INFORMATION SHEET

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

Boehringer Ingelheim

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 (EMEA) 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

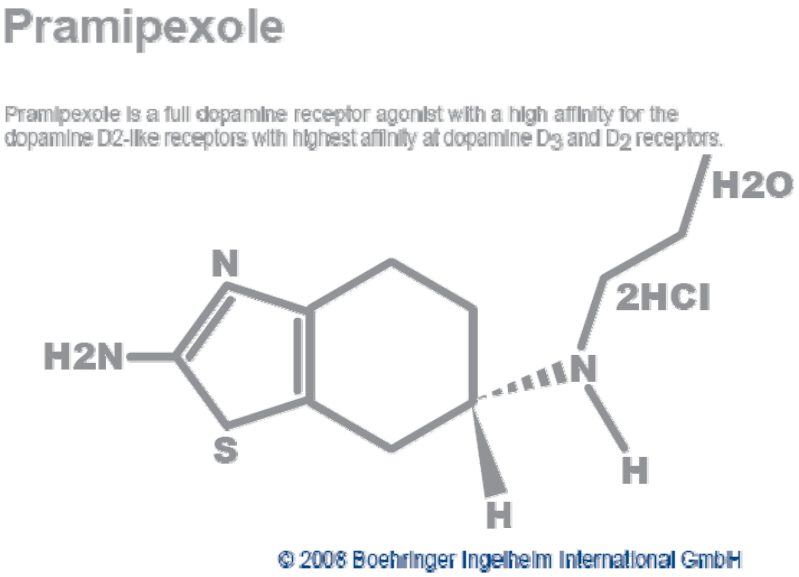
combination with levodopa. It is currently worldwide the most prescribed dopamine agonist for the treatment of PD.[1]

- 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 D_3 might be responsible for the antidepressant properties of this compound.[15]



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

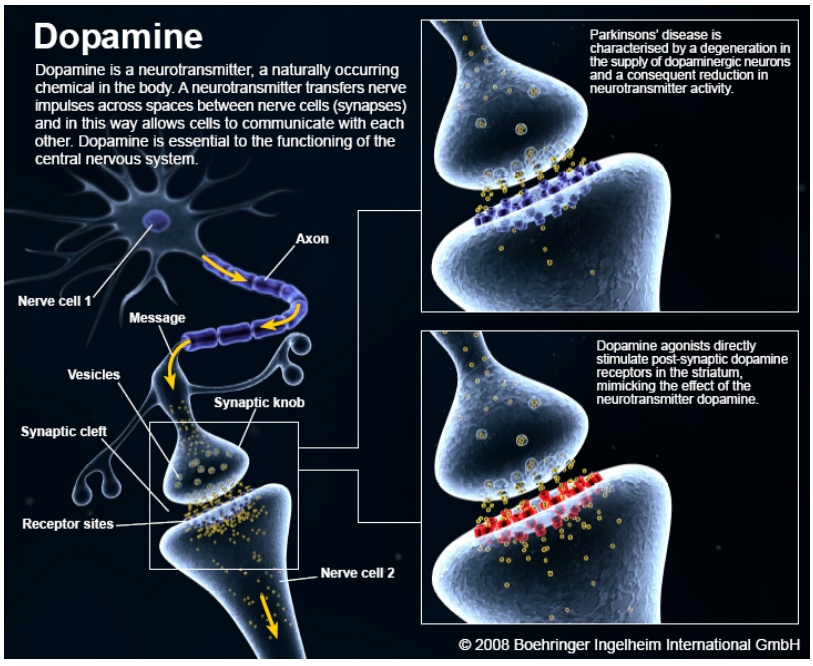
- Results from a long-term clinical trial with Mirapexin®/Sifrol® - CALM-PD - have shown that initial treatment with Mirapexin®/Sifrol® in the early stages of the disease can significantly delay motor complications as compared to levodopa.[18,21] These results played a pivotal role in recent guidelines 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 (**IN**vestigating the effect of short-term treatment with pramipexole or levodopa on [123I]β-CIT and **SPECT** 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 Im**P**act of P**R**amipexole **O**n **U**nderlying **D**isease)[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 **S**ymp**T**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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References

1. Mirapexin European SPC. Annex I: Summary of product characteristics. URL: http://www.emea.europa.eu/humandocs/PDFs/EPAR/Mirapexin/H-134-PI-en.pdf. Date accessed September 2009.
2. Pogarell O *et al*. Pramipexole in patients with Parkinson's disease and marked drug resistant tremor: a randomised, double blind, placebo controlled multicentre study. *J Neurol Neurosurg Psychiatry* 2002; 72(6): 713-720.
3. Möller JC *et al.* Long-term efficacy and safety of pramipexole in advanced Parkinson's disease: Results from a European multicenter trial. *Mov Disord* 2005 May; 20(5):602-10.
4. Rektorova I *et al*. Pramipexole and pergolide in the treatment of depression in Parkinson's disease: a national multicentre prospective randomized study. *Eur J Neurol* 2003; 10(4): 399-406.
5. Reichmann H *et al*. Pramipexole in routine clinical practice. *CNS Drugs* 2003; 17(13): 965-973.
6. Lemke MR *et al*. Depression and Parkinson's disease. *J Neurol* 2004 Sep;251 Suppl 6:VI/24-7.
7. Lemke MR *et al*. Anhedonia, depression, and motor functioning in Parkinson's disease during treatment with pramipexole. *J Neuropsychiatry Clin Neurosci* 2005 Spring; 17(2): 214-20.
8. Rektorova I *et al*. Cognitive performance in people with Parkinson's disease and mild or moderate depression: effects of dopamine agonists in an add-on to L-dopa therapy. *Eur J Neurol* 2005; 12: 9-15.

9. Goldberg JF *et al*. Preliminary randomized, double-blind, placebo-controlled trial of pramipexole added to mood stabilizers for treatment-resistant bipolar depression. *Am J Psychiatry* 2004 Mar;161(3): 564-6.
10. Lemke MR. Depressive symptoms in Parkinson's disease. *Eur J Neurol* 2008 Apr; 15 Suppl 1:21-5.
11. Künig G *et al*. Pramipexole, a nonergot dopamine agonist, is effective against rest tremor in intermediate to advanced Parkinson's disease. *Clin Neuropharm* 1999; 22: 301-305.
12. Leentjens A *et al*. The effect of pramipexole on mood and motivational symptoms in Parkinson's disease: a meta-analysis of placebo-controlled studies. *Clin Ther.* 2009 Jan;31(1):89-98.
13. Barone P *et al.* Pramipexole ameliorates depression in Parkinson's disease: A randomized double-blind vs placebo trial. Abstract S43.004 presented at AAN 61st Annual Meeting, Seattle, USA, 30 April 2009.
14. Andersohn F *et al*. Cardiac and noncardiac fibrotic reactions caused by ergot- and nonergot-derived dopamine agonists.
15. Maj J *et al*. The effect of repeated treatment with pramipexole on the central dopamine D_3 system. *J Neural Trans* 2000; 107(12): 1369-1379.
16. Wynalda MA *et al*. Assessment of potential interactions between dopamine receptor agonists and various human cytochrome P450 enzymes using a simple *in vitro* inhibition screen. *Drug Metab Dispos* 1997; 25(10): 1211-1214.
17. Pressley JC *et al.* The impact of comorbid disease and injuries on resource use and expenditures in parkinsonism. *Neurology* 2003; 60; 87-93.
18. Parkinson Study Group, Holloway RG *et al.* Pramipexole vs levodopa as initial treatment for Parkinson's disease. *Arch Neurol* 2004; 61(7): 1044-1053.
19. Clarke CE *et al*. Pramipexole for levodopa-induced complications in Parkinson's disease (Review). *Cochrane Database of Systematic Reviews* 2006; 3: 1-19.
20. Poewe W *et al.* Efficacy of pramipexole and transdermal rotigotine in advanced Parkinson's disease: a double-blind, double-dummy, randomised controlled trial. *Lancet Neurol* 2007; 6(6):513-20.
21. Parkinson Study Group. Pramipexole vs levodopa as initial treatment for Parkinson disease: A randomized controlled trial. *JAMA* 2000: 284:1931-38.
22. Miyasaki JM *et al*. Practice parameter: Initiation of treatment for Parkinson's disease: An evidence-based review. *Neurology* 2002; 58; 11-17.
23. Corbin A *et al*. Maintained pramipexole monotherapy treatment results in significantly lower dyskinesia rates in early Parkinson's disease: A result of the CALM-PD study after 4 years. Poster Presentation P-04 / 2.231 11 December 2007 XVII WFN World Congress of Parkinson's Disease and Related Disorders.
24. Parkinson Study Group CALM Cohort Investigators. Long-term effect of initiating pramipexole vs levodopa in early Parkinson disease. *Arch Neurol* 2009;66(5): 563-570.
25. Parkinson Study Group. Dopamine transporter brain imaging to assess the effects of pramipexole vs levodopa on Parkinson disease progression. *JAMA* 2002; 287(13): 1653-1661.
26. Hirsch E *et al*. Melanised dopaminergic neurons are differentially susceptible to degeneration in Parkinson's disease, *Nature* 1988; 334: 345–348.
27. Lang AE, Obeso JA. Challenges in Parkinson's disease: restoration of the nigrostriatal dopamine system is not enough. *Lancet Neurol* 2004; 3: 309-316.
28. Braak H *et al*. Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging* 2003; 24: 197-211.
29. Braak H *et al.* Stages in the development of Parkinson's disease related pathology. *Cell Tissue Res* 2004; 318: 121-134.
30. Hornykiewicz O, Kish SJ. Biochemical pathophysiology of Parkinson's disease. *Adv Neurol* 1987; 45: 19-34.
31. Riederer P, Wuketich S. Time course of nigrostriatal degeneration in Parkinson's disease. A detailed study of influential factors in human brain amine analysis. *J Neural Transm* 1976; 38, 277-301.
32. Koller WC. When does Parkinson's disease begin? *Neurology* 1992; 42(Suppl 4): 27-31.
33. Jennings DL, Tabamo RT, Seibyl JS, Marek KM. InSPECT: Investigating the effect of short-term treatment with pramipexole or levodopa on [^{123}I]ß-CIT and SPECT imaging. Abstract 465 at 11th International Congress of Parkinson's Disease and Movement Disorders, Istanbul 2007.
34. Schapira A *et al*. PROUD: The impact of early vs. delayed treatment with pramipexole on new onset Parkinson's disease. Poster P1366 presented at the 12th Congress of the European Federation of Neurological Sciences, Madrid, Spain, 24 August 2008.
35. Barone P *et al*. Depression and antidepressant use in Parkinson's disease: Results from the PRODEST-PD study. Poster P1122 presented at 11th Congress of EFNS, Brussels, 26 Aug 2007.
36. Barone P *et al*. Pramipexole versus sertraline in the treatment of depression in Parkinson's disease: a national multicenter parallel-group randomized study. *J Neurol* 2006; 253(5): 601-7.