Kuvan

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
IB/0079	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	08/11/2024	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).

II/0078	Submission of the final report from study KOGNITO, listed as a category 3 study in the RMP. This is a Phase IV Open-Label, Single-Cohort Study of the Long-Term Neurocognitive Outcomes in 4-to 5-Year-Old Children with Phenylketonuria Treated with Sapropterin Dihydrochloride (Kuvan) for 7 Years. The RMP version 16.1 has also been submitted. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	13/06/2024	n/a		
IA/0077	A.7 - Administrative change - Deletion of manufacturing sites	04/07/2023	n/a		
IA/0076/G	This was an application for a group of variations. B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.e.2.c - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	05/09/2022	n/a		
PSUSA/2683/ 202112	Periodic Safety Update EU Single assessment - sapropterin	07/07/2022	n/a		PRAC Recommendation - maintenance
II/0073	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	07/07/2022	n/a		

IB/0075	B.II.f.z - Stability of FP - Other variation	23/03/2022	n/a		
IB/0072	B.II.b.5.f - Change to in-process tests or limits applied during the manufacture of the finished product - Addition or replacement of an in-process test as a result of a safety or quality issue	15/12/2021	n/a		
IB/0071	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	15/04/2020	n/a		
IA/0070/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS 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)	10/04/2020	n/a		
II/0068	Update of Section 5.1 of the Summary Product Characteristics (SmPC) in order to reflect new paediatric information based on study PKU-015 evaluating the effect of Kuvan on neurocognitive function, maintenance of blood phenylalanine concentrations, safety, and population pharmacokinetics in young children with phenylketonuria.	16/01/2020	04/02/2021	SmPC	Based on the review of the submitted data, new clinical SmPC information (section 5.1) related to the long term efficacy and safety of Kuvan was added. In young children with phenylketonuria (PKU), efficacy parameters were within the average range for the normative population. No additional adverse reactions were identified with long-term use of Kuvan for a mean duration of 6.5 years in children

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				less than 7 years of age at study entry.
IB/0069	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	28/10/2019	n/a		
PSUSA/2683/ 201812	Periodic Safety Update EU Single assessment - sapropterin	14/06/2019	n/a		PRAC Recommendation - maintenance
IAIN/0067/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.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing	05/04/2019	n/a		
IA/0066/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) 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)	17/03/2019	n/a		

IB/0064/G	This was an application for a group of variations. B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation 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)	15/02/2019	n/a		
II/0061	Update of section 5.2 of the Summary of Product Characteristics (SmPC) for Kuvan in order to update the information related to the interaction with P-glycoprotein (P-gp) and breast cancer resistant protein (BCRP). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/01/2019	20/05/2019	SmPC	Based on the submission of drug-drug interaction study performed in 24 healthy subjects to investigate the effects of Kuvan on the pharmacokinetics of a sensitive P-gp substrate (digoxin) when given concomitantly, section 5.2 was updated to include further information on the potential for Kuvan to inhibit p-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) in the gut at the therapeutic doses. In healthy subjects, administration of a single dose of Kuvan at the maximum therapeutic dose of 20 mg/kg had no effect on the pharmacokinetics of a single dose of digoxin (P-gp substrate) administered concomitantly. Based on the in vitro and in vivo results, co-administration of Kuvan is unlikely to increase systemic exposure to drugs that are substrates for BCRP.
IB/0063/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.1.b - Replacement or addition of a	16/01/2019	n/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.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process				
II/0060	Update of the section 4.8 of the Summary of Product Characteristics (SmPC) to add oesophagitis as a new adverse drug reaction with a frequency unknown. The Package Leaflet (PL) is updated accordingly and editorial changes are made related to the information on sodium content in the SmPC and PL. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	11/10/2018	20/05/2019	SmPC and PL	
IA/0062/G	This was an application for a group of variations. B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	30/08/2018	n/a		

PSUSA/2683/201712	Periodic Safety Update EU Single assessment - sapropterin	14/06/2018	n/a		PRAC Recommendation - maintenance
II/0059	C.I.3.z - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Other variation	07/06/2018	20/05/2019	SmPC	
II/0052	Based on a review of the post-marketing experience and in order to harmonise the safety information with the CCDS, update of section 4.8 of the Kuvan SmPC to add the following adverse events regarding gastrointestinal tract: dyspepsia, nausea and gastritis. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to implement the latest QRD template and bring up to date sections 17 and 18 of Annex IIIA. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	12/04/2018	12/06/2018	SmPC, Labelling and PL	
IA/0056/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.II.e.2.c - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.II.e.4.a - Change in shape or dimensions of the	06/03/2018	n/a		

	container or closure (immediate packaging) - Non-sterile medicinal products B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier				
IB/0054/G	This was an application for a group of variations. 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.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.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	05/01/2018	n/a		
IB/0055	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	21/12/2017	n/a		
X/0047	Annex I_2.(d) Change or addition of a new pharmaceutical form	18/05/2017	13/07/2017	SmPC, Labelling and	

				PL	
II/0048/G	This was an application for a group of variations. Update of section 4.9 of the SmPC to add information regarding shortening of QT interval at high doses following review of data of study QTC-001. Submission of the clinical study report EMR700773-004 (pilot study assessing the effect of sapropterin on cognitive abilities, study prematurely terminated due to enrolment issues) In addition, the MAH took the opportunity of this procedure to clarify the wording of section 4.2 and section 3 of the PL. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	22/06/2017	12/06/2018	SmPC and PL	Following the review of data of study QTC-001, a phase I study to assess the effect of Kuvan at supra-therapeutic dose on QTc intervals, it was agreed to update the SmPC section 9 to add information that shortening of the QT interval was observed and should be taken into consideration in managing patients who have a pre-existing shortened QT interval.
PSUSA/2683/201612	Periodic Safety Update EU Single assessment - sapropterin	09/06/2017	n/a		PRAC Recommendation - maintenance
IB/0050	B.II.b.5.f - Change to in-process tests or limits applied during the manufacture of the finished product - Addition or replacement of an in-process test as a result of a safety or quality issue	20/04/2017	n/a		

II/0046	Update of section 4.5 to delete the statement that no interaction studies have been performed and section 5.2 to reflect the relevant results of in vitro pharmacokinetic drug interactions studies BMN162-14-021, 022, 023, BMN162-15-036 and 101. In addition, the MAH took the opportunity of this procedure to improve the wording of section 4.2 and implement minor administrative changes in the SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/03/2017	13/07/2017	SmPC	Following the review of in vitro studies BMN162-14-021, 022, 023, BMN162-15-036 and 101, the CHMP agrees that sapropterin did not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4/5, nor induce CYP1A2, 2B6, or 3A4/5. This information is reflected in section 5.2 of the SmPC.
IA/0051	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)	17/03/2017	n/a		
IB/0045/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites 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.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.4.b - Change to in-process tests or limits	05/10/2016	n/a		

	applied during the manufacture of the AS - Addition of a new in-process test and limits B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method 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) B.I.d.1.c - Stability of AS - Change in the re-test period/storage period or storage conditions - Change to an approved stability protocol 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.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.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				

PSUSA/2683/201512	Periodic Safety Update EU Single assessment - sapropterin	09/06/2016	n/a		PRAC Recommendation - maintenance
IAIN/0044	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	25/05/2016	n/a		
IAIN/0043	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	18/03/2016	n/a		
IAIN/0041	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	27/01/2016	11/01/2017	Annex II and PL	
T/0040	Transfer of Marketing Authorisation	25/11/2015	07/01/2016	SmPC, Labelling and PL	
IA/0039	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	07/08/2015	n/a		
IB/0038	B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	30/07/2015	n/a		
II/0033	Extension of indication for the 'treatment of hyperphenylalaninaemia (HPA) in adults and paediatric patients of 4 years of age and over with	21/05/2015	22/06/2015	SmPC and PL	Please refer to the scientific discussion Kuvan EMEA/H/C/000943/II/0033 for further information.

	phenylketonuria (PKU) who have shown to be responsive to such treatment' to include the paediatric population of all ages. Consequently, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC and the Package Leaflet are updated accordingly. The requested variation proposed amendments to the SmPC and Package Leaflet. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
PSUSA/2683/ 201412	Periodic Safety Update EU Single assessment - sapropterin	11/06/2015	n/a		PRAC Recommendation - maintenance
II/0032	To change an impurity limit of the finished product. B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range	22/01/2015	n/a		
II/0034	Update of section 4.6 of the SmPC following the evaluation of pregnancy data from MAH-sponsored trials, post-marketing safety database and literature. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	18/12/2014	22/06/2015	SmPC	Following the evaluation of pregnancy data from sponsored trials, post-marketing safety database and literature, section 4.6 of the SmPC has been updated to reflect the data available. These up-to-date data support confirmed that the notion that dietary control of blood phenylalanine levels during pregnancy is necessary.
IA/0036/G	This was an application for a group of variations. B.II.b.2.a - Change to importer, batch release	10/12/2014	n/a		

	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 B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure				
IG/0500	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	17/11/2014	n/a		
IG/0461	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	22/07/2014	n/a		
PSUV/0029	Periodic Safety Update	12/06/2014	n/a		PRAC Recommendation - maintenance
IB/0030/G	This was an application for a group of variations. B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - 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	16/05/2014	n/a		

R/0026	Renewal of the marketing authorisation.	19/09/2013	13/11/2013	SmPC, Annex II, Labelling and PL	
IA/0028	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)	12/11/2013	n/a		
IB/0027	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	13/08/2013	n/a		
IA/0025	A.7 - Administrative change - Deletion of manufacturing sites	26/02/2013	n/a		
IB/0022/G	This was an application for a group of variations. B.I.b.1.h - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition or replacement (excl. Biol. or immunol. substance) of a specification parameter as a result of a safety or quality issue 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 as a result of a safety or quality issue B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting	03/12/2012	n/a		

	material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method 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 B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure 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				
IA/0024/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites	29/10/2012	n/a		
IG/0224	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	11/10/2012	n/a		
IB/0018/G	This was an application for a group of variations. B.I.b.1.h - Change in the specification parameters	15/06/2012	n/a		

	and/or limits of an AS, starting material/intermediate/reagent - Addition or replacement (excl. Biol. or immunol. substance) of a specification parameter as a result of a safety or quality issue B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate 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 as a result of a safety or quality issue B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)				
IB/0017/G	This was an application for a group of variations. B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - 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	15/06/2012	n/a		
II/0015	Update of section 4.8 of the SmPC following assessment of the 5th PSUR, to reflect cases of hypersensitivity that have been reported. The	19/04/2012	25/05/2012	SmPC and PL	In August 2011 the MAH submitted the 5th PSUR including the relevant safety information for Kuvan. The CHMP concluded in the assessment report that the SmPC should

	Package Leaflet is updated in accordance. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. 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				be updated regarding hypersensitivity/allergic reactions and anaphylactic type reactions. This variation addresses this request. The review of the cumulative post-marketing data presented in the 5th PSUR shows that a causal role of Kuvan in the development of "allergic reactions", "asthma" or "rash" could not be established in most of the cases. However, isolated reports suggest that the administration of Kuvan may be associated with hypersensitivity. Twenty reports of hypersensitivity reactions were identified by the MAH. In two of these cases the reported hypersensitivity reactions were observed within a rather short temporal link in the absence of history of allergies, which may suggest some relationship with the treatment. In three other cases reporting skin rash, a positive rechallenge was reported, which appear to support, with a reasonable possibility, a causal relationship. As the causal association between Kuvan and hypersensitivity reactions cannot be excluded for these cases, the product information regarding allergic/hypersensitivity reactions has been updated. This new identified risk does not affect the benefit/risk ratio of Kuvan which remains positive.
IA/0016/G	This was an application for a group of variations. B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.II.d.1.c - Change in the specification parameters	11/04/2012	n/a		

	and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method				
IA/0014	B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place	16/12/2011	n/a		
II/0012	Following the review of the PSUR 3, MAH has applied to update SmPC to reflect changes in the reporting of convulsion cases in the sections 4.4 and 4.5 of the SmPC. In addition, numbers in the section 5.1 of the SmPC have been rounded for better readability. The MAH also took the opportunity to update Annex IIB "Other conditions" with the latest wording as per October 2010 CHMP announcement regarding the Pharmacovigilance system and to update local representatives in the Package Leaflet. 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	23/06/2011	26/07/2011	SmPC, Annex II and PL	Following the review of the PSUR 3 the CHMP recommended reviewing the product information in order to accurately reflect the post marketing reports of convulsion. The MAH therefore applied to amend Product Information. The risk of convulsion was evaluated using various sources including 10-year post-marketing surveillance program, Merck Serono Safety Database and literature review. Subsequently the sections 4.4 "Special warnings and Precautions for use" and 4.5 "Interactions with other medicinal products and other forms of interaction" of the current SmPC have been updated to reflect changes to the Core Data Sheet to reflect data in relation to convulsions and exacerbation of convulsions.
IG/0076/G	This was an application for a group of variations. C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV	01/07/2011	n/a		

	C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details 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				
T/0011	Transfer of Marketing Authorisation	21/12/2010	21/01/2011	SmPC, Labelling and PL	
IB/0010	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)	10/06/2010	n/a	SmPC	
II/0007	Update of the Detailed Description of the Pharmacovigilance system (DDPS). Update of DDPS (Pharmacovigilance)	22/04/2010	12/05/2010	Annex II	With this variation the MAH submitted a new version of the DDPS (core version 9.0) in accordance with the current Pharmacovigilance guideline. After assessing the documentation the CHMP concluded that the submitted DDPS contained all required elements. Consequently, Annex II has been updated with the new version number of the agreed DDPS.
IA/0009	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	25/03/2010	n/a		
II/0006	Introduction of an alternative manufacturing process for the active substance. Quality changes	18/03/2010	24/03/2010		

IB/0008/G	This was an application for a group of variations. 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	23/03/2010	n/a		
II/0003	Change in an in-process control of the finished product. Quality changes	23/07/2009	12/08/2009		
IB/0005	IB_17_a_Change in re-test period of the active substance	07/08/2009	n/a		
N/0004	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	30/06/2009	n/a	PL	
IA/0002	IA_08_b_01_Change in BR/QC testing - repl./add. manuf. responsible for BR - not incl. BC/testing	19/12/2008	n/a	Annex II and PL	
IA/0001	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	19/12/2008	n/a		