Translated from ***Rev Prescrire*** **November 2006; 26 (277): 731**

pramipexole

New Indication

Restless legs: still no satisfactory drug treatment

● **Negative risk-benefit balance (as with ropinirole).**



Restless legs syndrome consists of generally harmless but unpleasant sensory and motor symptoms affecting the lower limbs. They appear at rest, when a person is sitting or lying down. The symptoms are more intense in the evening and at night, and are relieved by moving the affected limb. A small minority of patients find these symptoms especially disturbing, mainly because their sleep is disturbed. Restless legs syndrome does not lead to any physical complications (1).

Various drug and non drug treatments have been tried but none has shown any substantial efficacy in the few available comparative trials (1).

Ropinirole, a dopamine receptor agonist, was the first drug to be approved for this syndrome in France (2). However, it is only marginally beneficial and can lead to potentially severe adverse effects (2). Furthermore, as with levodopa, long-term ropinirole therapy can aggravate restless legs syndrome.

Pramipexole (Sifrol°, Boehringer Ingelheim), a dopamine agonist used for Parkinson's disease, is now approved in the EU for the treatment of the restless legs syndrome.

Limited initial efficacy. The main placebo-controlled randomised controlled trial of pramipexole included 345 patients who were treated for 12 weeks (3,4).

On the basis of a specific rating scale developed for restless legs syndrome, the International RLS study group rating scale (IRLS), the number of "responders" was significantly higher with pramipexole than with placebo (about 62% versus 42%).

The number of "responders" on the global clinical impression scale (CGI-I) was about 72% with pramipexole and 51% with the placebo. These rates were similar to those obtained in clinical trials of ropinirole (2).

Gradual aggravation with time. Two non comparative prospective follow-up studies and two retrospective analyses of several dozen patients showed that, during the first year of treatment, the symptoms of up to one-third of patients became worse (5-9). In one analysis, around half of the patients taking pramipexole had increased the dose (double the initial dose on average) (9).

The marketing authorisation committee (CHMP) of the European Medicines Agency (EMEA) discussed this gradual reduction in efficacy, and concluded that the efficacy of pramipexole beyond three months had not been demonstrated (4). The CHMP asked the company to conduct a placebo-controlled trial lasting 6 months. (The CHMP had already asked for at least one trial lasting a minimum of 6 months, before the manufacturer submitted the initial application for market approval. The manufacturer had refused, claiming that there would be too many treatment withdrawals in the placebo group).

Classic adverse effects observed with dopamine agonists were reported in the observational studies discussed above, including nausea, headache, insomnia (potentially compounding sleep disturbances caused by restless legs syndrome), daytime drowsiness, and dizziness. Several patients found that they fell asleep suddenly and abruptly (3).

In practice. It is better to avoid treating patients with restless legs syndrome with pramipexole (or with ropinirole). It's better to wait until a satisfactory treatment is available.

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SIFROL°
Tablets

- **0.18 mg** or **0.70 mg** of pramipexole per tablet

■ **New indication:** *"Symptomatic treatment of moderate to severe idiopathic restless legs syndrome."* [EU marketing authorisation, centralised procedure]

dopamine agonist

Selected references from Prescrire's literature search.

In response to our request for information, Boehringer Ingelheim sent us some basic administrative documents and published data.

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3- Winkelman JW et al. "Efficacy and safety of pramipexole in restless legs syndrome" *Neurology* 2006; 67: 6 pages.
4- European Medicines Agency - CHMP "European Public Assessment Report - Scientific discussion - Sifrol": 29 pages; posted on the EMEA website on 14 September 2006.
5- Trenkwalder C et al. "Sustained efficacy of pramipexole in restless legs syndrome" *Sleep Med* 2005; 6 (suppl. 2): S73.
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8- Silber MH et al. "Pramipexole in the management of restless legs syndrome: an extended study" *Sleep* 2003; **26** (7): 819-821.
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