EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Mirapexin

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification [1] issued on	Commission Decision Issued[2] / amended on	Product Information affected[3]	Summary
WS/2626	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.8 of the SmPC to add 'spontaneous penile erection' to the list of adverse	14/03/2024		SmPC, Annex II, Labelling and PL	

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

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	drug reactions (ADRs) with frequency 'rare', based on the outcome of a cumulative review of data from clinical, literature and post-marketing sources. The Package Leaflet (PL) is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the PL, introduce minor editorial changes to the product information (PI) and bring it in line with the updated QRD template version 10.3. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
PSUSA/2491/202304	Periodic Safety Update EU Single assessment - pramipexole	09/11/2023	05/01/2024	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2491/202304.
IG/1657/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	04/09/2023	n/a		
WS/2399/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	08/06/2023	05/01/2024	PL	

	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation A.7 - Administrative change - Deletion of manufacturing sites B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.1.b - Replacement or addition of a				

	manufacturing site for the FP - Primary packaging site B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products				
WS/2352	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	15/12/2022	n/a		
PSUSA/2491/ 202204	Periodic Safety Update EU Single assessment - pramipexole	01/12/2022	n/a		PRAC Recommendation - maintenance
WS/2169	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	16/12/2021	09/01/2023	SmPC, Annex II, Labelling and PL	
N/0100	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	08/09/2021	19/10/2021	PL	
IG/1334	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	26/03/2021	n/a		

WS/1897	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	29/10/2020	n/a		
IG/1289/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	16/10/2020	19/10/2021	Annex II and PL	
IG/1281	B.III.1.a.1 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - New certificate from an already approved manufacturer	25/08/2020	n/a		
PSUSA/2491/201904	Periodic Safety Update EU Single assessment - pramipexole	12/12/2019	21/02/2020	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2491/201904.
IG/1198	A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites	24/01/2020	n/a		

	(excluding manufacturer for batch release)				
IG/1176	B.III.1.a.1 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - New certificate from an already approved manufacturer	12/12/2019	n/a		
WS/1672	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.7.b - Deletion of - a strength	12/09/2019	21/02/2020	SmPC, Labelling and PL	
WS/1647/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.d.1.g - Change in the specification parameters and/or limits of the finished product - Addition or replacement (excluding biological or immunological product) of a specification parameter wit its corresponding test method as a result of a safety or quality issue C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	12/09/2019	n/a		
WS/1631/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No	25/07/2019	21/02/2020	Annex II and PL	

	1234/2008. A.7 - Administrative change - Deletion of manufacturing sites B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold				
WS/1510	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	11/04/2019	n/a		

	To introduce RMP version 10.0, the RMP has been converted into the new RMP template as per GVP Module V Revision 2 (EMA/838713/2011 Rev 2). In addition, the applicant takes the opportunity to adapt the medical search strategies and data retrieval approach without any impact on the overall safety conclusion. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required				
IG/1033	A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	14/12/2018	n/a		
N/0087	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	20/06/2018	06/02/2019	Labelling and PL	
WS/1318	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	08/02/2018	06/02/2019	SmPC and PL	

PSUSA/2491/201604	Periodic Safety Update EU Single assessment - pramipexole	15/12/2016	16/02/2017	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2491/201604.
WS/0909	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.4 of the SmPC in order to add a precautionary statement pertaining to the potential occurrence of 'remnants in stool' for the prolonged-release tablet formulation. The Package Leaflet is updated accordingly. In addition, the Worksharing applicant (WSA) took the opportunity to update the list of local representatives for Portugal and Spain in the Package Leaflet and to bring the PI in line with the latest QRD template version 9.1. Furthermore, the worksharing applicant took the opportunity to correct mistakes made during implementation of QRD v.8.0 and to correct linguistic mistake in the Estonian product information. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	01/04/2016	16/02/2017	SmPC, Annex II, Labelling and PL	Some patients have reported the occurrence of remnants in faeces which may resemble intact pramipexole prolonged-release tablets. If patients report such an observation, the physician should reassess patient's response to therapy.
IG/0607	A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	16/10/2015	n/a		

IG/0605/G	This was an application for a group of variations. B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place	16/10/2015	n/a		
IG/0606/G	This was an application for a group of variations. A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release) A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release) A.7 - Administrative change - Deletion of manufacturing sites	16/10/2015	n/a		
WS/0648	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	23/10/2014	08/10/2015	SmPC, Annex II and PL	

IG/0432	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	16/04/2014	n/a		
IG/0417	B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place	14/03/2014	n/a		
PSUSA/2491/201304	Periodic Safety Update EU Single assessment - pramipexole	18/12/2013	28/02/2014	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2491/201304.
N/0076	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	03/07/2013	28/02/2014	PL	
WS/0326	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of SmPC sections 4.4 and 4.8 in order to update the safety information by implementing class labelling for the risk of impulse control disorders. C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH	15/11/2012	30/11/2012	SmPC and PL	Based on a recent review of the available post-marketing data in relation to the risk of development of impulse control disorders when using medicinal products containing levodopa, dopamine agonists and/or Catechol-O-methyltransferase (COMT) inhibitors, the CHMP/PhVWP recommended a class labelling to update and harmonise the product information of relevant products to reflect related behavioural symptoms including compulsive spending or buying, binge eating and compulsive eating and that the adverse reaction can occur irrespective of the indication and at normal doses. The class labelling also provided for regular monitoring of patients and harmonised wording for a careful review of treatment if symptoms occur. The Package Leaflet was updated in accordance and additional advice for the patient's family and carers was

					provided.
WS/0311	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.8 of the SmPC in order to include inappropriate antidiuretic hormone secretion as an adverse drug reaction based on post-marketing data. The Package Leaflet is updated in accordance. Furthermore a more detailed description of the outer appearance of the immediate release tablets was included in the Package Leaflet. In addition, editorial changes were made and the list of local representatives for Latvia was updated. Furthermore, the Product Information was brought in line with the latest QRD template version 8.0. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	18/10/2012	19/11/2012	SmPC, Annex II, Labelling and PL	A cumulative review of post-marketing reports showed an increased number of cases of inappropriate antidiuretic hormone secretion in recent years. As a causal relationship between the use of pramipexole and development of inappropriate antidiuretic hormone secretion could not be excluded, it was included as an adverse reaction in the product information.
IG/0211	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	05/09/2012	n/a		
WS/0255/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of the Description of Pharmacovigilance System (DDPS).	24/05/2012	24/05/2012		Changes to an existing pharmacovigilance system as described in the DDPS. The MAH update the Detailed Description of the Pharmacovigilance System (DDPS) for Aptivus, MicardisPlus, Mirapexin, Onduarp, Pradaxa, Sifrol, Trajenta, Twynsta and Viramune.

	C.I.9.z - Changes to an existing pharmacovigilance system as described in the DDPS - Other variation C.I.9.z - Changes to an existing pharmacovigilance system as described in the DDPS - Other variation C.I.9.f - Changes to an existing pharmacovigilance system as described in the DDPS - Deletion of topics covered by written procedure(s) describing pharmacovigilance activities C.I.9.d - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the safety database C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system				
WS/0134/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Change in the specification of the finished product to replace the test Uniformity of Content (Ph Eur 2.9.6) with Uniformity of Dosage Units (Ph Eur 2.9.40). Minor change in the HPLC method used for assay/content and uniformity of dosage units to improve the process descriptions by adding holding	23/06/2011	23/06/2011		

	times for the standard and test solutions. B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure				
WS/0133	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Extension of the bulk product holding time for 0.18 mg, 0.35 mg and 0.7 mg tablets. B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation	23/06/2011	23/06/2011		
WS/0128	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.8 to include 'cardiac failure' as a new side effect. In addition, information has been added to section 4.8 about the estimation of frequencies for listed side effects observed post marketing. The PL has been updated accordingly. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	19/05/2011	17/06/2011	SmPC and PL	Based on an analysis of safety data and recent findings from a pharmacoepidemiological study, the MAH proposes to include 'cardiac failure' as a new side effect in section 4.8 of the SmPC. In addition, the frequencies of listed side effects observed post marketing have been calculated according to the guidance in the current version of the SmPC guideline. The frequencies for these side effects remain unchanged compared with the current SmPC. The PL has been amended accordingly.

WS/0101	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Extension of shelf-life of the finished product (prolonged-release tablets) from 2 years to 3 years. B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	17/02/2011	18/03/2011	SmPC	
WS/0061	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of Section 5.3 of SPC to include non-clinical information concerning delayed sexual development observed in rats as agreed in the assessment of FUM 040 (Sifrol) / 038 (Mirapexin). In addition, the MAH corrected minor errors in the English version of Annex I and Annex II and in Annexes I, II and IIIB of the Danish translation. C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH	18/11/2010	20/12/2010	SmPC and Annex II	In FUM 040 (Sifrol)/FUM 038 (Mirapexin) the MAH submitted the final study reports for a clinical trial (248.642) and a non-clinical study (U09-1156). In the assessment of these reports the CHMP concluded that the MAH should submit a variation application to include information on a delayed sexual development observed in rats. With this procedure the MAH subsequently updated section 5.3 of the SPC to include the requested information.
N/0065	The Marketing Authorisation Holder (MAH) took the	10/12/2010	n/a	PL	

	opportunity to update details of the local representatives in Annex IIIB. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)				
WS/0042	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. To update section 4.2 of the SPC with specific information on missed dose based on new data. The PL is updated accordingly. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	23/09/2010	25/10/2010	SmPC and PL	The MAH performed a simulation of the pramipexole plasma concentration after an inadvertently missed dose of pramipexole prolonged-release tablets. Based on this analysis the product information is revised to include specific information on missed dose in section 4.2 of the SPC and section 3 of the as follows: "When the intake of a dose is missed, Sifrol prolonged-release tablets should be taken within 12 hours after the regularly scheduled time. After 12 hours, the missed dose should be left out and the next dose should be taken on the following day at the next regularly scheduled time." Part 3 of the Package Leaflet was updated accordingly.
WS/0041/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of the section 4.5 of the SPC to include the results of an evaluation of hOCT2 inhibitors and of section 4.8 of the SPC to include new side effects and revise frequency categories based on data submitted with PSUR 13. The Package Leaflet has been updated accordingly. C.I.4 - Variations related to significant modifications	23/09/2010	25/10/2010	SmPC and PL	In the assessment of line extension procedure EMEA/H/C/133,134/X/51,59, the CHMP requested that the MAH should performs an in depth evaluation of hOCT2 inhibitors which may potentially interfere with the active tubular secretion of pramipexole. Following the assessment of this evaluation the CHMP recommended that section 4.5 of the SPC should be amended to include zidovudine, cisplatin, quinine, and procainamide. Furthermore, based on the data provided in PSUR No. 13 a revision of the Product Information was proposed by the MAH, including the identification of new side effects (hiccups, diplopia and decreased appetite), an adaptation to the revised MedDRA terminology and changes of several

	of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH				frequency categories. The CHMP considered the proposed changes to be in line with the assessment of PSUR 13 and accepted the proposed changes.
II/0064	Update of the Summary of Product Characteristcs (SPC) to include the negative results of a study in children and adolescents (age 6-17) diagnosed with Tourette's Disorder and the recommendation for not using Mirapexin in children or adolescents with Tourette's Disorder. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	20/05/2010	01/07/2010	SmPC	With this variation application the MAH submitted the results of a 6-week placebo-controlled study in 63 children and adolescents aged 6-17 years (inclusive) with Tourette's Disorder in which the efficacy and safety of five different total daily doses of pramipexole (0.0625, 0.125, 0.25, 0.375 and 0.5 mg) were administered. The primary endpoint in this study was the change from baseline to the end of the 6-week treatment period in the Total Tic Score (TTS) of the Yale Global Tic Severity Scale (YGTSS). No significant difference was found in the treatment effects on the change from baseline in TTS for patients treated with pramipexole and patients treated with placebo. Adverse reactions was reported in at least 5% of patients, and the adverse reactions profile was very similar to what is known from the use of pramipexole in the marketed indication in adults. The CHMP subsequently recommended and inclusion of this information in section 4.2 and 5.1 of the SPC.
WS/0003	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of the SPC for the immediate release formulations to include information on effect of	22/04/2010	17/06/2010	SmPC and PL	Based on the results of a long-term (26 weeks) study in patients with idiopathic moderate to severe Restless Legs Syndrome to evaluate augmentation and rebound, the CHMP concluded that augmentation is seen, but is not related to treatment with pramipexol. Rebound after abrupt discontinuation is seen in about 10% of patients. The CHMP

	abrupt discontinuation on worsening of symptom severity as compared to baseline (rebound) in sections 4.2 and 5.1, updated information regarding symptoms starting earlier than usual, be more intense and involve other limbs (augmentation) to reflect the results of study 248.629 in section 4.4 and information on long-term efficacy in Restless Legs Syndrome (RLS) in section 5.1. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH				also concluded that another important issue with pramipexol in RLS is low efficacy (although better then placebo). Based on these conclusions the CHMP recommended an update of the SPC for the immediate release formulations for which RLS is indicated. In addition, the details of the local representatives for Bulgaria, Romania, Estonia and Lithuania in the package leaflet were updated for all presentations.
X/0062	Annex I_2.(c) Change or addition of a new strength/potency	18/03/2010	10/06/2010	Labelling and PL	
IA/0063	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	01/12/2009	n/a		
X/0059	Annex I_2.(d) Change or addition of a new pharmaceutical form	25/06/2009	08/10/2009	SmPC, Labelling and PL	
II/0060	Update of section 4.8 of the SPC to include the terms 'dyspnoea' and 'pneumonia'. The Package Leaflet has been updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	19/03/2009	17/04/2009	SmPC and PL	The MAH presented the results of pooled safety analyses of placebo-controlled clinical phase II and phase III trials in Parkinson's disease and Restless Legs Syndrome. The CHMP considered that, despite the fact that an association between the use of pramipexole and dyspnoea or pneumonia is not strictly proven, the tendencies and

					frequencies are sufficiently high to warrant an inclusion of both adverse events in the product information.
II/0056	Update of section 4.8 of the SPC with the terms compulsive shopping, vomiting, restlessness, amnesia, visual disturbance, hyperphagia, syncope and weight decrease. The frequency for the terms hypersexuality and pathological gamling has also been included. In addition, compulsive shopping has been added to section 4.4 of the SPC. The PL is being updated accordingly. The local representative section has also been amended. Update of Summary of Product Characteristics and Package Leaflet	18/12/2008	26/01/2009	SmPC and PL	Following the CHMP assessment of PSUR 11, covering the period 7 October 2007 to 6 April 2008 and including the analysis of spontaneously reported adverse events, clinical trial data and scientific literature, the CHMP concluded that the MAH should include additional Adverse Drugs Reactions (ADRs) in the Summary of Product Characteristics (SPC). Based on an analysis of the data provided, 'compulsive shopping', 'vomiting', 'restlessness', 'amnesia', 'visual disturbance', 'hyperphagia', 'syncope' and 'weight decrease' have been introduced to section 4.8 of the SPC and section 4 of the Package Leaflet. A short descriptive text of the results from the DOMINION study were also included in section 4.8 of the SPC, including the suggested risk factors found and highlighting that the symptoms are seen with all types of dopaminergic treatment. In addition, compulsive shopping has been added to section 4.4 of the SPC as suggested by the Committee in the assessment of PSUR 11. The PL was being updated acco0rdingly with the new ADRs and in addition the local representative section was amended.
IA/0058	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	04/09/2008	n/a		
IA/0057	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	04/09/2008	n/a		
II/0053	Update of section 4.8 of the SPC and PL.	24/07/2008	03/09/2008	SmPC and PL	The MAH updated section 4.8 of the SPC (undesirable

	Update of Summary of Product Characteristics and Package Leaflet				effects) to separate Adverse Drug Reactions by indication (Parkinson's disease and Restless Legs Syndrome). In addition other minor amendments have been introduced throughout the product information.
IB/0055	IB_27_b_Change to test proc. of immediate packaging - other changes (incl. replacement/addition)	14/07/2008	n/a		
IA/0054	IA_32_a_Change in batch size of the finished product - up to 10-fold	07/07/2008	n/a		
N/0050	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/05/2008	n/a	PL	
IB/0051	IB_38_c_Change in test procedure of finished product - other changes	15/04/2008	n/a		
IA/0052	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	31/03/2008	n/a		
II/0048	Update of sections 4.4 and 4.8 of the SPC and relevant section of the PL Update of Summary of Product Characteristics and Package Leaflet	24/01/2008	29/02/2008	SmPC and PL	Following the evaluation of the 9th PSUR the MAH was requested to update of section 4.8 of SPC and relevant sections of the PL to reflect the occurrence of hypersexuality and allergic reactions like hypersensitivity, rash and pruritus. In addition, the MAH amended the undesirable effects frequencies for hypotension (low blood pressure), hallucinations, dizziness, abnormal dreams, insomnia and peripheral oedema (excess of fluid, usually in the legs).

II/0049	Update of or change(s) to the pharmaceutical documentation	21/02/2008	26/02/2008		
R/0047	Renewal of the marketing authorisation.	19/07/2007	17/09/2007	SmPC, Annex II, Labelling and PL	Based on the CHMP review of the available information and on the basis of a re-evaluation of the benefit risk balance, the CHMP is of the opinion that the quality, safety and efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considered that the benefit/risk profile of Mirapexin continues to be favourable.
II/0040	Update of section 4.4 and 4.8 of SPC and relevant section of the PL to reflect the occurrence of new advers events, including behavioural changes, hyperkinesia and weight increase. Update of Summary of Product Characteristics and Package Leaflet	28/06/2006	04/08/2006	SmPC and PL	Based on the analysis of spontaneously reported adverse events, literature cases and clinical trials an emerging evidence for a causal relationship between abnormal dreams, abnormal behaviour, delusion, paranoia, increased eating, hyperkinesia, weight increase and pramipexole administration was seen. The undesirable effects section has been updated to reflect these effects and a warning has been included to consider dose reduction or taper discontinuation if behavioural changes occur.
IA/0046	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	16/06/2006	n/a		
IA/0045	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	16/06/2006	n/a		
IB/0044	IB_38_c_Change in test procedure of finished product - other changes	11/05/2006	n/a		

IA/0043	IA_09_Deletion of manufacturing site	18/04/2006	n/a		
IA/0042	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	18/04/2006	n/a		
IA/0041	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	18/04/2006	n/a		
II/0036	Extension of Indication	23/02/2006	06/04/2006	SmPC, Annex II and PL	Please refer to the Scientific Discussion: Mirapexin H-134-II-36-SD
IB/0038	IB_10_Minor change in the manufacturing process of the active substance	25/01/2006	n/a		
IA/0039	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	16/11/2005	n/a		
IA/0037	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	21/10/2005	n/a		
II/0035	Update of section 4.8 of the SPC and section 4 of the PL. Update of Summary of Product Characteristics and Package Leaflet	17/02/2005	29/03/2005	SmPC and PL	Section 4.8 of the SPC and the section 4 of the PL were updated to add information on that, as described in the literature for dopamine agonists used for the treatment of Parkinson's disease, patients treated with pramipexole, especially at high doses, have been reported as showing pathological gambling, which was generally reversible upon treatment discontinuation.
II/0033	Change(s) to the manufacturing process for the finished product	17/02/2005	22/02/2005		
II/0034	Change(s) to container	20/01/2005	27/01/2005		

II/0032	Update of section 4.8 of the SPC and section 4 of the PL. Update of Summary of Product Characteristics and Package Leaflet	16/09/2004	28/10/2004	SmPC and PL	The section 4.8 of the SPC and the section 4 of the PL were updated based on data from clinical trials and spontaneous reports in order to add information on an association between altered libido increase or decrease) and pramipexole treatment.
T/0029	Transfer of Marketing Authorisation	08/06/2004	22/07/2004	SmPC, Labelling and PL	The EMEA, having considered the application in accordance with Commission Regulation (EC) No 2141/96 of 7 November 1996 and having found that the documents submitted in support of such application are complete and that the person to whom the transfer should be granted is established within the European Economic Area, recommended the transfer of the Marketing Authorisation for the above mentioned medicinal product to Boehringer Ingelheim International GmbH. .
IB/0030	IB_14_a_Change in manuf. of active substance without Ph. Eur. certificate - change in manuf. site	02/07/2004	n/a		
N/0031	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	28/06/2004	n/a	PL	
IB/0028	IB_10_Minor change in the manufacturing process of the active substance	18/02/2004	n/a		
IB/0027	IB_10_Minor change in the manufacturing process of the active substance	18/02/2004	n/a		
IA/0026	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	28/01/2004	n/a		

IA/0025	IA_05_Change in the name and/or address of a manufacturer of the finished product	19/01/2004	n/a	Annex II and PL	
IA/0024	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site IA_08_b_02_Change in BR/QC testing - repl./add. manuf. responsible for BR - incl. BC/testing	22/10/2003	n/a	Annex II and PL	
IA/0023	IA_01_Change in the name and/or address of the marketing authorisation holder	22/10/2003	n/a	SmPC, Labelling and PL	
I/0022	01_Withdrawal of the manufacturing authorisation for a site of manufacture	02/09/2003	18/09/2003		
I/0021	01_Change in the name of a manufacturer of the medicinal product 11a_Change in the name of a manufacturer of the active substance	14/08/2003	n/a		
I/0019	13_Batch size of active substance	19/02/2003	04/03/2003		
I/0018	17_Change in specification of the medicinal product	19/02/2003	04/03/2003		
R/0017	Renewal of the marketing authorisation.	25/07/2002	08/11/2002	SmPC, Annex II, Labelling and PL	Following the CHMP Position statement on dopaminergic substances (CPMP/578/02, Rev 1), information was included on the association with somnolence and episodes of sudden sleep onset, particularly in patients with Parkinson's disease, that sudden onset of sleep during daily activities, in some cases without awareness or warning signs, has been reported uncommonly and that patients

					must be informed of this and advised to exercise caution while driving or operating machines during treatment with Mirapexin. Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines and that a reduction of dosage or termination of therapy may be considered. The CHMP was of the opinion that the quality, safety and efficacy of this medicinal product continues to be adequately demonstrated and therefore considered by consensus that the benefit/risk profile of Mirapexin continues to be favourable for the indication "Mirapexin tablets are indicated for treatment of the signs and symptoms of idiopathic Parkinson's disease, 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)".
I/0015	24_Change in test procedure of active substance	05/07/2002	09/07/2002		
I/0014	20a_Extension of shelf-life or retest period of the active substance	05/07/2002	09/07/2002		
I/0013	14_Change in specifications of active substance 24_Change in test procedure of active substance	05/07/2002	09/07/2002		
I/0012	13_Batch size of active substance	05/07/2002	09/07/2002		
I/0011	12a_Change in specification of starting material/intermediate used in manuf. of the active	05/07/2002	09/07/2002		

	substance				
II/0010	Update of section 4.8 of the SPC following PSUR 6. Update of Summary of Product Characteristics and Package Leaflet	17/01/2002	18/04/2002	SmPC and PL	The adverse event "confusion" was added to the adverse events having been reported more frequently during the use of Mirapexin than under placebo.
II/0007	Extension of Indication	26/07/2001	21/10/2001	SmPC and PL	The indication was extended to include treatment of early Parkinson's disease. In early PD, pramipexole delays the onset of late motor complications compared to levodopa. In contrast, the average improvement of motor symptoms is smaller with pramipexole than with levodopa. However, in 47% of pramipexole patients the control of motor symptoms is still considered sufficient without supplementary levodopa (compared to 61% in the levodopa group). The safety profile of pramipexole differed from that of levodopa (oedema and somnolence being significantly more frequent during pramipexole treatment whereas dry mouth, sweating, dyskinesia/wearing off and conjunctivitis being significantly more frequent during levodopa treatment) but it is not evident which safety profile is the more favourable one. The section 4.1 of the SPC was updated to extend the indication to the following: Mirapexin tablets are indicated for treatment of the signs and symptoms of idiopathic Parkinson's disease, 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). Information was added to section 4.2 of the SPC regarding tapering off, as a slow tapering off

					would intuitively decrease the risk of NMS. In a post marketing interaction study with pramipexole and L-dopa reasonable reassurance was provided that pramipexole did not have any clinically relevant effect on the pharmacokinetics of levodopa in males and females. Consequently the respective warnings in section 4.5 of the SPC were removed. In section 5.1 of the SPC was updated to include information on that in a controlled double blind clinical trial of 2-year duration, initial treatment with pramipexole significantly delayed the onset of motor complications, and reduced their occurrence compared to initial treatment with levodopa. Thi
I/0009	03_Change in the name and/or address of the marketing authorisation holder	14/09/2001	n/a	SmPC, Labelling and PL	
I/0008	01_Change following modification(s) of the manufacturing authorisation(s)	14/09/2001	n/a	Annex II and PL	
I/0006	20_Extension of shelf-life as foreseen at time of authorisation	30/03/2001	02/04/2001		
II/0004	Update of Summary of Product Characteristics	29/06/2000	20/10/2000	SmPC	
I/0005	20_Extension of shelf-life as foreseen at time of authorisation	16/06/2000	27/07/2000	SmPC	
II/0003	Update of Summary of Product Characteristics and Package Leaflet	29/07/1999	29/11/1999	SmPC and PL	

X/0002	X-3-iii_Addition of new strength	20/05/1999	26/10/1999	SmPC, Annex II, Labelling and PL	
N/0001	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	02/07/1998	16/09/1998	Labelling and PL	