Orkambi

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/10455 /202305	Periodic Safety Update EU Single assessment - lumacaftor / ivacaftor	25/01/2024	05/04/2024	SmPC and PL	Please refer to Orkambi EMEA/H/C/PSUSA/00010455/202305 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation
IG/1695/G	This was an application for a group of variations.	08/12/2023	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).

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	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.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				
X/0078/G	This was an application for a group of variations. Extension application to add a new strength of 75 mg of lumacaftor and 94 mg of ivacaftor fixed dose combination granules, grouped with a type II variation (C.I.6.a). Extension of indication to include treatment of cystic fibrosis for children aged 1 to less than 2 years old of age who are homozygous for the F508del mutation in the CFTR gene, based on final results from study 122, a 2-part study of CF subjects 1 to <2 years of age homozygous for F508del. As a consequence, sections 4.1, 4.2, 4.5, 4.6, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Annex II has also been updated. In addition, the MAH took the opportunity to implement minor updates in the Product Information. Version	26/04/2023	04/07/2023	SmPC, Labelling and PL	Please refer to Scientific Discussion "Orkambi EMEA/H/C/003954/X/0078/G".

	11.4 of the RMP has also been approved. Annex I_2.(c) Change or addition of a new strength/potency C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IA/0084	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	29/05/2023	n/a		
SW/0083	Post Authorisation Safety Study results - EMEA/H/C/PSR/S/0039 – Variation	23/02/2023	26/04/2023	Annex II	As the PASS is finalized, removal of the additional monitoring statement and the black triangle from the product information is warranted. Annex II of the product information is also updated to remove the PASS. Therefore, in view of available data regarding the PASS final study report, the PRAC considered that changes to the product information and to the conditions of the marketing authorisation were warranted.
IAIN/0082	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	09/03/2023	04/07/2023	Annex II and PL	
IA/0081	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	05/12/2022	n/a		
PSUSA/10455 /202205	Periodic Safety Update EU Single assessment - lumacaftor / ivacaftor	01/12/2022	n/a		PRAC Recommendation - maintenance

IG/1530	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	28/06/2022	n/a		
IG/1460	A.1 - Administrative change - Change in the name and/or address of the MAH	13/12/2021	20/10/2022	SmPC, Labelling and PL	
PSUSA/10455 /202105	Periodic Safety Update EU Single assessment - lumacaftor / ivacaftor	02/12/2021	n/a		PRAC Recommendation - maintenance
IA/0075/G	This was an application for a group of variations. A.z - Administrative change - Other variation B.II.e.5.b - Change in pack size of the finished product - Deletion of a pack size(s)	15/10/2021	20/10/2022	SmPC and PL	
IA/0073	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)	03/08/2021	n/a		
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	03/06/2021	n/a		
IAIN/0070	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	20/04/2021	n/a		
IB/0067	B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a	14/04/2021	n/a		

	re-test period/storage period supported by real time data				
IA/0068	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	12/02/2021	n/a		
PSUSA/10455 /202005	Periodic Safety Update EU Single assessment - lumacaftor / ivacaftor	14/01/2021	n/a		PRAC Recommendation - maintenance
IG/1312/G	This was an application for a group of variations. 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.I.d.1.c - Stability of AS - Change in the re-test period/storage period or storage conditions - Change to an approved stability protocol 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	04/12/2020	n/a		
IB/0063	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	25/11/2020	n/a		

R/0056	Renewal of the marketing authorisation.	17/09/2020	18/11/2020	SmPC, Annex II, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Orkambi in the approved indication remains favourable, but recommended that one additional five-year renewal be required based on the following pharmacovigilance grounds: The following pharmacovigilance issues require a second renewal of the marketing authorisation: • There is an ongoing PASS for Orkambi which aims to evaluate the long-term safety of lumacaftor/ivacaftor (LUM/IVA) therapy in patients with cystic fibrosis (CF). Given that this study is categorised as category 1 and the results are considered key to benefit risk it is considered appropriate to have a second renewal of the marketing authorisation. • There is limited exposure and post-marketing data available for the recent approvals in paediatric patients (6-12 years and 2-5 years of age). • There is a planned PAES study to compare disease progression among children with CF homozygous for F508del-CFTR and aged 2 through 5 years at the time of Orkambi treatment initiation versus disease progression among concurrent matched cohort of children with CF who have never received Orkambi treatment, in addition to a longitudinal historical cohort. This study is expected to provide verification of the impact of Orkambi treatment on clinical outcomes (including long term safety) and disease progression and to confirm current efficacy and safety assumptions. Therefore, based upon the limited safety profile of Orkambi, the CHMP concluded that the MAH should submit

					one additional renewal application in 5 years' time.
N/0064	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/11/2020	20/10/2022	PL	
N/0061	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	21/09/2020	20/10/2022	PL	
II/0055	Update of section 4.8 of the SmPC with safety data in children from the Phase 3, open-label, multicentre rollover study for Study 115 Part B, designed to evaluate long-term safety of Orkambi treatment for 96 weeks in patients with cystic fibrosis, 2 years of age and older, homozygous for F508del. The MAH also took the opportunity to update the SmPC in line with the latest version of the QRD template v10.1. The Package Leaflet is updated accordingly. In addition, the RMP version 8.0 is acceptable. In addition, the RMP is updated and version 7,1 is submitted. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	09/07/2020	18/11/2020	SmPC, Annex II, Labelling and PL	Long-term safety data from a 96-week rollover extension study in 57 patients aged 2 years and older who were homozygous for the F508del mutation in the CFTR gene were generally consistent with the 24-week parent study in patients aged 2 to 5 years (trial 8) and safety data in patients aged 6 to 11 years.
II/0049	Update of section 4.8 of the SmPC with the safety data and section 5.1 with the (secondary) efficacy data from the Phase 3, open-label, rollover study for Studies 109 and Study 011 Part B designed to evaluate the long-term safety and tolerability of Orkambi treatment for 96 weeks in patients with cystic fibrosis, 6 years of age and older, homozygous	09/07/2020	18/11/2020	SmPC	Patients with CF aged 6 years and older from trial 6 and trial 7 were included in a phase 3, multicentre, rollover extension study (trial 9). This extension trial was designed to evaluate the safety and efficacy of long-term treatment of lumacaftor/ivacaftor. Of the 262 patients who received any treatment in trial 6 or trial 7, 239 (91%) were dosed and received active treatment (patients 6 to <12 years of

	for F508del. The MAH also took the opportunity to include minor changes to section 4.5 of the Granules SmPC and sections 4.8 and 5.2 of the Tablets and Granules SmPC which were considered acceptable by CHMP. In addition, the RMP version 8.0 is acceptable. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				age received lumacaftor 200 mg q12h/ivacaftor 250 mg q12h; patients ≥12 years of age received lumacaftor 400 mg q12h/ivacaftor 250 mg q12h) in the extension study for up to an additional 96 weeks (i.e. up to a total of 120 weeks). Overall, long term safety data from a 96-week rollover extension study (Trial 9) in 239 patients aged 6 years and older who were homozygous for the F508del mutation in the CFTR gene were generally consistent with the 24-week parent studies in patients aged 6 to 11 years (Trial 6 and Trial 7).
IG/1180/G	This was an application for a group of variations. 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 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	17/06/2020	n/a		
IB/0059	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)	29/05/2020	18/11/2020	SmPC	
IB/0057/G	This was an application for a group of variations. B.II.b.1.e - Replacement or addition of a	16/04/2020	n/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.g.5.b - Implementation of changes foreseen in an approved change management protocol - Requires further supporting data				
IB/0058	B.II.g.4.b - Changes to an approved change management protocol - Minor changes that do not change the strategy defined in the protocol	08/04/2020	n/a		
II/0053/G	This was an application for a group of variations. B.II.g.2 - Introduction of a post approval change management protocol related to the finished product B.II.g.2 - Introduction of a post approval change management protocol related to the finished product	16/01/2020	n/a		
PSUSA/10455 /201905	Periodic Safety Update EU Single assessment - lumacaftor / ivacaftor	28/11/2019	n/a		PRAC Recommendation - maintenance
IA/0054	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	14/11/2019	n/a		
IA/0052/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	20/09/2019	n/a		

	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) 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.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.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits				
PSUSA/10455 /201811	Periodic Safety Update EU Single assessment - lumacaftor / ivacaftor	14/06/2019	n/a		PRAC Recommendation - maintenance
IB/0048	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	28/05/2019	n/a		

IB/0047	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	10/05/2019	n/a		
IA/0045/G	This was an application for a group of variations. B.II.b.3.z - Change in the manufacturing process of the finished or intermediate 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	04/03/2019	n/a		
IAIN/0046/G	This was an application for a group of variations. A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing	15/02/2019	11/02/2020	Annex II and PL	
IAIN/0044/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) B.II.b.1.a - Replacement or addition of a	15/02/2019	n/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 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 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				
IB/0042	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	30/01/2019	n/a		
X/0034/G	This was an application for a group of variations. The MAH applied for an addition of a new pharmaceutical form (granules) and an addition of two new strengths (100/125 mg and 150/188 mg) for paediatric use (2 to 5 years). In addition, the MAH updated sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.3, 6.3 and 6.4 of the SmPC of the	15/11/2018	15/01/2019	SmPC, Labelling and PL	

	tablets formulation to bring it in line with the safety updates proposed with the new paediatric granules formulation and its extension for use in 2-5 years old. Annex II, the PL and RMP v5.4 have been updated accordingly. Annex II, the PL and RMP v5.4 have been updated accordingly. Annex I_2.(c) Change or addition of a new strength/potency Annex I_2.(d) Change or addition of a new pharmaceutical form C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IA/0040/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	10/12/2018	n/a		
PSUSA/10455 /201805	Periodic Safety Update EU Single assessment - lumacaftor / ivacaftor	29/11/2018	n/a		PRAC Recommendation - maintenance

IG/1018/G	This was an application for a group of variations. 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.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	28/11/2018	n/a		
T/0039	Transfer of Marketing Authorisation	26/10/2018	26/11/2018	SmPC, Labelling and PL	
IB/0036	B.II.f.1.e - Stability of FP - Change to an approved stability protocol	15/10/2018	n/a		
PSUSA/10455 /201711	Periodic Safety Update EU Single assessment - lumacaftor / ivacaftor	28/06/2018	23/08/2018	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10455/201711.
IB/0035	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	27/06/2018	n/a		
II/0030/G	This was an application for a group of variations. B.I.b.1.f - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Change outside the	22/03/2018	n/a		

	approved specifications limits range for the AS B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure 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				
PSUSA/10455 /201705	Periodic Safety Update EU Single assessment - lumacaftor / ivacaftor	14/12/2017	19/02/2018	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10455/201705.
WS/1284	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.c.1.z - Change in the specification parameters and/or limits of an excipient - Other variation	15/02/2018	n/a		
IB/0032/G	This was an application for a group of variations. 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.e - Stability of FP - Change to an approved stability protocol	14/02/2018	23/08/2018	SmPC, Labelling and PL	
IB/0031	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	07/02/2018	n/a		

IG/0881	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	11/01/2018	n/a		
X/0020	Annex I_2.(c) Change or addition of a new strength/potency	09/11/2017	08/01/2018	SmPC, Annex II, Labelling and PL	
II/0017	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	14/12/2017	19/02/2018	SmPC, Labelling and PL	
IB/0025	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	08/12/2017	n/a		
IB/0026/G	This was an application for a group of variations. 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 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.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)	06/12/2017	n/a		

WS/1187/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.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	14/09/2017	n/a		
II/0021	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	14/09/2017	08/01/2018	SmPC	
PSUSA/10455 /201611	Periodic Safety Update EU Single assessment - lumacaftor / ivacaftor	22/06/2017	24/08/2017	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10455/201611.
IA/0023/G	This was an application for a group of variations. 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 B.I.a.4.c - Change to in-process tests or limits	16/08/2017	n/a		

	applied during the manufacture of the AS - Deletion of a non-significant in-process test 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.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)				
II/0018/G	This was an application for a group of variations. 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.g.1.a - Introduction of a new design space or extension of an approved design space for the finished product - One or more unit operations in the manuf. process of the FP including the resulting IPCs and/or test procedures	30/03/2017	n/a		
WS/1047	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.13 - Other variations not specifically covered	26/01/2017	n/a		

	elsewhere in this Annex which involve the submission of studies to the competent authority				
IB/0015/G	This was an application for a group of variations. B.II.c.1.a - Change in the specification parameters and/or limits of an excipient - 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.f.1.e - Stability of FP - Change to an approved stability protocol B.II.c.1.a - Change in the specification parameters and/or limits of an excipient - Tightening of specification limits	14/12/2016	n/a		
II/0014	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	08/12/2016	24/08/2017	SmPC	
PSUSA/10455 /201605	Periodic Safety Update EU Single assessment - lumacaftor / ivacaftor	01/12/2016	n/a		PRAC Recommendation - maintenance
II/0011/G	This was an application for a group of variations. Grouping variation of 2 in-vitro studies to evaluate the potential off target activity of M6- ivacaftor to address post-authorisation measure MEA005. The MAH submitted a revised RMP to reflect information from these studies. In addition the MAH took the	15/09/2016	n/a		

	opportunity to update administrative aspects of the RMP. 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				
IG/0701	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	04/08/2016	n/a		
II/0005/G	This was an application for a group of variations. 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 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	23/06/2016	23/12/2016	SmPC and Annex II	
IB/0010	B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g.	10/06/2016	23/12/2016	SmPC, Labelling and	

	tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes			PL	
IA/0009/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.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	20/05/2016	n/a		
IB/0008/G	This was an application for a group of variations. 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.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.e.5.b - Implementation of changes foreseen in an approved change management protocol - Requires further supportive data	18/05/2016	n/a		
II/0002	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	28/04/2016	23/12/2016	SmPC and PL	
IB/0004	B.II.b.5.f - Change to in-process tests or limits applied during the manufacture of the finished	23/03/2016	n/a		

	product - Addition or replacement of an in-process test as a result of a safety or quality issue				
IA/0006	B.I.c.1.a - Change in immediate packaging of the AS - Qualitative and/or quantitative composition	29/02/2016	n/a		
IB/0007/G	This was an application for a group of variations. B.II.c.1.z - Change in the specification parameters and/or limits of an excipient - Other variation B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	23/02/2016	n/a		
IB/0003	B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	07/01/2016	23/12/2016	SmPC, Labelling and PL	