



INFORMATION SHEET

Pramipexole (Mirapexin[®]/Sifrol[®])
in Parkinson's Disease

FOR NON-US HEALTHCARE MEDIA ONLY

KEY SUMMARY

1. Mirapexin[®]/Sifrol[®] (pramipexole*) is a selective non-ergot dopamine agonist approved as immediate release 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 It is worldwide to date the most prescribed dopamine agonist for the treatment of PD, with over five million patient-years exposure.
2. Mirapexin[®]/Sifrol[®] has been shown to significantly improve motor symptoms in both early and advanced PD, including tremor in patients with treatment-resistant tremor.²
3. While emerging data in trials with pramipexole immediate release suggested that Mirapexin[®]/Sifrol[®] has a positive effect on depressive symptoms associated with PD,³⁻¹² results from an international, placebo-controlled trial conducted by Barone *et al*,¹³ demonstrate that Mirapexin[®]/Sifrol[®] can also improve PD-related depressive symptoms, a common, disabling non-motor symptom of PD, in addition to its established efficacy in treating the motor symptoms of Parkinson's disease.
4. 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 formulation for Mirapexin[®] / Sifrol[®].**

* See below for further trade names

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

Mirapexin[®]/Sifrol[®] (pramipexole): What it is and how it works

What is Mirapexin[®]/Sifrol[®] (pramipexole)?

- Pramipexole (known under the trade names Mirapexin[®], Sifrol[®], Mirapex[®] and Pexola[®]) is a compound from Boehringer Ingelheim research, first approved as immediate release formulation in 1997 for the treatment of the signs and symptoms of idiopathic Parkinson's disease (PD), as monotherapy or in

combination with levodopa. It is currently worldwide the most prescribed dopamine agonist for the treatment of PD.¹

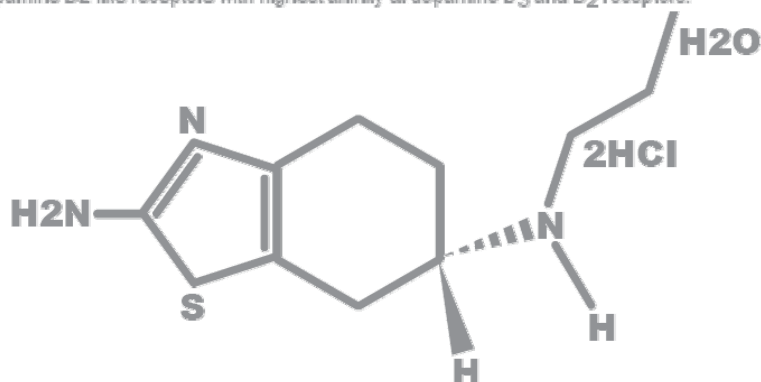
- Mirapexin[®]/Sifrol[®] immediate release is also approved for the symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome.¹

Mirapexin[®]/Sifrol[®] mechanism of action

- Mirapexin[®]/Sifrol[®] is a non-ergot dopamine agonist and differs from ergot dopamine agonists by virtue of its chemical structure and its receptor selectivity. Whereas studies have suggested that ergot-derived dopamine agonists can cause fibrotic reactions at the heart valve, no increased risk with the non-ergot dopamine agonists such as pramipexole has been seen.¹⁴
- It has been suggested that the affinity of pramipexole for D₃ might be responsible for the antidepressant properties of this compound.¹⁵

Pramipexole

Pramipexole is a full dopamine receptor agonist with a high affinity for the dopamine D₂-like receptors with highest affinity at dopamine D₃ and D₂ receptors.



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Physiology, method of administration and pharmacokinetic properties

- Mirapexin[®]/Sifrol[®] permits flexible dosing and titration.¹
- The bioavailability of Mirapexin[®]/Sifrol[®] is greater than 90% with a long elimination half-life of 8-12 hours. Mirapexin[®]/Sifrol[®] can be administered without regard to food intake.¹
- Mirapexin[®]/Sifrol[®] is the only non-ergot dopamine agonist not appreciably metabolised by the P450 system.¹⁶ (Drugs metabolised by this hepatic enzyme system can be subject to potentially dangerous hepatic drug-drug interactions when taken concomitantly with other drugs that inhibit or induce the activity of the P450 enzymes). This minimises concerns about possible drug-drug interactions which is of particular importance as PD predominantly affects the elderly generation who are often prescribed multiple medications, e.g. up to 66% of PD patients suffer from concomitant hypertension and approximately 30% from diabetes and might therefore need to take additional medications.¹⁷

Mirapexin[®]/Sifrol[®]: The evidence base

The efficacy and tolerability of Mirapexin[®]/Sifrol[®]

- Mirapexin[®]/Sifrol[®] has been shown to significantly improve tremor in patients with treatment-resistant tremor.² In clinical studies, Mirapexin[®]/Sifrol[®] has also been shown to successfully manage the symptoms of PD in the longer term beyond four years.^{2,18}
- In addition, Mirapexin[®]/Sifrol[®] can prevent and control motor complications such as dyskinesia (involuntary jerking movements) related to levodopa, by delaying the need for levodopa and reducing levodopa dosage when combined with pramipexole.^{18,19}

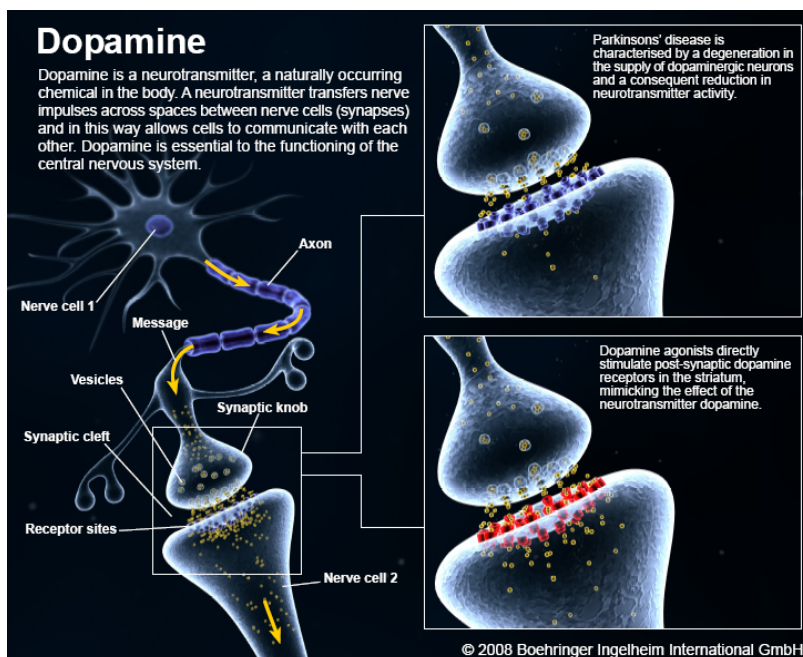
- As an adjunct to levodopa, Mirapexin[®]/Sifrol[®] enables patients to lead more active lives by reducing 'off' time and improving motor function during 'on' and 'off' times.^{18,20} Periods of improved motor functioning are referred to as the 'on' state and periods of reduced mobility, at the end of the dosing interval, as the 'off' state.

Mirapexin[®]/Sifrol[®] in the early stages of Parkinson's disease

- Results from a long-term clinical trial with Mirapexin[®]/Sifrol[®] - CALM-PD - have shown that initial treatment with Mirapexin[®]/Sifrol[®] in the early stages of the disease can significantly delay motor complications as compared to levodopa.^{18,21} These results played a pivotal role in recent guidelines by the American Academy of Neurology which support the advantages of starting treatment with a dopamine agonist.²²
- In the CALM-PD trial, 301 patients were randomised to double-blind therapy with Mirapexin[®]/Sifrol[®] or levodopa; adjuvant therapy was allowed as rescue if necessary. After four years it was observed that initial treatment with Mirapexin[®]/Sifrol[®] reduced the risk of developing dyskinesias (involuntary jerking movements, themselves very disabling) by more than 50% versus initial treatment with levodopa.^{18,21,23} A further analysis of the CALM-PD study has confirmed the potential benefits of treatment with Mirapexin[®]/Sifrol[®], particularly in younger adult PD patients, where the lower incidences of dyskinesias and wearing off compared to levodopa are an advantage in the early stages of the disease. The study also highlights that PD patients need an individualised, tailored treatment approach that takes into account the disease stage, co-morbidities (e.g. depressive symptoms) and co-medication (e.g. their metabolism).²⁴

Research into clinical benefits of early versus delayed Mirapexin[®]/Sifrol[®] treatment

- Although there is significant ongoing research in this area, at present there are no therapies that have clearly been demonstrated to have a neuroprotective effect by preventing further dopaminergic cell death, thus slowing or postponing PD progression.
- Important data from the CALM-PD study using single-photon emission computed tomography (SPECT) show that patients receiving pramipexole demonstrated a significantly slower rate of decline in dopaminergic functioning than patients who received initial treatment with levodopa.²⁵ This is of particular significance in view of the fact that patients are believed to have already lost an estimated 50 to 80% of dopaminergic neuronal functioning before symptoms or abnormal signs of functioning are detected.²⁶⁻³²



- These CALM-PD findings have been further substantiated by the INSPECT study (**I**nvestigating the effect of short-term treatment with pramipexole or levodopa on [¹²³I]β-CIT and **S**PECT imaging). Initial results from this study show that neither levodopa nor Mirapexin[®]/Sifrol[®] had a short-term effect on the pharmacological mechanisms that regulate dopamine transporters (DAT)³³ which are the markers used in single-photon emission computed tomography (SPECT) imaging. This imaging method was used for

the CALM-PD study. By ruling out short-term interference of levodopa and Mirapexin[®]/Sifrol[®] with DATs, the INSPECT study strengthened the earlier findings of the CALM-PD study.

- While previous studies with Mirapexin[®]/Sifrol[®], such as the CALM-PD study^{25,33} and *in vitro* studies, have suggested potential clinical benefits of early treatment, the PROUD (Assessment of Potential ImPact of PRamipexole On Underlying Disease)³⁴ study presents a further approach to investigating the potential clinical benefits of early treatment of patients with PD by comparing imaging and clinical endpoints of PD progression, a key focus of current research. The PROUD study is the first to combine measurements of clinical outcomes in a PD patient with measurements of dopamine transporter density of certain brain areas (basal ganglia), through a SPECT imaging arm of the study.

Effect of Mirapexin[®]/Sifrol[®] in the treatment of depressive symptoms of PD

- Results from the PRODEST (**PRO**file of **DE**pressive **SympT**oms in Parkinson's Disease) study shown that up to 40% of the studied PD patients continued to experience depressive symptoms in spite of receiving an antidepressant treatment. This implies that the depressive symptoms in PD may be distinct from what is known as a depressive syndrome, suggesting the need for a different approach in treating depressive symptoms in PD.³⁵
- While emerging data had suggested that Mirapexin[®]/Sifrol[®] may have a positive effect on depressive symptoms associated with PD,³⁻¹² this has recently been demonstrated for the first time in a large-scale, prospective, randomised, double-blind, placebo-controlled trial.¹³ The results also confirm the findings from an earlier clinical study where Mirapexin[®]/Sifrol[®] had shown an antidepressive effect comparable to that of an SSRI (selective serotonin reuptake inhibitor) when treating PD-related depressive symptoms,³⁶ and support data from other trials which suggested that Mirapexin[®]/Sifrol[®] may have a positive effect on depressive symptoms and motivation associated with PD.³⁻¹²

Mirapexin[®]/Sifrol[®] product information

- For full information on the product profile, please refer to the country-specific summary of product characteristics / patient information leaflet.

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