

# Pramipexole (Sifrol) for severe primary restless legs syndrome

(pram-i-PECKS-ole)

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## Summary

- Pramipexole is a non-ergot-derived dopamine agonist that is also approved for treating Parkinson's disease.
- Pramipexole reduces the symptoms of restless legs syndrome for some people and is PBS listed for severe primary cases.
- Diagnose restless legs syndrome by confirming that the patient meets all 4 clinical criteria. Grade severity using the IRLS rating scale.
- Consider possible causes of secondary restless legs syndrome, including iron deficiency, pregnancy or renal failure and differential diagnoses such as muscle cramps, arthritis, neuropathy or drug-induced akathisia.
- Try non-drug measures, including exercise and sleep hygiene.
- Consider pramipexole for severe frequent symptoms.
- Nausea and somnolence are common but are generally mild and transient.
- Sudden-onset daytime sleep (sleep attacks) can occur and rare cases of compulsive behaviour have been reported.
- Evidence for efficacy beyond 3 months is limited and observations suggest that it declines over time.

## PBS listing

### Restricted benefit

Severe primary (idiopathic) restless legs syndrome with an International Restless Legs Syndrome Study Group Rating Scale (IRLS) score  $\geq 21$  before starting pramipexole.\*

Patients must meet all 4 of the diagnostic criteria for restless legs syndrome (see Box 1).

Pramipexole is not PBS subsidised for restless legs syndrome secondary to other causes.

### Reason for PBS listing

The Pharmaceutical Benefits Advisory Committee (PBAC) recommended listing pramipexole for severe primary restless legs syndrome on the basis that it was no worse than levodopa with benserazide in effectiveness and safety for the same cost. The comparison was based on 1 unpublished randomised controlled trial.<sup>1</sup>

In response to an earlier submission, the PBAC rejected the claim that pramipexole was superior overall to levodopa with benserazide, noting that pramipexole was associated with higher rates of nausea and other gastrointestinal adverse events, while levodopa with benserazide was associated with more nervous system adverse events.<sup>2</sup>

### Place in therapy

Pramipexole is the only dopamine agonist currently PBS listed for treating the symptoms of restless legs syndrome. It may be useful if *frequent* symptoms *severely* affect a patient's quality of life and non-drug measures prove ineffective. Modest symptomatic benefits need to be weighed against common adverse effects, as well as the possibility of sleep attacks or other less common serious problems. Evidence for efficacy beyond 3 months is limited and observations suggest that it declines over time.

\* The date and IRLS score must be recorded when starting pramipexole.

## Restless legs syndrome is an idiopathic sensorimotor disorder

Restless legs syndrome consists of a pattern of symptoms involving an urge to move the legs because of unpleasant sensations. Symptoms are worse or only present at rest, worse or only present in the evening or night-time, and are relieved by movement (see Diagnose from symptoms and medical history). The diagnosis covers a spectrum from mild and harmless to severe and distressing. As the pathology is unknown and no objective test exists, diagnosis is based on patient report of symptoms, according to consensus criteria.

## Pramipexole is a non-ergot-derived dopamine agonist

Pramipexole is a dopamine agonist, first developed for treating Parkinson's disease. Although it has been registered in Australia for this indication for some time, it has been marketed only since June 2008. Pramipexole and ropinirole, another non-ergot-derived dopamine agonist, are the first drugs approved by the TGA for restless legs syndrome. Currently only pramipexole is PBS subsidised for restless legs syndrome.

## Pramipexole may be useful for severe restless legs syndrome

If the patient reports significant distress from restless legs syndrome that cannot be managed by non-drug measures (see Suggest non-drug measures), consider drug treatment in the context of a full discussion about the potential symptomatic benefit and possibility of adverse effects.

Australian guidelines recommend a non-ergot-derived dopamine agonist for pharmacotherapy of restless legs syndrome when symptoms are *frequent* (e.g. daily).<sup>3</sup> Indirect and unpublished data, together with experience with other dopamine agonists, suggest that pramipexole is less likely than levodopa preparations to worsen symptoms with long-term use (a phenomenon known as augmentation), but that levodopa preparations are better tolerated.<sup>4,5</sup> Refer to a specialist if initial treatment is not effective.<sup>3</sup>

The safety and efficacy of pramipexole have not been evaluated in children and adolescents under 18 years old.<sup>6</sup> Children and adolescents with restless legs syndrome that cannot be managed by non-drug measures should be assessed by a specialist.

Guidelines recommend levodopa with either carbidopa or benserazide for occasional use in *intermittent* restless legs syndrome<sup>3</sup>, but augmentation limits levodopa's usefulness for treating daily symptoms.

## Diagnose from symptoms and medical history

Patients must meet all 4 diagnostic criteria, assessed on patient report of symptoms (see Box 1). Exclude differential diagnoses, consisting of other conditions that cause discomfort or involuntary movements of the limbs. These include leg cramps, positional discomfort, arthritis, neuropathy, and drug-induced akathisia (e.g. as side effects of antipsychotics, metoclopramide, or antidepressants).<sup>4,7,8</sup>

If there is doubt about the diagnosis, refer to a neurologist with an interest in movement disorders, or a sleep specialist.

Many people with restless legs syndrome also experience periodic limb movements in sleep (PLMS), possibly with associated sleep disturbance. However, periodic limb movements in sleep are not sufficient to diagnose restless legs syndrome and do occur independently of it.<sup>3</sup>

### Box 1: Consensus essential diagnostic criteria for restless legs syndrome<sup>9</sup>

1. An urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs (sometimes the urge to move is present without the uncomfortable sensations and sometimes the arms or other body parts are involved in addition to the legs).
2. The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting.
3. The urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues.
4. The urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night (when symptoms are very severe, the worsening at night may not be noticeable but must have been previously present).

Supportive clinical features:

- Positive family history of restless legs syndrome
- Response to dopaminergic drug treatment
- Periodic limb movements.

### Grade severity with the IRLS Rating Scale

To assess the severity and significance of restless leg symptoms, and to determine eligibility for PBS-subsidised drug treatment, use the International Restless Legs Syndrome Study Group Rating Scale questionnaire. Scores on this scale correlate with the subjective clinical global impression (CGI) ratings of expert examiners (correlation coefficient  $r = 0.74$ ).<sup>10</sup>

The questionnaire consists of 10 items asking the patient to report the severity of the primary symptoms, sleep quality and day-to-day disability. Scores on the scale range from 0–40, with scores of 11–20 designated *moderate*, 21–30 designated *severe*, and 31–40 designated *very severe*.

The questionnaire is freely available for individual clinical practice after completing a user agreement form. The form and questionnaire are available on-line to be printed out and administered by GPs. See [www.mapitrust.org/services/questionnairelicensing/cataloguequestionnaires/65-irls](http://www.mapitrust.org/services/questionnairelicensing/cataloguequestionnaires/65-irls)

### Investigate possible causes of secondary restless legs syndrome

Known reversible causes of restless legs syndrome include iron deficiency, pregnancy and renal failure.<sup>3</sup>

Test serum ferritin concentration. Iron-replacement therapy may benefit individuals with low-normal serum ferritin concentrations. Guidelines suggest a cut-off of 50 micrograms/mL.<sup>8</sup>

### Suggest non-drug measures

Many people manage their restless leg symptoms using a variety of non-drug measures (see Box 2).<sup>4</sup> The efficacy of these measures has not been assessed rigorously, but they are largely low cost and low risk. One small randomised controlled trial found that a 12-week program of regular aerobic exercise and lower-body resistance training significantly improved restless legs syndrome symptoms.<sup>11</sup>

More than a third of patients in clinical trials of pharmacological treatments had a major improvement in restless leg symptoms while receiving placebo.<sup>12</sup>

Discuss sleep hygiene measures if restless leg symptoms are causing insomnia.<sup>3</sup>

### Pramipexole is modestly effective

In one 12-week double-blind trial in people with moderate to severe restless legs syndrome, the treating physicians rated 66% of participants receiving pramipexole as 'much' or 'very much' improved, compared with 40% of participants receiving placebo.<sup>13</sup> Other placebo-controlled trials reported similar results.<sup>14</sup>

While trials consistently found improvements in patient-reported sleep quality, daytime sleepiness was not improved significantly.<sup>13,15,16</sup>

### Effectiveness of pramipexole may decrease over time

In non-comparative trials of up to 9 months, most patients continued to respond to pramipexole.<sup>6</sup> While efficacy did not decrease over periods up to 12 weeks in randomised controlled trials, observations suggest that pramipexole becomes less effective over time.

Meta-regression analysis of short-term trials, as well as an unpublished 46-week non-comparative trial found that symptoms became worse with time during pramipexole treatment.<sup>14,17</sup> Increasing pramipexole doses were recorded in 1 of 2 case series during long-term treatment.<sup>18,19</sup>

### Chronic dopaminergic therapy can cause augmentation of symptoms

Augmentation is a common consequence of chronic use of levodopa in restless legs syndrome, and can also occur with dopamine agonists. Augmentation typically involves daytime symptoms becoming more frequent or intense than they were before treatment began, or shifting to an earlier time in the day.<sup>9</sup>

Refer patients experiencing augmentation to a specialist. Most cases can be reversed with a change in dosing frequency, by lowering the dose, by switching drugs or by stopping dopaminergic therapy.<sup>3</sup>

Controlled trials of pramipexole have been too short to establish how often augmentation occurs or how to manage it.<sup>6</sup> In a retrospective case-series analysis, over an average of 2 years of pramipexole treatment, one-third of patients developed augmentation, on average 9 months after starting treatment.<sup>19</sup>

## Safety issues

The adverse-effect profile of pramipexole is largely a consequence of its activity at dopamine receptors. The frequency of adverse events increases with dose<sup>20</sup> (note that doses are higher in Parkinson's disease than in restless legs syndrome). There was 1 report of hallucinations in clinical trials for restless legs syndrome from a total of 889 people who received pramipexole.<sup>6</sup> Postural hypotension was not significant in trials, but blood pressure monitoring may be required, especially at the start of therapy and in severe cardiovascular disease.<sup>6</sup>

Report suspected adverse reactions to the Therapeutic Goods Administration (TGA) online ([www.ebs.tga.gov.au](http://www.ebs.tga.gov.au) [then click 'Adverse reactions to a Medicine']) or by using the 'Blue Card' distributed with *Australian Prescriber*. For information about reporting adverse reactions, see the TGA website ([www.tga.gov.au](http://www.tga.gov.au)).

### Pramipexole can cause somnolence and sleep attacks

Somnolence was a common drug-related adverse effect in restless legs trials.<sup>6</sup> Sudden onset of sleep during daily activities — in some cases without awareness or warning signs ('sleep attack') — has been reported in people with Parkinson's disease receiving pramipexole<sup>21</sup>, as have a few cases during clinical trials for restless legs syndrome.<sup>6,16,17,22</sup>

### Advise patients not to drive or perform other dangerous tasks until they are used to the effects of pramipexole.

Patients who have a sleep attack should refrain from driving and other dangerous activities until they receive medical advice (see Information for patients). Consider dose reduction or discontinue pramipexole in these cases.<sup>6</sup>

### Pramipexole is not recommended in pregnancy or breastfeeding

There is a lack of clinical data in pregnancy, along with evidence that pramipexole impairs implantation and disrupts early pregnancy in rats (ADEC Category B3).<sup>6</sup> Pramipexole is expected to inhibit lactation because of its effects on prolactin. It may be excreted into breast milk and should not be used during breastfeeding.<sup>6</sup>

### Nausea is very common, especially early in treatment

Among people receiving pramipexole in clinical trials, 16% reported nausea, and 1% discontinued treatment because of it. The symptoms were generally mild and transient.<sup>6</sup> Nausea and fatigue were reported by women more often than men.<sup>23</sup> In one case series, 5% of patients received a prescription for domperidone (Motilium) for nausea.<sup>18</sup>

### Dopamine agonists may cause compulsive behaviours

There have been several reports of pathological gambling by people taking pramipexole for restless legs syndrome.<sup>24,25</sup> The risk may be lower than in Parkinson's disease where higher doses of dopamine agonists are used. Other compulsive behaviours that occur rarely with dopamine agonists prescribed for Parkinson's disease include hypersexuality and binge eating.<sup>26</sup>

Inform patients and carers that there is a small risk but that the consequences can be serious, and to seek medical advice if concerned.<sup>6</sup>

### Theoretical risk of retinal degeneration

Pramipexole caused retinal degeneration in albino rats during preclinical safety testing. Similar tests with pigmented rats found no effect, and assessment of a group of Parkinson's disease patients treated with pramipexole for an average of 4 years found no increased rate of retinal degeneration.<sup>6</sup>

## Dosing issues

For restless legs syndrome, pramipexole is taken as a single daily dose 2–3 hours before bedtime. The starting dose is pramipexole 125 micrograms daily. Increase as required every 4–7 days to a maximum of 750 micrograms daily.<sup>6</sup> Note that even the lowest dose significantly reduces symptoms, and that there is no documented increase in response rate with doses higher than 500 micrograms daily.<sup>15,23</sup>

Lengthen the time between titration steps to 14 days for people with creatinine clearance 20–60 mL/minute.<sup>23</sup>

Assess response to treatment regularly (e.g. after 3 months) to decide if pramipexole should be stopped or the dose adjusted to improve the balance of efficacy

and adverse effects. If initial treatment is not effective, refer to a specialist.<sup>3</sup>

Centrally active dopamine antagonists (i.e. antipsychotics or metoclopramide) diminish the effect of pramipexole. These drugs should not be used with pramipexole.<sup>6</sup>

Some renally excreted drugs may interact with pramipexole, with reduced clearance of either or both drugs. This group consists of drugs that inhibit the active renal tubular secretion of basic (cationic) drugs and drugs that are eliminated by this pathway, and includes amantadine, cimetidine, digoxin, diltiazem, quinine, ranitidine, triamterene, trimethoprim, and verapamil. Consider dose reductions when administering these drugs with pramipexole, and observe for signs of dopamine overstimulation, such as dyskinesias, agitation or hallucinations.<sup>6</sup>

At the usual doses for restless legs syndrome, pramipexole can be stopped without tapering. However, some patients in clinical trials experienced a worsening of symptoms after stopping pramipexole abruptly. Most cases of worsening resolved within a week.<sup>6</sup>

## Information for patients

Advise patients:

- that pramipexole may cause sudden attacks of sleepiness in some people
- if they have a sleep attack at any time to refrain from driving and contact a doctor
- that pramipexole could make them more susceptible to compulsive behaviours

- to take the tablets with water, with or without food, 2–3 hours before bedtime
- that nausea and sleepiness are common side effects, but these may decrease with time
- not to drive or perform dangerous tasks requiring constant attention until accustomed to the side effects
- that sedatives or alcohol may worsen any drowsiness
- to contact their doctor if their symptoms worsen.<sup>27</sup>

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

### Discuss non-drug approaches to managing restless leg symptoms

See Box 2 for examples. Patient support groups such as Restless Legs Syndrome Australia can offer advice and support, including suggestions for useful coping strategies and non-drug measures. See [www.rls.org.au](http://www.rls.org.au) for details.

#### Box 2. Commonly used low-risk measures to manage restless leg symptoms<sup>9,28</sup>

- Very hot or very cold baths
- Physical activity, particularly involving the limbs, just before bedtime (excessive exercise may increase symptoms)
- Stretching
- Massage
- Relaxation techniques (e.g. biofeedback, meditation, or yoga)
- Engrossing mental activity (e.g. reading, doing needlework, or playing video games)

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