



INFORMATION SHEET

Mirapexin[®]/Sifrol[®] Prolonged-Release
(once daily formulation)

FOR NON-US HEALTHCARE MEDIA ONLY

KEY SUMMARY

1. Mirapexin[®]/Sifrol[®] (pramipexole) is a selective non-ergot dopamine agonist approved as immediate release formulation since 1997 for the treatment of the signs and symptoms of idiopathic Parkinson's disease (PD), as monotherapy (without levodopa) or in combination with levodopa.¹ In June 2009, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) issued a positive opinion recommending the approval of a once daily Mirapexin[®]/Sifrol[®] prolonged-release tablet for the treatment of PD in all EU/EEA countries.*
2. Mirapexin[®]/Sifrol[®] immediate release is worldwide to date the most prescribed dopamine agonist for the treatment of PD, with over five million patient-years exposure. Its immediate release formulation is also approved for the symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome.^{1,**}
3. Studies have shown that the Mirapexin[®]/Sifrol[®] prolonged-release formulation combines the trusted clinical benefits of Mirapexin[®]/Sifrol[®] immediate release with the convenience of a single daily dose.²⁻⁵

* All 27 Member States of the European Union plus Norway and Iceland

** Mirapexin[®]/Sifrol[®] is currently registered as immediate release formulation only

About the Mirapexin[®]/Sifrol[®] prolonged-release formulation

- The positive recommendation issued by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) was based on the results of clinical trials in early and advanced PD patients, which have shown favourable safety, efficacy and tolerability results comparable to those of the long-established immediate release formulation.²⁻⁵ A new drug application (NDA) for a once daily, extended release formulation of Mirapex[®] is also in review with the U.S. Food and Drug Administration (FDA) for the treatment of Parkinson's disease (currently available worldwide as immediate release formulation only).
- In addition to the proven efficacy on the core symptoms in early and advanced Parkinson's disease,¹ once approved the Mirapexin[®]/Sifrol[®] once daily tablet can provide added convenience for patients and their care givers with a once daily dosing.²⁻⁵ Although not specifically studied in Mirapexin[®]/Sifrol[®]

prolonged-release trials, it has been shown that adherence to PD treatment is a challenge and that once daily dosing may help improve patient compliance.⁶

- It has been shown that patients already taking Mirapexin[®]/Sifrol[®] immediate release tablets may be switched overnight to the Mirapexin[®]/Sifrol[®] prolonged-release formulation, at the same daily dose.⁷ After switching to the once daily Mirapexin[®]/Sifrol[®], the dose may be adjusted depending on the patient's therapeutic response.
- The once daily administration of Mirapexin[®]/Sifrol[®] prolonged-release formulation has been shown to cause less frequent fluctuations in the pramipexole plasma concentration over 24 hours compared to the Mirapexin[®]/Sifrol[®] immediate release formulation.⁸
- As with the Mirapexin[®]/Sifrol[®] immediate release formulation, the prolonged-release, once daily regimen will permit flexible dosing and titration.¹

Clinical evidence – Mirapexin[®]/Sifrol[®] prolonged-release formulation

Mirapexin[®]/Sifrol[®] prolonged-release in early Parkinson's disease^{2,3,5}

- **Trial design:** Randomised, double-blind trial comparing the efficacy, safety and tolerability of Mirapexin[®]/Sifrol[®] (pramipexole) prolonged-release and immediate release formulations versus placebo, after 33 weeks of treatment, in patients with early PD.⁵
- **Results:** A confirmatory statistical analysis conducted at week 18 demonstrated that the Mirapexin[®]/Sifrol[®] prolonged-release formulation was superior to placebo. A total of 253 patients were included in this analysis. In these patients, the adjusted mean change in the UPDRS II+III score from baseline to week 18 was –5.1 points in the placebo group, –8.1 points in the Mirapexin[®]/Sifrol[®] prolonged-release group (p=0.0282 vs. placebo), and –8.4 points in Mirapexin[®]/Sifrol[®] immediate release group (p=0.0153 vs. placebo).²

A descriptive statistical analysis showed maintenance of efficacy after 33 weeks of treatment compared to 18 weeks of treatment in both Mirapexin[®]/Sifrol[®] groups, while placebo patients worsened from week 18 to week 33.³

Non-inferiority between Mirapexin[®]/Sifrol[®] prolonged-release and immediate release was assessed at week 33. A total of 420 patients were included in this analysis. The adjusted mean change in the UPDRS II+III score from baseline to week 33 were –8.6 points in the Mirapexin[®]/Sifrol[®] prolonged-release group (n = 213) and –8.8 points in the Mirapexin[®]/Sifrol[®] immediate-release group (n = 207), a between-group difference of –0.2 points, 95% CI=[–2.2; 1.7]. The lower bound of the 95% CI (–2.2 points) was higher than the pre-defined non-inferiority margin of –3 points, demonstrating non-inferiority between Mirapexin[®]/Sifrol[®] prolonged-release and Mirapexin[®]/Sifrol[®] immediate release at week 33.⁵

Note:

The Unified Parkinson's Disease Rating Scale (UPDRS) is a comprehensive tool, which was developed to follow the longitudinal course of PD-related disability and impairment. The UPDRS II+III score was used as the primary efficacy endpoint in both trials. UPDRS Part II relates to activities of daily living and UPDRS Part III relates to motor symptoms. The UPDRS II+III score ranges from 0 (no disability) to 160 (worst disability).

Mirapexin[®]/Sifrol[®] prolonged-release in advanced Parkinson's disease⁴

- **Trial design:** Randomised, placebo-controlled, double-blind trial comparing Mirapexin[®]/Sifrol[®] (pramipexole) prolonged-release and immediate release formulations versus placebo, as adjunctive therapy to levodopa, after 18 weeks of treatment, in patients with advanced PD.
- **Results:** The results of the study in the 507 advanced PD patients confirmed at 18 weeks the high therapeutic benefit of Mirapexin[®]/Sifrol[®] prolonged-release, demonstrating results comparable to pramipexole's already long-established immediate release formulation.

In these patients, the adjusted mean change in UPDRS II+III score from baseline to week 18 was -6.1 points for placebo, -11.0 points for prolonged-release (p=0.0001 vs. placebo) and -12.8 points for immediate release (p<0.0001 vs. placebo).

The adjusted mean change in percentage off-time (known as a period of dramatically reduced motor functioning at the end of the dosing interval) was -8.8 points for placebo, -13.3 points for Mirapexin[®]/Sifrol[®] prolonged-release (corresponding to an improvement of -2.1 hours from baseline; p=0.0122 vs. placebo) and -15.9 for immediate release (corresponding to an improvement of -2.5 hours from baseline; p<0.0001 vs. placebo).

A descriptive statistical analysis showed maintenance of efficacy after 33 weeks of treatment compared to 18 weeks of treatment in both pramipexole groups.

Adverse event rates were similar for Mirapexin[®]/Sifrol[®] prolonged-release (54.9%) compared to placebo (55.6%) and numerically lower than Mirapexin[®]/Sifrol[®] immediate release (64.0%).

Switch from the Mirapexin[®]/Sifrol[®] immediate release to the once daily prolonged-release formulation⁷

- **Trial design:** Randomised, double-blind, parallel-group study conducted in 156 patients with early PD on stable dose of Mirapexin[®]/Sifrol[®] (pramipexole) immediate release. This 9-week study assessed the efficacy and safety of an overnight switch from Mirapexin[®]/Sifrol[®] immediate release to a Mirapexin[®]/Sifrol[®] prolonged-release formulation, at the same daily dose. Patients were randomised overnight to the Mirapexin[®]/Sifrol[®] once daily, prolonged-release or to the Mirapexin[®]/Sifrol[®] immediate release formulation (2:1 ratio). Primary efficacy endpoint was the proportion of patients successfully switched (no worsening of UPDRS II+III >15% from baseline and no drug-related adverse event leading to withdrawal).
- **Results:** 95.5% of patients completed the trial. 87 of 103 (84.5%) were successfully switched (with or without dose adaptation) to the once daily formulation; 72 of these 87 patients (82.8%) were successfully switched without dose adaptation. These data support a 1:1 switch from Mirapexin[®]/Sifrol[®] immediate release to Mirapexin[®]/Sifrol[®] prolonged-release.⁷

As every PD patient will have a different range of symptoms or requirements, the formulation will enable greater opportunity for tailored treatment to suit the individual needs of the patient and physician. Once approved, the once daily Mirapexin[®]/Sifrol[®] prolonged-release formulation can provide enhanced convenience for many Parkinson's patients while continuing to deliver the benefits of the long established three times daily formulation currently used by millions of patients worldwide.

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