Neupro

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
PSUSA/2667/ 202302	Periodic Safety Update EU Single assessment - rotigotine	12/10/2023	07/12/2023	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2667/202302.
IA/0096/G	This was an application for a group of variations.	19/04/2023	n/a		

[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).

	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure A.7 - Administrative change - Deletion of manufacturing sites				
IA/0095	B.II.c.2.a - Change in test procedure for an excipient - Minor changes to an approved test procedure	01/02/2023	n/a		
WS/2350/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.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.c.1.b - Change in the specification parameters and/or limits of an excipient - Addition of a new specification parameter to the specification with its corresponding test method B.II.c.1.z - Change in the specification parameters and/or limits of an excipient - Other variation	13/10/2022	n/a		
IA/0093	B.II.c.2.a - Change in test procedure for an excipient - Minor changes to an approved test procedure	16/02/2022	n/a		
IB/0091	A.z - Administrative change - Other variation	10/02/2022	n/a		
IA/0092	B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the	10/12/2021	n/a		

	dossier) - Deletion of a supplier				
N/0090	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	08/11/2021	04/02/2022	PL	
WS/2000	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.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	11/02/2021	n/a		
WS/1963	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	14/01/2021	04/02/2022	SmPC and PL	
IA/0088	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	09/12/2020	n/a		
PSUSA/2667/	Periodic Safety Update EU Single assessment -	01/10/2020	n/a		PRAC Recommendation - maintenance

202002	rotigotine				
WS/1689	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	16/01/2020	11/01/2021	SmPC and PL	
WS/1602/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.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.III.2.a.1 - Change of specification(s) of a former non EU Pharmacopoeial substance to fully comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - AS	04/07/2019	n/a		
IG/1072	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	28/02/2019	n/a		
WS/1381	This was an application for a variation following a worksharing procedure according to Article 20 of	07/06/2018	08/11/2018	SmPC and PL	

	Commission Regulation (EC) No 1234/2008. Update of section 4.8 of the SmPC in order to add an adverse drug reaction: Dropped Head Syndrome based on new pharmacovigilance data; The Package Leaflet is updated accordingly. In addition, the Worksharing applicant (WSA) took the opportunity to correct some discrepancies found within the PIL of Greece, Cyrus and Romania and to update the Neupro Annex A in alignment with Leganto Annex A for the description of the multipack size. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
PSUSA/2667/ 201702	Periodic Safety Update EU Single assessment - rotigotine	12/10/2017	11/12/2017		Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2667/201702.
WS/1238/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.e.z - Change in container closure system of the Finished Product - Other variation C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	09/11/2017	08/11/2018	SmPC, Labelling and PL	

IAIN/0081	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	20/10/2017	08/11/2018	Annex II and PL	
T/0080	Transfer of Marketing Authorisation	23/08/2017	28/09/2017	SmPC, Labelling and PL	
N/0074	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	20/06/2017	28/09/2017	PL	
IAIN/0078/G	This was an application for a group of variations. B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished	01/06/2017	28/09/2017	SmPC, Labelling and PL	

	product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes				
IAIN/0076	B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	01/06/2017	28/09/2017	SmPC, Labelling and PL	
WS/0950	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.1.c - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer uses a substantially different route of synthesis or manufacturing conditions	10/11/2016	n/a		
N/0073	Update of the package leaflet with revised contact details of the local representatives for Lithuania, Estonia, Latvia, Portugal and Finland. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	08/11/2016	16/02/2017	PL	
IG/0710	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	26/07/2016	n/a		

WS/0886/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.a.3.b.5 - Changes in the composition (excipients) of the finished product - Other excipients - Change that is supported by a bioequivalence study 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.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold B.II.b.5.a - Change to in-process tests or limits applied during the manufacture of the finished product - Tightening of in-process limits B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	25/02/2016	16/02/2017	SmPC, Labelling and PL	

	B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation B.II.c.1.a - Change in the specification parameters and/or limits of an excipient - Tightening of specification limits B.II.c.2.a - Change in test procedure for an excipient - Minor changes to an approved test procedure B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits 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.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation 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 B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) 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) B.II.f.1.d - Stability of FP - Change in storage conditions of the finished product or the diluted/reconstituted product				
R/0069	Renewal of the marketing authorisation.	19/11/2015	22/01/2016	SmPC, Annex II, Labelling and PL	Based on the review of the available information the CHMP is of the opinion that the quality, the safety and the efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considers that the benefit/risk profile of Neupro continues to be favourable. The CHMP is of the opinion that the renewal can be granted with unlimited validity.
WS/0751/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. Submission of two final reports of studies which investigated the potential risk of cardiovalvular fibrosis in Parkinson's disease patients treated with rotigotine. The RMP version 4 is updated accordingly. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	25/06/2015	n/a		

WS/0684	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 include the adverse event "dopamine dysregulation syndrome". The package leaflet is amended accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/02/2015	22/01/2016	SmPC and PL	A safety signal assessment to evaluate the association of dopamine dysregulation syndrome (DDS) with rotigotine was recently conducted and this safety signal was confirmed. As a result, the rotigotine company core data sheet (CCDS) was updated to include DDS as an additional AE term under undesirable effects. Consequently, the product information has been updated in this type II variation to include DDS.
WS/0674	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.2 and 5.2 of the SmPC to amend information about the paediatric population following the conduct of a dose-escalation Study SP1004 in paediatric patients with Idiopathic Restless Legs Syndrome. Section 4.2 is updated in line with the current QRD template for paediatric information. The MAH also took the opportunity to make minor editorial corrections in the package leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/02/2015	22/01/2016	SmPC and PL	
IG/0520/G	This was an application for a group of variations.	26/01/2015	n/a		

	B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site 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				
WS/0659	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. To include an alternative manufacturer of the starting material for the active substance. B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	18/12/2014	n/a		To include an alternative manufacturer of the starting material for the active substance.
PSUV/0063	Periodic Safety Update	25/09/2014	19/11/2014	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUV/0063.
WS/0450	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	23/01/2014	19/11/2014	SmPC and PL	The present Type II variation application was meant to update the rotigotine EU Product Information (Summary of Product Characteristics [SmPC] and Patient Information Leaflet [PIL]) to include the changes made to the CCDS as

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				a result of review of clinical and post-marketing data. CHMP requested that the terms 'delusion' and 'delirium' be kept in the warning on abnormal thinking and behaviour, and agreed on the changes proposed regarding peripheral oedema, agitation, impulse control disorders and hypersensitivity reactions. Additionally, editorial and orthographical changes have been made in SmPC sections 4.2, 4.4, 4.8 and 5.1 to facilitate reading. The patient leaflet was amended to align with the SmPC changes outlined above.
WS/0385	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 PI in line with QRD template 9.0. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	27/06/2013	31/07/2013	SmPC, Annex II, Labelling and PL	All parts of the product information were brought in line with QRD template 9.0 including standard text to encourage reporting of adverse reactions by healthcare professionals and patients as well as the update of Annex II to reflect the requirement of PSUR submissions in line with the EURD list and of RMP updates.
WS/0394	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Change to the specification limits of the finished product. B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits	27/06/2013	n/a		

IG/0222	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	16/11/2012	n/a		
WS/0293	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 5.1 of the SmPC in order to include summary descriptions of two clinical studies in relation to the use of equipotent doses for rotigotine as compared to ropinirole and other dopamine agonists as well as to amend the wording on the comparability of efficacy of rotigotine versus ropinirole, as observed in one of the pivotal trials. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	15/11/2012	14/01/2013	SmPC	The update is based on data from two clinical trials, supported by three additional studies, investigating the efficacy and safety of rotigotine patches in equipotent doses to the oral dopamine agonists ropinirole, pramipexole and cabergoline. One of the studies indicated that effective control of Parkinson's disease symptoms can be achieved when switching from an oral dopamine agonists to rotigotine patch. Section 5.1 of the SmPC was updated to reflect relevant information on these two studies and to correct a statement on the comparability of efficacy of rotigotine and ropinirole observed in a previous pivotal trial.
WS/0286/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 sections 4.4 and 4.8 of the SmPC in order to update the safety information in relation to binge eating and aggression and to implement a class labelling for impulse control disorders. The Package Leaflet was updated in accordance. C.I.3.a - Implementation of change(s) requested	15/11/2012	14/01/2013	SmPC and PL	Following a request from the CHMP based on the review of PSUR data, aggression/aggressive behaviour as well as binge eating and compulsive eating were included as rare adverse reactions in the product information. Furthermore, 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 all products concerned. To this end, the product information was updated to reflect related

	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 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				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. Regular monitoring of patients and a careful review of treatment, if symptoms occur, is recommended. The Package Leaflet was updated in accordance and advice for the patient's family and carers was provided.
WS/0226/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. - to change the quantitative composition of the rotigotine transdermal patches for some excipients included in the drug containing self adhesive mass of the reformulated product. - to update the manufacturing process for the reformulated product. - to replace the details of the current approved batch sizes. - to add an editorial update to replace details formerly approved for a theoretical batch size. - to remove some of the current approved details to align with current manufacturing practice. - to tighten some specification limits. - to update the specification for compendial excipients to include USP and/or USP-NF testing in	19/07/2012	23/08/2012	SmPC, Annex II, Labelling and PL	

	addition to current approved Ph.Eur. - to update some of non-compendial excipients. - to update some of the release and shelf-life specification of the finished product. - to tighten some of the shelf-life specification limit. - to tighten some of the release and shelf life specification limits. - to delete some of testing from the release and shelf-life specifications. - to update the release and shelf-life specification for drug release. - to change the some test procedures. - to change some the analytical procedures. - to change the storage conditions for the reformulated, room temperature stable product from "store in a refrigerator (2°C-8°C)" to "do not store above 25°C". - to extend the shelf life of the finished product from 18 months to 24 months. B.II.a.3.b.5 - Changes in the composition (excipients) of the finished product - Other excipients - Change that is supported by a bioequivalence study B.II.b.3.b - Change in the manufacturing process of the finished product - Substantial changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product B.II.b.4.z - Change in the batch size (including batch size ranges) of the finished product - Other variation B.II.b.5.a - Change to in-process tests or limits applied during the manufacture of the finished				

	product - Tightening of in-process limits B.II.b.5.a - Change to in-process tests or limits applied during the manufacture of the finished product - Tightening of in-process limits B.II.b.5.a - Change to in-process tests or limits applied during the manufacture of the finished product - Tightening of in-process limits B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new tests and limits B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new tests and limits B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation B.II.c.1.a - Change in the specification parameters				

	and/or limits of an excipient - Tightening of specification limits B.II.c.1.a - Change in the specification parameters and/or limits of an excipient - Tightening of specification limits B.II.c.1.c - Change in the specification parameters and/or limits of an excipient - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.II.c.1.c - Change in the specification parameters and/or limits of an excipient - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.II.c.1.z - Change in the specification parameters and/or limits of an excipient - Other variation B.II.c.1.z - Change in the specification parameters and/or limits of an excipient - Other variation B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter (e.g. deletion				

	of an obsolete parameter B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure 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) B.II.f.1.d - Stability of FP - Change in storage conditions of the finished product or the diluted/reconstituted product B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method				
N/0054	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	14/12/2011	26/03/2012	Labelling and PL	
IG/0129	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	09/12/2011	n/a		

II/0052	Section 5.1 of the SPC is proposed to be updated to include new clinical data from a phase 3 study to evaluate the effect of rotigotine on early morning motor function, sleep quality, nocturnal symptoms and non-motor symptoms in subjects with idiopathic Parkinson's disease. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	21/07/2011	24/08/2011	SmPC	The MAH conducted a Phase 3, double-blind, placebo-controlled, 2-arm trial of rotigotine in 287 subjects with early-stage or advanced-stage idiopathic Parkinson's disease. The purpose of the trial was to evaluate the effect of transdermal delivery of rotigotine on the control of early morning motor function, sleep quality, nocturnal symptoms, and non-motor symptoms in subjects with idiopathic Parkinson's disease. Subjects were titrated to their optimal dose of rotigotine or placebo in weekly increments of 2mg/24h, starting at 2mg/24h, to a maximum dose of 16mg/24h over 8 weeks, followed by a maintenance period of 4 weeks. A statistically significant improvement was seen in the co-primary outcome measures early morning motor function, assessed by the Unified Parkinson's Disease Rating Scale (UPDRS) Part III, and nocturnal sleep disturbances, measured by the modified Parkinson's Disease Sleep Scale (PDSS-2).
II/0051	Section 5.1 of the SmPC is proposed to be updated to provide a more precise description of rotigotine activity at dopamine and 5-HT1A receptors, and to provide more information regarding the mode of action for the treatment of Restless Legs Syndrome. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	21/07/2011	24/08/2011	SmPC	Section 5.1 of the SmPC has been amended to provide a more precise description of the rotigotine activity and mechanism of action for rotigotine in regards to dopamine and 5HTA1 receptors. This change is editorial and not based on new data presented. Based on Cerep study 817014 submitted in support of this application, a statement has been added regarding 5HT2B receptor activity of rotigotine. Finally, more information with regard to the mode of action of rotigotine as a treatment of Restless Legs Syndrome (RLS) has been added to section 5.1.
II/0050	The SmPC is proposed to be updated in section 4.9	21/07/2011	24/08/2011	SmPC, Annex	The SmPC has been updated in section 5.2 to provide

	to provide more information regarding handling of suspected overdose, and in section 5.2 to provide information about the biphasic elimination of rotigotine. In addition, section 4.8 has been updated to precise the study data base used for the ADR table, and a statement on the post-marketing experience has been added. The patient leaflet has been amended for overdose handling in section 3 and 'involuntary movements' and 'convulsions' have been added as likely side effects caused by overdosing in this section. Annex II has been amended to be in line with the current QRD template, and the version number of the RMP has been updated. In addition, a few typographical errors have been corrected in the annexes. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data			II, Labelling and PL	information about the biphasic elimination of rotigotine. In support of this change, the MAH conducted two studies to verify that a two compartment model would fit the concentrations obtained after patch removal. Section 4.9 has been amended to provide more information regarding handling of suspected overdose, and the PL has been aligned with the SmPC with regards to overdose symptoms. Section 4.8 has been updated to precise the study data base used for the ADR table. In addition, a statement on the post-marketing experience has been added to section 4.8.
IA/0053/G	This was an application for a group of variations. A.1 - Administrative change - Change in the name and/or address of the MAH A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS A.5.a - Administrative change - Change in the name and/or address of a manufacturer responsible for batch release	24/08/2011	n/a	SmPC, Annex II, Labelling and PL	

II/0046/G	This was an application for a group of variations. Change to the specifications of the finished product and deletion and update to test methods. B.II.d.1.f - Change in the specification parameters and/or limits of the finished product - Deletion of a specification parameter which may have a significant effect on the overall quality of the finished product B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.b - Change in test procedure for the finished product - Deletion of a test procedure if an alternative method is already authorised	19/05/2011	19/05/2011		
IA/0049/G	This was an application for a group of variations. C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD 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	04/05/2011	n/a		
IA/0047/G	This was an application for a group of variations.	06/04/2011	n/a		

	A.5.b - Administrative change - Change in the name and/or address of a manufacturer 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 of the finished product, including quality control sites (excluding manufacturer for batch release)				
II/0044	Section 4.4 of the SPC has been amended to reflect long term study data on augmentation generated in patients with restless legs syndrome (RLS). This amendment was requested by the CHMP following submission of study SP710 data to address augmentation (FUM020). In addition, the version number of the RMP has been updated, and the version number of the DDPS has been deleted from Annex IIB of the Product Information as recommended by the EMA. The list of contact details for the local representatives in the PL has also been updated. 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	20/01/2011	21/02/2011	SmPC, Annex II and PL	With this variation application, section 4.4 of the Neupro SPC has been amended to reflect long term study data on augmentation generated in patients with restless legs syndrome (RLS). This amendment was requested by the CHMP following submission of a case-by-case analysis of study SP710 data to address augmentation (FUM020). Analysis of a 5-year open-label treatment study showed that augmentation occurred in 11.9% of patients treated with the approved dosages for RLS (1-3 mg/24 h), and that 5.1% were considered clinically significant. The majority of augmentation episodes occurred in the first and second years of treatment. This study also allowed 4 mg/24 h dosing, which showed higher rates of augmentation. The 4 mg/24 h dosage is, however, not approved for the treatment of RLS.
IB/0045/G	This was an application for a group of variations.	14/12/2010	n/a		

	B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the currently approved batch size B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test				
R/0040	Renewal of the marketing authorisation.	23/09/2010	29/11/2010	SmPC, Annex II, Labelling and PL	
IB/0039	B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	03/06/2010	n/a		
IB/0042	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)	26/05/2010	n/a	SmPC	
IA/0041/G	This was an application for a group of variations. C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of the QPPV	21/05/2010	n/a	Annex II	

	C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD C.I.9.g - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the site undertaking pharmacovigilance activities 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				
IA/0038	B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	12/05/2010	n/a		
II/0037	Update of section 4.8 of the Summary of Product Characteristics (SPC) to bring the section in line with MedDRA version 9.1. Section 4.4 was amended to include a warning on allergic type reactions associated with sodium metabisulphite (E223) and to update the information on neuroleptic malignant syndrome. Additions are proposed to Restless Legs Syndrome (RLS) specific paragraphs in section 4.4 and 5.1 of the SPC for the 2 mg/24 h patch to distinguish the information presented for RLS from that for Parkinson’s disease. Relevant sections of the	21/01/2010	15/03/2010	SmPC, Labelling and PL	Following the assessment of PSUR 5, the CHMP requested the MAH to revise section 4.8. Specifically, ADRs terms have been removed or newly included and frequencies have been updated. For some terms the assignment to a system organ class (SOC) has been changed as defined in the updated MedDRA version 9.1. Safety data have been presented for each indication, in order to avoid presenting both Restless Legs Syndrome (RLS) and Parkinson's disease (PD) data in formulations that have only one of these two indications (1 and 3 mg for RLS and 4, 6 and 8 mg for PD). Section 4.4 was also amended to include a

	Labelling and Package Leaflet (PL) have been amended accordingly. In addition, minor typographical errors have been corrected in the PL. Update of Summary of Product Characteristics, Labelling and Package Leaflet				warning on allergic type reactions associated with sodium metabisulphite (E223) and to update the information on neuroleptic malignant syndrome. Relevant sections of the Labelling and Package Leaflet have been amended accordingly.
N/0036	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	22/10/2009	n/a	Labelling and PL	
II/0035	Update of section 4.8 of Summary of Product Characteristics (SPC) to include information on augmentation rates at the CHMP request. This update is based on results of placebo controlled clinical studies (SP790, SP792) and 1-year, open-label follow-up studies (SP791, SP793) conducted in Restless Legs Syndrome (RLS) patients. Update of Summary of Product Characteristics	23/07/2009	31/08/2009	SmPC	Following the assessment of the results from a case-by-case analysis on SP791 and SP793 (open label extension of study SP792) data to address the safety concern over augmentation rate, the CHMP concluded that the high frequency of augmentation in Restless Legs Syndrome (RLS) should be reflected in the SPC, even though clinically significant augmentation was much lower, because of the stringent criteria for evaluable patients. On the basis of the results of placebo controlled clinical studies (SP790, SP792) and 1-year, open-label follow-up studies (SP791, SP793), the CHMP recommended the following information to be reflected in section 4.4 of the SPC: - Augmentation may occur. Augmentation refers to the earlier onset of symptoms in the evening (or even the afternoon), increase in severity of symptoms, and spread of symptoms to involve other body parts. Based on two open-label follow-up studies with one year duration, symptoms reflecting clinically relevant and not relevant augmentation may be as high as 9.4%. However, based on two 6-month, double-blind, placebo-controlled studies, clinically relevant augmentation was observed in 1.5% of rotigotine-treated

					patients versus 0.5% of placebo treated patients. In two open-label, follow-up studies over a subsequent 12 months, the rate of clinically relevant augmentation was 2.9%. None of these patients discontinued therapy because of augmentation."
II/0034	Update of section 4.8 of Summary of Product Characteristics (SPC) to include information on discontinuation rates at the CHMP request. This update is based on results of clinical studies SP791, SP793 and additional 3-year data from an ongoing study (SP710) conducted in Restless Legs Syndrome (RLS) patients. Update of Summary of Product Characteristics	23/07/2009	31/08/2009	SmPC	Following the assessment of the results from open label extension studies SP790 and SP793, the CHMP concluded that long term data on rotigotine to treat Restless Legs Syndrome (RLS) supported previous evidence on efficacy, safety and tolerability. Moreover, results were not significantly different between studies. However discontinuation rates were kept high (up to 38%) and the CHMP requested an update of section 4.8 of the SPC to reflect this information. Subsequently the MAH provided additional 3-year data from an ongoing study (SP710) also conducted in RLS patients. At 1 year in SP791, SP793, and SP710, 27%, 38%, and 25% of subjects discontinued from the respective study. At 2 years in SP710, an additional 10% of subjects discontinued, with 65% of subjects remaining in the trial. At 3 years in SP710, an additional 11% of subjects discontinued, with 54% of subjects remaining in the trial. The CHMP therefore recommended the following information to be included in section 4.8 of the SPC: - The discontinuation rate was studied in 3 clinical trials ranging up to 3 years in duration. The percentage of subjects discontinuing was 25-38% over the first year, 10% in the second year, and 11% in the third year. Periodic assessment of efficacy should be performed, along

					with evaluation of safety, including augmentation.
II/0031	Update of the Detailed Description of the Pharmacovigilance System (DDPS) in Module 1.8.1 of the Neupro Marketing Authorisation to version 7.0 dated 5 June 2009. Annex II has been updated to reflect the new version number of the DDPS. Changes to QPPV Update of DDPS (Pharmacovigilance)	25/06/2009	16/07/2009	Annex II	With this variation the MAH submitted an updated DDPS (version 5.0). After assessing the documentation the CHMP concluded that the submitted DDPS contains all required elements. The Annex II was therefore updated to include the version number of the new DDPS.
II/0030	This variation refers to the submission of a bioequivalence study (SP951) comparing patches from the originally approved manufacturing process using rotigotine Form 1, with patches manufactured using rotigotine Form 2, according to the new manufacturing process in place and to the lifting of the following restrictions: - pack size limitation : pack size will be limited to no more than 1 month supply; - not to expand/promote the current Parkinson's disease treatment population; - not to pursue the planned launches of Neupro for Parkinson's disease indication in those European (EU) countries where the product is not yet available; - not to launch the product for the indication Restless Legs Syndrome within the EU. Consequently, Annex II is updated to reflect that the related commitments to address the quality defect in relation to the crystal formation in the patches are considered fulfilled.	29/05/2009	24/06/2009	Annex II	As part of a commitment to address the quality defect in relation to crystal formation in the patches, the MAH submitted the results of a bioequivalence study (SP951) and subsequently requested the lifting of the restrictions laid out in the commitments made at the time of Urgent Safety Restriction and article 20 procedure in relation to pack size limitation and initiation of new patient treatment. Based on the review of these data, the CHMP concluded that bioequivalence of rotigotine transdermal patch (4.5mg/10cm2) from the modified manufacturing process using polymorphic form 2 as drug substance for patch production and from the originally approved manufacturing process using polymorphic form 1 as drug substance for patch production was established. Furthermore, taking into account that all the related commitments undertaken by the MAH have been fulfilled to address the quality defect in relation to the crystal formation in the patches, the CHMP recommended the lifting of the restrictions, as requested by the MAH.

	Quality changes				
IB/0033	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	27/05/2009	n/a	SmPC	
IB/0032	IB_33_Minor change in the manufacture of the finished product	12/05/2009	n/a		
II/0028	Change to shelf-life and update to the pharmaceutical documentation. Quality changes	19/02/2009	02/04/2009	SmPC	
II/0029	The Marketing Authorisation Holder applied to change the drug substance specification to be specific for rotigotine form 2 according to a previous commitment. Quality changes	19/02/2009	06/03/2009		
II/0024	The MAH has applied for changes of the product regarding the storage condition, the shelf life and the release and shelf life specifications following an Urgent Safety Restriction. New safety warning	25/09/2008	06/11/2008	SmPC	
IA/0027	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	13/10/2008	n/a		
II/0025	The MAH has applied for an update of the Drug	25/09/2008	01/10/2008		

	Substance Part following an Urgent Safety Restriction. Change(s) to the manufacturing process for the active substance				
IB/0026	IB_10_Minor change in the manufacturing process of the active substance	18/09/2008	n/a		
X/0020	Annex I_2.(c) Change or addition of a new strength/potency	24/04/2008	29/08/2008	SmPC, Labelling and PL	
II/0019	Extension of indication for Neupro 1mg/24h, 2mg/24h and 3mg/24h transdermal patches to include symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome in adults. Consequential changes are made to all Neupro presentations. Extension of Indication	24/04/2008	29/08/2008	SmPC, Annex II, Labelling and PL	The CHMP variation assessment report will be published as part of the EPAR, following review/deletion of confidential information.
A20/0023	Pursuant to Article 20 of Regulation (EC) No 726/2004, the European Commission requested on 29 May 2008, the opinion of Committee for Medicinal Products for Human Use (CHMP) on measures necessary to ensure the quality and the effective use of Neupro further to the CHMP review on the reoccurrence of a quality defect (crystal formation up to 40% of the visible surface area of the patch) and its impact on the risk benefit balance.	03/06/2008	04/08/2008	SmPC, Annex II, Labelling and PL	

N/0022	Update of the list of local representatives in section 6 of the Package Leaflet. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	28/01/2008	n/a	PL	
IB/0021	IB_33_Minor change in the manufacture of the finished product	18/12/2007	n/a		
IB/0018	IB_37_b_Change in the specification of the finished product - add. of new test parameter	03/08/2007	n/a		
IA/0017	IA_13_a_Change in test proc. for active substance - minor change	04/06/2007	n/a		
IA/0016	IA_13_a_Change in test proc. for active substance - minor change	04/06/2007	n/a		
IA/0015	IA_13_a_Change in test proc. for active substance - minor change	04/06/2007	n/a		
IA/0014	IA_13_a_Change in test proc. for active substance - minor change	04/06/2007	n/a		
IA/0013	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	04/06/2007	n/a		
IA/0012	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	04/06/2007	n/a		

IA/0011	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	04/06/2007	n/a		
IA/0010	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	04/06/2007	n/a		
IA/0009	IA_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening of spec.	04/06/2007	n/a		
IB/0008	IB_12_b_02_Change in spec. of active subst./agent in manuf. of active subst. - test parameter	16/04/2007	n/a		
IA/0007	IA_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening of spec.	23/03/2007	n/a		
N/0006	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	22/02/2007	n/a	Labelling and PL	
II/0003	The variation refers to an extension of the therapeutic indication to include 'the treatment of the signs and symptoms of advanced idiopathic Parkinson's disease 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).' Consequential changes were made to relevant sections of the Summary Product Characteristics	16/11/2006	09/01/2007	SmPC and PL	The CHMP variation assessment report will be published as part of the EPAR, following review/deletion of confidential information.

	(SPC). The Package Leaflet (PL) was updated accordingly. In addition, contact details of Bulgaria and Romania local representatives were also included. Extension of Indication				
N/0005	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	16/11/2006	n/a	PL	
N/0002	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/08/2006	n/a	PL	
IA/0004	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	02/08/2006	02/08/2006	SmPC, Labelling and PL	
IA/0001	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	17/05/2006	n/a		