PART VI SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR SIFROL/MIRAPEXIN (PRAMIPEXOLE)

This is a summary of the risk management plan (RMP) for Sifrol/Mirapexin. The RMP details important risks of pramipexole, how these risks are minimised, and how more information will be obtained about Sifrol/Mirapexin's risks and uncertainties (missing information).

Sifrol/Mirapexin's Summary of Product Characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Sifrol/Mirapexin should be used.

This summary of the RMP for Sifrol/Mirapexin should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Sifrol/Mirapexin’s RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Sifrol/Mirapexin tablets, including prolonged release tablets are authorised in adults for the treatment of signs and symptoms of idiopathic Parkinson’s disease (PD), alone (without levodopa) or in combination with levodopa, i.e. over the course of the disease, through to late stages when the effect of levodopa wears off or becomes inconsistent and fluctuations of the therapeutic effect occur (end of dose or “on/off” fluctuations). Sifrol/Mirapexin tablets are indicated in adults for symptomatic treatment of moderate to severe idiopathic Restless legs syndrome (RLS) (see SmPC for the full indication). It contains pramipexole as the active substance and it is given by oral administration.

Further information about the evaluation of Sifrol/Mirapexin’s benefits can be found in Sifrol/Mirapexin’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage.

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of Sifrol/Mirapexin, together with measures to minimise such risks and the proposed studies for learning more about Sifrol/Mirapexin’s risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed including Periodic Benefit-Risk Evaluation Report assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A List of important risks and missing information

Important risks of Sifrol/Mirapexin are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Sifrol/Mirapexin. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Important identified risks	• Impulse control disorders (ICDs) such as compulsive shopping, pathological gambling, hypersexuality, binge eating and other impulse control behaviour • Hallucinations and confusion • Cardiac failure • Dopamine agonist withdrawal syndrome (DAWS)
Important potential risks	• Dystonia (such as antecollis, camptocormia, pleurothotonus)
Missing information	• None

List of important risks and missing information

II.B Summary of important risks

Important identified risk: Impulse control disorders such as compulsive shopping, pathological gambling, hypersexuality, binge eating and other impulse control behaviour	
Evidence for linking the risk to the medicine	ICDs are considered a class effect of dopamine agonists including pramipexole. However, non-pharmacological risk factors have also been identified for the patient population. The incidence figures reported in published literature to date vary widely, seemingly dependent on individual study methodology and differing populations assessed. In addition, country specific and cultural differences in the frequencies and reporting of ICDs are likely. Controlled prospective studies are lacking. General occurrence of ICDs in pramipexole placebo-controlled trials across both indications was low. Based on clinical and post authorisation data, ICDs, such as binge eating, compulsive shopping, pathological gambling, hypersexuality and other abnormal behaviour were defined as an important identified risk for pramipexole.

II.B Summary of important risks (cont'd)

Important identified risk: Impulse control disorders such as compulsive shopping, pathological gambling, hypersexuality, binge eating and other impulse control behaviour (cont'd)	
Risk factors and risk groups	ICDs have been observed more commonly in patients treated with a dopamine agonist than in patients not taking a dopamine agonist (17.1% vs. 6.9%; odds ratio [OR]=2.72; 95% confidence interval [CI]: 2.08, 3.54; P<0.001). ICD frequency was similar for pramipexole and ropinirole (17.7% vs. 15.5%; OR=1.22; 95% CI: 0.94, 1.57; P=0.14). Although dopamine replacement therapy is reported to be the main risk factor for the occurrence of ICDs in PD patients, non-pharmacological risk factors for ICDs have also been identified in that population, such as early age at disease onset, male gender, personal or family history of alcohol abuse or pathological gambling, novelty seeking personality, and cognitive or psychiatric disorders. ICDs have also been reported in RLS patients. Some studies have reported that even untreated patients with RLS had preferences toward 'risky choices' in the Iowa Gambling Task), which could lead to the development of impulse control disorders. Thus, ICDs in idiopathic RLS may be due to not only dopaminergic treatment but also to a specific predisposition profile associated with the disorder. Furthermore, PD patients with RLS reported significantly more ICDs than those without RLS (50% vs. 26%, P=0.03), especially compulsive eating disorders, and a different psycho-behavioural profile with more hyperdopaminergic behaviour, and therefore it has been postulated that RLS per se could be a risk factor for impulsive behaviour in PD.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 and 4.8. Package Leaflet (PL) section 2 and 4. Prescription-only medicine. Additional risk minimisation measures: None.
Important identified risk: Hallucinations and confusion	
Evidence for linking the risk to the medicine	Hallucinations and confusion are recognised side effects of dopamine agonist therapy and are included in the SmPCs. In placebo-controlled trials across both indications, 6.78% pramipexole-treated patients reported hallucination and confusion vs. 3.37% in the placebo group.
Risk factors and risk groups	A facilitating role of treatment on PD-associated psychosis is demonstrated at least for dopaminergic agonists, but there is no simple dose-effect relationship between dopaminergic treatment, and the presence or severity of hallucinations. The main endogenous non-modifiable risk factor is cognitive impairment. Other associated factors include older age/longer duration of PD, disease severity, altered dream phenomena, daytime somnolence, and possibly depression and dysautonomia. In a 12-year follow-up study on 230 PD patients from Norway, the independent risk factors for new-onset PD-associated psychosis were higher levodopa-equivalent dose at baseline (OR=1.26 per 100 mg; 95% CI: 1.06, 1.50; P=0.01), probable rapid eye movement sleep behaviour disorder at baseline (OR=3.52; 95% CI: 1.27, 9.79; P=0.02), higher age at motor onset (OR=1.07; 95% CI: 1.02, 1.12; P=0.003), and follow-up time (OR=1.19; 95% CI: 1.08, 1.32; P=0.001).

II.B Summary of important risks (cont'd)

Important identified risk: Hallucinations and confusion (cont'd)	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4, 4.7 and 4.8. PL section 2 and 4. Prescription-only medicine. Additional risk minimisation measures: None.
Important identified risk: Cardiac failure	
Evidence for linking the risk to the medicine	General occurrence of cardiac failure in placebo-controlled trials with pramipexole across both indications was low. An epidemiological study on the use of pramipexole and other dopamine agonists (trial 248.672) showed that the rate of heart failure was increased with the current use of any dopamine agonist compared to no use. The use of pramipexole was not associated with an increased rate of heart failure when compared to all other dopamine agonists collectively. However, due to its medical relevance, BI has taken a conservative approach and has considered cardiac failure an important identified risk for pramipexole. In a recent meta-analysis, the use of non-ergot dopamine agonists in PD patients was not associated with an increased risk of incident heart failure, nor was it shown to increase the overall mortality, or the risk of cardiovascular events compared to the PD patients on monotherapy with levodopa alone.
Risk factors and risk groups	The main risk factors for heart failure are cardiovascular disease and the risk factors associated with coronary heart disease (such as hypertension and hypercholesterolaemia), as well as components of the metabolic syndrome such as insulin resistance. Recent literature has postulated a potential association between PD and myocardial dysfunction in terms of left ventricular hypertrophy, concentric remodelling and diastolic dysfunction.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 and 4.8. PL section 2 and 4. Prescription-only medicine. Additional risk minimisation measures: None.
Important identified risk: Dopamine agonist withdrawal syndrome (DAWS)	
Evidence for linking the risk to the medicine	DAWS has been described in the literature to be a withdrawal syndrome consisting of non-motor symptoms, such as apathy, anxiety, depression, fatigue, sweating and pain, that occurs among patients who undergo tapering of their dose of dopamine agonist therapy. An association between administration of pramipexole and DAWS has so far not been established by BI. Post-authorisation data do not allow to assess the reported 'withdrawal symptoms' with regard to 'DAWS' due to missing case details such as de-challenge and re-challenge information. The reported symptoms could equally likely resemble titration effects after dose reduction, neuroleptic malignant syndrome after acute drug withdrawal, or be part of the complex clinical course, e.g. pre-existing/concomitant psychiatric disorders of the PD patient population. Concerning the RLS indication, the described symptoms more likely resemble symptoms of augmentation or rebound, both of which are described in the SmPC. The literature is comprised largely of retrospective (or preliminary) findings and understanding of this symptom complex is still evolving. However, BI has taken a conservative approach and has added DAWS to the important identified risks, as requested by the Pharmacovigilance Risk Assessment Committee in 2016.

II.B Summary of important risks (cont'd)

Important identified risk: Dopamine agonist withdrawal syndrome (DAWS) (cont'd)	
Risk factors and risk groups	DAWS has been predominantly reported in patients with PD. Thus, the question was raised as to whether PD itself or the higher dopamine agonist doses that are used in PD may be a risk factor for DAWS. The presence of ICDs and higher dopaminergic doses are thought to be the main risk factors for the development of DAWS, and in this context, it has been speculated that these patients may have a higher susceptibility to addiction syndromes. A study has shown that among patients with ICDs, the additional history of smoking increased the likelihood of DAWS, which again raised the question of general vulnerability to addiction. In the same study, DAWS was not found to be associated with any specific type of dopamine agonist, or the speed of taper or total vs. partial withdrawal of the dopamine agonist. Not only higher daily dose of dopamine agonists and the duration of dopamine agonist use are thought to be risk factors, but also concomitant prescription of levodopa. Recent data on DAWS have shown that patients with deep brain stimulation may have a higher risk.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 and 4.8. Prescription-only medicine. Additional risk minimisation measures: None.
Important potential risk: Dystonia (such as antecollis, camptocormia, pleurothotonus)	
Evidence for linking the risk to the medicine	Dystonia is a disabling movement disorder characterised by sustained contraction of muscles that may affect various parts of the body and may be associated with various central nervous system disorders including PD and multiple system atrophy. While drugs such as neuroleptics are known to potentially cause dystonia, the specific role of dopamine agonists in the development of posture abnormalities is unclear. The frequency of the observed events in placebo-controlled clinical trials with pramipexole was lower than that observed in placebo-treated patients. Post-authorisation data are limited and based on individual case reports. PD patients are reported with dystonia during adjustment of various dopaminergic drugs. Thus, dystonia is considered likely explained by disease progression or titration effects of dopaminergic drugs, respectively. Based on the case details available, it cannot be clarified how pramipexole may potentially contribute to the events. After having reviewed post authorisation data, it was concluded that there is no clear causal relationship for all forms of dystonia; however, there seems to be at least a reasonable suspicion of a causal relationship for 'antecollis' (forward flexion of the head and neck). Less evidence for causality was found for other forms of dystonia, such as camptocormia (bent spine syndrome) and pleurothotonus (Pisa syndrome). However, BI has followed a conservative approach and considered dystonia (such as antecollis, camptocormia, pleurothotonus) an important potential risk for pramipexole, in agreement with Pharmacovigilance Risk Assessment Committee's proposal in 2017.
Risk factors and risk groups	In addition to the mainly affected PD patient population, the safety information available did not indicate specific risk factors regarding dystonia in patients treated with pramipexole. Post-authorisation data indicate that PD patients experience dystonia during dose adjustment of various dopaminergic drugs. Thus, dystonia is considered likely explained by disease progression or titration effects of dopaminergic drugs.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4. Prescription-only medicine. Additional risk minimisation measures: None.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies that are conditions of the marketing authorisation or are a specific obligation for Sifrol/Mirapexin.

II.C.2 Other studies in post-authorisation development plan

There are no ongoing or planned additional pharmacovigilance studies or other activities in the pharmacovigilance plan.

ABBREVIATIONS

BI	Boehringer Ingelheim
CI	Confidence interval
DAWS	Dopamine agonist withdrawal syndrome
EPAR	European Public Assessment Report
ICD	Impulse control disorders
OR	Odds ratio
PD	Parkinson’s disease
PL	Package Leaflet
RLS	Restless legs syndrome
RMP	Risk management plan
SmPC	Summary of Product Characteristics
US	United States (of America)