-derived dopamine agonists such as pramipexole, as well as entacapone and selegiline.

In advanced Parkinson’s disease, combining levodopa with an adjunct can allow reduction of levodopa doses and may reduce levodopa-associated motor complications. As levodopa adjunctive therapy, rasagiline is likely to be less effective than dopamine agonists at reducing off-time and motor symptoms (see section: Indirect comparisons suggest less efficacy than dopamine agonists). Rasagiline may therefore be more useful in people with less severe motor symptoms and levodopa-associated motor complications. Rasagiline adjunctive therapy is an option for people at increased risk of adverse effects associated with dopamine agonists (e.g. impulse control disorders) and those who need to change drug treatment because of intolerance of dopamine agonists or entacapone (Table 1).

<table>
<thead>
<tr>
<th>Drug</th>
<th>PBS listing</th>
<th>Selected common adverse effects</th>
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</thead>
<tbody>
<tr>
<td>Levodopa-with-decarboxylase-inhibitor combinations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>levodopa/benserazide (Madopar)</td>
<td>Yes</td>
<td>Anorexia, vomiting, nausea, dyskinesia, ‘off’ time, hallucination, confusion, sudden sleep onset, drowsiness, depression, orthostatic hypotension</td>
</tr>
<tr>
<td>levodopa/carbidopa (Sinemet, Sinemet CR, Kinson, Levo/Carbidopa Sandoz, Duodopa)</td>
<td>Yes</td>
<td>Side effects as for levodopa and entacapone</td>
</tr>
<tr>
<td>levodopa/carbidopa/entacapone (Stalevo)</td>
<td>Yes</td>
<td>Side effects as for levodopa and entacapone</td>
</tr>
<tr>
<td>Non-ergot derived dopamine agonists</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pramipexole (Sifrol, Simipex)</td>
<td>Yes</td>
<td>Nausea, vomiting, dizziness, orthostatic hypotension</td>
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<tr>
<td>apomorphine (Apopmine)</td>
<td>Yes</td>
<td>Nausea, vomiting, dizziness, orthostatic hypotension</td>
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<tr>
<td>ropinirole (Requip)</td>
<td>No</td>
<td>Nausea, vomiting, dizziness, orthostatic hypotension</td>
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<tr>
<td>rotigotine (Neupro)</td>
<td>No</td>
<td>Nausea, vomiting, dizziness, orthostatic hypotension</td>
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<tr>
<td>Catechol-O-methyltransferase (COMT) inhibitors</td>
<td></td>
<td></td>
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<tr>
<td>entacapone (Comtan)</td>
<td>Yes</td>
<td>Diarrhoea, dyskinesia, hallucination, nausea, vomiting, confusion, paranoia</td>
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<tr>
<td>Monoamine oxidase B (MAO-B) inhibitors</td>
<td></td>
<td></td>
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<tr>
<td>selegiline (Eldepryl, Selgene)</td>
<td>Yes</td>
<td>Insomnia, nausea, orthostatic hypotension, dyskinesia</td>
</tr>
<tr>
<td>rasagiline (Azilect)</td>
<td>Yes</td>
<td>See Safety issues</td>
</tr>
<tr>
<td>N-methyl-D-aspartate (NMDA) receptor antagonist</td>
<td></td>
<td></td>
</tr>
<tr>
<td>amantadine (Symmetrel)</td>
<td>Yes</td>
<td>Nausea, vomiting, hallucinations, dizziness, nightmares</td>
</tr>
</tbody>
</table>

1. TGA approved, available on private prescription only
2. Available as standard release, slow release and rapid release
Rasagiline may be a useful additional adjunct for people already being treated with levodopa and a dopamine agonist but still experiencing off-time or dyskinesia. Additional dopaminergic therapies were allowed in trials; however, there are no published studies designed to evaluate combinations of more than two Parkinson’s disease therapies, and specialist advice is recommended. 5,6,14

Evidence of disease modification not demonstrated
The ADAGIO trial was designed to investigate if rasagiline has disease modifying properties by comparing the change in outcomes when rasagiline treatment was started immediately and when treatment was delayed for the first 36 weeks of this 72-week trial. The evidence for suggesting a disease modifying role for rasagiline was inconclusive. Rasagiline 1 mg/day but not 2 mg/day reached the pre-specified endpoints. 7,11,16

In Australia rasagiline is only approved for symptomatic treatment of Parkinson’s disease. 3

How does it compare?
Rasagiline efficacy as monotherapy has not been directly compared with any other Parkinson’s disease drugs. As adjunctive therapy rasagiline has only been directly compared with entacapone. 8 Therefore it is not clear how rasagiline compares with other therapies in terms of benefit and adverse events. Efficacy of rasagiline (1 mg/day) monotherapy compared with placebo has been assessed in people with early Parkinson’s disease in two randomised trials (TEMPO: 26 weeks, n = 404; ADAGIO: 36 weeks, n = 1176). As levodopa adjunctive therapy rasagiline has been compared with levodopa therapy alone in two randomised trials of people with advanced Parkinson’s disease (LARGO: 18 weeks, n = 687; PRESTO: 26 weeks, n = 472). 4–7 The LARGO study also included a group receiving entacapone adjunctive therapy (200 mg with every levodopa dose). 6

Rasagiline monotherapy significantly improves motor symptoms compared with placebo
Rasagiline significantly improved (i.e. reduced worsening of) motor symptoms and ability to perform activities of daily living compared with placebo. Total Unified Parkinson’s Disease Rating Scale (UPDRS)* scores were improved compared with placebo in both key monotherapy trials (Table 2). 4,7  In the TEMPO study a responder analysis (reported as a secondary outcome) highlighted that the number of trial participants whose total UPDRS score worsened by more than 3 points (likely to be a minimal clinically significant change) over 26 weeks was significantly reduced with rasagiline compared with placebo (34% vs 51%, p = 0.004). 4

Inconclusive evidence for delaying levodopa requirement
Rasagiline delayed the requirement for levodopa in the ADAGIO trial (odds ratio [OR] 0.41, 95% confidence interval [CI] 0.25 to 0.65) but not the TEMPO trial (OR 0.63, 95% CI 0.3 to 1.34), although neither trial was designed to investigate this. 4,7

Rasagiline adjunctive therapy significantly reduces off-time
Rasagiline adjunctive therapy significantly reduced off-time compared with levodopa alone in people on optimised levodopa therapy with advanced Parkinson’s disease in the LARGO and PRESTO trials (Table 3). 4,7

<table>
<thead>
<tr>
<th>Mean improvement vs placebo in total UPDRS score</th>
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<tbody>
<tr>
<td>TEMPO (at 26 weeks)</td>
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<tr>
<td>ADAGIO (at 36 weeks)</td>
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CI = confidence interval

<table>
<thead>
<tr>
<th>Mean reduction in off-time vs levodopa alone*</th>
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<tr>
<td>PRESTO (at 26 weeks)</td>
</tr>
<tr>
<td>LARGO (at 18 weeks)</td>
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</table>

* Baseline mean daily off-time average: ~6 hours.
In the LARGO trial 19% more (51% vs 32%) rasagiline-treated than placebo-treated trial participants reported > 1 hour reduction in off-time (responder analysis as a secondary outcome).\textsuperscript{5,6}

**Rasagiline adjunctive therapy also improved some other symptoms**

Compared with levodopa alone, significant improvements in both motor symptoms during on-time and the ability to complete activities of daily living during off-time were also identified (as secondary outcomes) in both key studies of rasagiline adjunctive therapy.\textsuperscript{5,6}

**Rasagiline adjunctive therapy may increase dyskinesia**

As with other levodopa adjunctive therapies, rasagiline may increase dyskinesia. There was a significant mean increase in dyskinesia compared with levodopa therapy alone in the PRESTO trial (22 minutes, 95% CI 0 to 44, p = 0.05) but not the LARGO trial (5 minutes, 95% CI –17 to +28, p = 0.62).\textsuperscript{5,6} The reason for the disparity between the two trials is not known, although combinations of rasagiline and entacapone were permitted in the PRESTO trial but not the LARGO trial. In both trials levodopa dose adjustment was precluded after the first 6 weeks. During this first 6 weeks a small decrease in required levodopa was reported.\textsuperscript{5,6}

**Rasagiline efficacy as adjunctive therapy may be similar to that of entacapone**

The LARGO study was designed to compare the efficacy of each levodopa adjunctive therapy with that of levodopa treatment alone, not with each other. However, a post-hoc comparison performed at 18 weeks suggests that the effects of rasagiline and entacapone in reducing off-time as levodopa adjunctive therapy may be similar (mean difference in off-time rasagiline vs entacapone: 1 minute, 95% CI –2 to +2 minutes).\textsuperscript{6,8} Furthermore, the number of trial participants experiencing more than 1 hour reduction in off-time (responder analysis as a secondary outcome) was also similar for rasagiline and entacapone adjunctive therapy (51% vs 45%).\textsuperscript{5,6}

**Indirect comparisons suggest efficacy is less than that of dopamine agonists**

Indirect comparisons, with levodopa monotherapy as a common comparator, suggest that the effect of MAO-B inhibitors, including rasagiline, in reducing off-time and motor symptoms is less than with dopamine agonists.\textsuperscript{15}

The only published indirect comparison of rasagiline with selegiline was with a formulation of selegiline not available in Australia.\textsuperscript{15}

**Safety issues**

The safety data for rasagiline from randomised controlled trials are derived mainly from the four key studies discussed above.\textsuperscript{4–7} A 4-month, postmarketing observational study (monotherapy: n = 209, adjunctive therapy: n = 545) has also been reported.\textsuperscript{20}

Report suspected adverse reactions to the Therapeutic Goods Administration (TGA) online (www.ebs.tga.gov.au) or by using the ‘Blue Card’ distributed three times a year with *Australian Prescriber*. For information about reporting adverse reactions, see the TGA website (www.tga.gov.au).

As a condition of rasagiline TGA approval, cases of hallucinations, orthostatic hypotension, melanoma and adverse reactions with antidepressants or tyramine will be monitored by the drug sponsor as part of a risk management plan.\textsuperscript{21}

In terms of incidence of adverse events, rasagiline has only been compared directly with entacapone.\textsuperscript{6} In this study the incidence of adverse events was similar for rasagiline and entacapone, with the exception of hallucinations, diarrhoea and nausea, which were increased (although not statistically significantly) with entacapone compared with rasagiline adjunctive therapy.\textsuperscript{6} Indirect comparisons (in which placebo was the common comparator) suggest that the incidence of adverse events with rasagiline monotherapy is lower than with pramipexole (OR 0.51, 95% CI 0.29 to 0.89).\textsuperscript{22}
Monotherapy: adverse events similar to those with placebo

In rasagiline monotherapy trials, incidence of adverse events was not significantly increased with rasagiline compared with placebo. In the TEMPO trial (but not the ADAGIO trial) headache was reported as a very common adverse event (experienced by > 10% of trial participants), with incidence increased with rasagiline over placebo (14.2% vs 10.1%). Other common adverse events (experienced by > 1% of trial participants) reported with increased incidence compared with placebo include those reported in Box 1.

Safety data for the ADAGIO trial are limited to events reported in > 5% of trial participants. Of these only fatigue was increased in rasagiline-treated compared with placebo-treated subjects. However, incidence was not significantly increased compared with placebo.

Box 1.
Common adverse events reported with rasagiline monotherapy in clinical trials

- Headache
- Dyspepsia
- Flu syndrome
- Depression
- Arthralgia
- Fatigue
- Dizziness

Adjunctive therapy: increased incidence of adverse events, including vomiting and dyskinesia

In the LARGO trial, incidence of adverse events with rasagiline adjunctive therapy was similar in frequency to that with levodopa therapy alone. However, in the PRESTO trial, the incidence of the following adverse events was increased compared with levodopa therapy alone:

- dyskinesia (18% vs 10%, p = 0.03)
- weight loss (9.4% vs 2.5%, p = 0.02)
- vomiting (6.7% vs 1.3%, p = 0.03)
- anorexia (5.4% vs 0.6%, p = 0.04)

Other common side effects plausibly related to dopaminergic therapy that were increased (although not statistically significantly) in trials compared with levodopa alone are listed in Box 2.

Do not use rasagiline with other MAO inhibitors (MAOIs)

Use of rasagiline is contraindicated with:

- non-selective MAOIs (e.g. antidepressants phenelzine and tranylcypromine or the antibiotic linezolid)
- MAO-A inhibitors (e.g. the antidepressant moclobemide)
- the MAO-B inhibitor selegiline.

These combinations may increase the risk of hypertensive crisis. Allow 14 days between discontinuing rasagiline and starting treatment with another MAOI.

Obtain specialist advice before combining rasagiline with antidepressants

MAO-B inhibitors, such as rasagiline, can contribute to serotonin toxicity; administration with antidepressants may increase the likelihood of this. It is contraindicated to combine rasagiline with MAOI antidepressants, the herbal remedy hypericum (St John’s wort) or fluvoxamine.
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(also see section: Do not use rasagiline with potent inhibitors of CYP1A2). Combination with fluoxetine should be avoided because of the risk of serotonin toxicity. Allow 14 days between discontinuing rasagiline and starting treatment with an MAOI antidepressant, fluoxetine or fluvoxamine; allow 5 weeks between ending fluoxetine treatment and starting rasagiline.3

Obtain specialist advice before combining rasagiline with non-contraindicated antidepressants. Current data are insufficient to identify the risk of serotonin toxicity from their use with rasagiline, and cases of serotonin toxicity have been reported in the postmarketing period after use of rasagiline with these antidepressants.3 The rasagiline Australian product information advises caution when using rasagiline with these antidepressants.3 However, some international guidelines advise to avoid combining rasagiline with antidepressants and allow 14 days between discontinuing rasagiline and initiating antidepressant therapy.9,25

Do not use in people with hepatic impairment
Rasagiline is contraindicated for people with hepatic impairment (i.e. Child–Pugh score Grade A [well-compensated disease] or worse). Rasagiline is primarily metabolised by the liver, and hepatic impairment may increase plasma concentrations of rasagiline.3

Do not use rasagiline with potent inhibitors of CYP1A2
Rasagiline is metabolised predominantly by the enzyme cytochrome P450 1A2 (CYP1A2). Do not co-prescribe rasagiline with potent inhibitors of CYP1A2 (e.g. ciprofloxacin, cimetidine or fluvoxamine), as this combination may increase plasma concentrations of rasagiline.3,12

Avoid food and drink containing very high levels of tyramine
Avoid consumption of very high levels of tyramine (> 150 mg) while taking rasagiline because of the possibility of hypertensive crisis. The risk of tyramine-induced hypertensive crisis is much greater with higher-than-recommended doses of rasagiline.4,23 Food and drink containing very high levels of tyramine include aged cheeses (e.g. English Stilton: ~115 mg/100 g) and some beers or ales (up to 113 mg/L).26,27 Red wines, including Chianti, are no longer considered to contain high levels of tyramine.27

A small tyramine challenge study (n = 149, participants did not have Parkinson’s disease) indicated that an average of 200 mg tyramine was required to cause an increase in blood pressure (≥ 30 mmHg from baseline for three consecutive readings) in people taking rasagiline 1 mg/day (a twofold increase in tyramine sensitivity).2

No cases of tyramine-induced hypertensive crisis were reported in the four key trials, which were conducted without dietary restriction.4,7 However, there have been reports of significantly elevated blood pressure and rare cases of hypertensive crisis in people taking the approved dose of rasagiline after ingesting unknown amounts of tyramine-rich food.3

Do not use rasagiline with sympathomimetic agents
Do not use rasagiline with sympathomimetic medications, including pseudoephedrine and phenylephrine, due to the risk of hypertensive crisis. These drugs are found in many nasal and systemic non-prescription cold remedies as well as in ophthalmic decongestants.3,24

Do not use rasagiline with certain opioid analgesics
Because of risk of serotonin toxicity or hypertensive crisis, use of rasagiline is contraindicated with: tramadol tapentadol pethidine methadone dextropropoxyphene.3

Do not use rasagiline with dextromethorphan
Rasagiline use with dextromethorphan, the active ingredient in some non-prescription cough suppressants, is contraindicated because of the risk of serotonin toxicity.3

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**ADDITIONAL INFORMATION**

For further information on the Child–Pugh classification of liver disease see the online version of this article at www.nps.org.au/radar or the Australian Prescriber article ‘Prescribing in liver disease’.8
People with Parkinson’s disease should undergo periodic skin examinations
People with Parkinson’s disease are at increased risk of melanoma and possibly other skin cancers and should undergo periodic skin examinations. It is unclear whether this risk is increased by any specific Parkinson’s disease therapies, including rasagiline. Rasagiline-treated patients will be monitored by the drug sponsor in Australia and the USA to investigate this potential link.

Reason for PBS listing
The Pharmaceutical Benefits Advisory Committee (PBAC) recommended an Authority required (Streamlined) listing of rasagiline for Parkinson’s disease on a cost-minimisation basis primarily against selegiline with entacapone as the secondary comparator. The indication of ‘Parkinson’s disease’ was based on rasagiline having TGA approval for use as both monotherapy (without levodopa) and adjunctive therapy (with levodopa). The PBAC accepted that rasagiline was non-inferior to selegiline based on indirect comparisons, although it was highlighted that clinical trials involving rasagiline and selegiline had many design differences that made comparison difficult (e.g. the trials explored different primary endpoints). The PBAC also accepted that rasagiline was non-inferior to entacapone based on post-hoc analysis and indirect comparisons of clinical trial data.

Dosing issues
The approved dose is rasagiline 1 mg once a day for either monotherapy or adjunctive therapy. Rasagiline can be taken at any time of day with or without food.

A higher dose has no additional benefit but may inhibit MAO-A and increase the risk of adverse events. No dose adjustment is required in people with moderate renal impairment (creatinine clearance of 30–50 mL/min).

Information for patients
Advise patients and carers to:

- avoid using rasagiline with non-prescription cough medicines, cold and flu tablets, eye drops and St John’s wort
- avoid foods and drinks such as aged cheeses and beer while taking rasagiline, as these can contain very high levels of tyramine, which may interact with rasagiline and cause dangerously high increases in blood pressure
- consult their doctor if they experience a change in symptoms or side effects, including an increase in dyskinesia (unpredictable twisting, jerking and dancing movements)
- inform any other health professional prescribing medication or treating them that they are taking rasagiline
- be vigilant for new moles or moles that change in appearance as well as for the emergence of skin lumps, as risk of melanoma and other skin cancers is increased with Parkinson’s disease.

Discuss the Azilect consumer medicine information (CMI) leaflet with the patient.

MEDICINE UPDATE
An NPS Medicine Update article on rasagiline is available for consumers. Medicine Update helps consumers ask the right questions about new medicines and helps them compare the potential benefits and harms of a new medicine with those of other medicines.
REFERENCES

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The information contained in NPS RADAR is derived from a critical analysis of a wide range of authoritative evidence and is current at the time of publication. Any treatment decisions based on the information provided in NPS RADAR should be made in the context of the clinical circumstances of each patient.

NPS RADAR articles may be updated when there is new evidence about safety or efficacy, or in case of regulatory or PBS listing changes.

Please refer to www.npsradar.org.au for the most recent version as well as any supplementary information.