Kalydeco

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
II/0126	Submission of the final report from study VX15-770-126 (study 126) listed as a category 3 study in the RMP; this is a phase 3, 2-arm, multicenter open-label study to evaluate the safety and pharmacodynamics of long-term ivacaftor treatment in subjects with cystic fibrosis who are less than 24	31/10/2024	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).

	months of age at treatment initiation and have an approved ivacaftor-responsive mutation. The RMP version 16.0 has also been approved. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
N/0129	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/09/2024		PL	
II/0124	Submission of the final report from Post-Authorisation Effectiveness Study (PAES) Study VX15-770-125. This is an observational study to evaluate the long-term effectiveness and safety of Kalydeco in children with cystic fibrosis who have a specified CFTR gating mutation and are aged 2 through 5 years at therapy initiation. Study 125 has been removed from the Annex II.D of the product information. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	11/07/2024		Annex II	Study VX15-770-125 (Study 125) is a Post-authorization Efficacy Study designed as a 6-year observational comparative cohort study to evaluate the long-term effectiveness and safety of Kalydeco in a real-world setting in children with cystic fibrosis (CF) caused by specific CFTR gating mutations. Due to the study design, the results are purely descriptive and, as such, subject to the limitations which are inherent to this kind of studies. Overall, the analysis of the results supports more favourable trends over time for the Kalydeco Cohorts. Whether this can be attributed to ivacaftor treatment cannot be fully ensured due to the flaws of the study design such as the number of children with missing data which was variable depending on the outcome measures and the years for follow-up considered, the potential lack of comparability of the children in the Kalydeco Cohorts with respect to the Concurrent Comparator Cohorts in spite of the matching process and the higher attrition rate in the Concurrent Comparator Cohorts. The CHMP concluded that no change to the SmPC or PIL are necessary. The study has been

					removed from the Annex II.D of the Product information.
IA/0128	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	10/07/2024	n/a		
IAIN/0127	A.1 - Administrative change - Change in the name and/or address of the MAH	12/06/2024		SmPC, Labelling and PL	
X/0115/G	This was an application for a group of variations. Extension application to introduce a new strength (13.4 mg of ivacaftor granules in sachet), grouped with a type II variation (C.I.6.a) in order to extend the indication of the granules presentations to include children with cystic fibrosis aged 1 to less than 4 months and weighing 3 kg or more who have an R117H CFTR mutation or one of the approved 9 gating (class III) mutations based on interim results from study VX15-770-124 (study 124); this is a phase 3, 2-part, open-label study to evaluate the safety, pharmacokinetics, and pharmacodynamics of ivacaftor (IVA) in subjects with CF who are less than 24 months of age at treatment initiation and have a CFTR gating mutation. As a consequence, sections 1, 2, 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2, 6.5 and 8 of the SmPC of the granules presentations and sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC of the tablets presentations are updated. The Labelling and the Package Leaflet are updated in accordance. Version 15.5 of the RMP has also been approved. In addition, the MAH took the opportunity to introduce minor	22/02/2024	25/04/2024	SmPC, Labelling and PL	Please refer to Scientific Discussion "Kalydeco EMEA/H/C/0002494/X/0115/G"

	editorial changes to the PI. 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 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 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)				
IB/0123	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	11/01/2024	n/a		
PSUSA/9204/202301	Periodic Safety Update EU Single assessment - ivacaftor	12/10/2023	19/12/2023	SmPC and Labelling	Please refer to Kalydeco EMEA/H/C/PSUSA/00009204/202301 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation
II/0120/G	This was an application for a group of variations. B.II.g.4.a - Changes to an approved change management protocol - Major changes 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	14/12/2023	n/a		

	manuf. process of the FP including the resulting IPCs and/or test procedures 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.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				
IG/1695/G	This was an application for a group of variations. A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release) A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release) A.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	08/12/2023	n/a		
X/0114/G	This was an application for a group of variations. Extension application to add a new strength (59.5 mg) of the granules pharmaceutical form grouped	14/09/2023	20/11/2023	SmPC, Labelling and PL	Please refer to Scientific Discussion "Kalydeco EMEA/H/C/0002494/X/0114/G"

	with an extension of indication for the authorised granules strength in a combination regimen with ivacaftor/tezacaftor/elexacaftor for the treatment of cystic fibrosis (CF) in paediatric patients aged 2 to less than 6 years who have at least one F508del mutation in the CFTR gene (see section 5.1). The RMP (version 15.1) has also been adopted. Type IB B.II.f.1.b - to extend the shelf-life of the granules pharmaceutical form of the finished product as packaged for sale from 3 to 4 years. The Product information has been updated accordingly and in line with the latest QRD template. In addition, information related to the use of Kalydeco in combination with ivacaftor/tezacaftor/elexacaftor are introduced in the Kalydeco granules Product information. 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 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)				
IAIN/0119	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	06/10/2023	19/12/2023	SmPC, Labelling and PL	

IAIN/0118	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	29/06/2023	20/11/2023	Annex II and PL	
IB/0116/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.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 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.g.5.a - Implementation of changes foreseen in an approved change management protocol - Requires no further supporting data 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.g.5.b - Implementation of changes foreseen in an approved change management protocol - Requires further supporting data 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 -	27/04/2023	20/11/2023	SmPC	

	Replacement/addition of a site where batch control/testing takes place B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier				
IAIN/0113/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.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 B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site	21/10/2022	02/12/2022	Annex II and PL	
IB/0111/G	This was an application for a group of variations. B.II.g.5.a - Implementation of changes foreseen in an approved change management protocol - Requires no further supporting data 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	18/08/2022	n/a		

	control/testing takes place B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products B.II.g.5.b - Implementation of changes foreseen in an approved change management protocol - Requires further supporting data				
IA/0112/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	08/08/2022	n/a		
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		
R/0106	Renewal of the marketing authorisation.	24/02/2022	29/04/2022	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 Kalydeco in the approved indications remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
WS/2048	This was an application for a variation following a worksharing procedure according to Article 20 of	27/01/2022	29/04/2022	SmPC	Study VX17-661-116, part A was a Phase 3, multicenter, rollover study designed to evaluate the long-term safety

	Commission Regulation (EC) No 1234/2008. Update of the Product information to provide the final clinical study report (CSR) Part A of Study VX17- 661-116 (A Phase 3, Open-label, Rollover Study to Evaluate the Safety and Efficacy of Long-term Treatment With Tezacaftor in Combination With Ivacaftor in Subjects With Cystic Fibrosis Aged 6 Years and Older, Homozygous or Heterozygous for the F508del-CFTR Mutation). Consequently the SmPC sections 4.2, 4.5, 4.8 and 5.1 and the package leaflet are updated accordingly. The RMP is also updated. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				and tolerability of Tezacaftor in combination with Ivacaftor in CF subjects 6 years of age and older, homozygous or heterozygous for the F508del-CFTR Mutation. A total of 130 subjects were enrolled. The treatment effects observed were generally consistent with those previously observed in CF subjects 6 through 11 years of age with F/F and F/RF genotypes. In particular, the improvements observed in the parent studies (Studies 113B and 115) in LCI2.5, SwCl, CFQ-R RD score and BMI z-score were maintained or improved slightly over 96 weeks of treatment, and BMI improved during the treatment period of up to 120 weeks. Overall, the safety profile was in line with the known safety profile of Symkevi and Kalydeco. These results are added in section 5.1 of Symkevi SmPC, and the study is mentioned in section 4.8 of Symkevi SmPC and section 5.1 of Kalydeco SmPC.For more information, please refer to the Summary of Product Characteristics
II/0096	Extension of indication for Kalydeco tablets in combination regiment with Kaftrio to include the treatment of adults, adolescents and children aged 6 years and older with cystic fibrosis who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. This application is based on the results of study VX18-445-106, a phase 3, open-label, multicentre study in subjects 6 through 11 years of age, with F/MF and F/F genotypes. As a consequence, sections 4.1, 4.2, 5.1, and 5.2 of the SmPC are updated. The Packaged Leaflet is updated in accordance. Changes	11/11/2021	07/01/2022	SmPC and PL	Please refer to Scientific Discussion 'Kalydeco – EMEA-H-C-002494-II-0096'

	were also made to the PI to bring it in line with the current Agency/QRD template. RMP version 13.0 is acceptable. The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP). C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IG/1460	A.1 - Administrative change - Change in the name and/or address of the MAH	13/12/2021	29/04/2022	SmPC, Labelling and PL	
IB/0108	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	08/12/2021	n/a		
WS/2085	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.4 and 4.8 of the Summary of Product Characteristics (SmPC) to add "liver injury" and "total bilirubin elevations" as new adverse reactions with a frequency unknown and reinforce corresponding existing warning following cases of liver injury and liver failure in the post marketing setting. The Package Leaflet (PL) is updated accordingly. Kaftrio's RMP is updated to version 3.1 to upgrade hepatoxicity from a potentially serious risk to an important identified risk.	14/10/2021	07/01/2022	SmPC and PL	In a patient with cirrhosis and portal hypertension liver failure leading to transplantation has been reported while receiving Ivacaftor/Tezacaftor/Elexacaftor (IVA/TEZ/ELX) in combination with ivacaftor. IVA/TEZ/ELX in combination with IVA should be used with caution in patients with pre existing advanced liver disease (e.g. cirrhosis, portal hypertension) and only if the benefits are expected to outweigh the risks. If used in these patients, they should be closely monitored after the initiation of treatment. Elevated transaminases are common in patients with CF and have been observed in some patients treated with IVA/TEZ/ELX in combination with IVA. In patients taking IVA/TEZ/ELX in combination with IVA, these elevations have sometimes been associated with concomitant

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				elevations in total bilirubin. Assessments of transaminases (ALT and AST) and total bilirubin are recommended for all patients prior to initiating treatment, every 3 months during the first year of treatment, and annually thereafter. For patients with a history of liver disease or transaminase elevations, more frequent monitoring should be considered. In the event of ALT or AST >5 x the upper limit of normal (ULN), or ALT or AST >3 x ULN with bilirubin >2 x ULN, dosing should be interrupted, and laboratory tests closely followed until the abnormalities resolve. Following the resolution of transaminase elevations, the benefits and risks of resuming treatment should be considered. Liver injury and total bilirubin elevations are added as new adverse reactions with a frequency "not known" as the frequency cannot be estimated from the available data. Kaftrio's RMP is updated to version 3.1 to upgrade hepatoxicity from a potential serious risk to an important identified risk.
IB/0104/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 B.II.g.5.a - Implementation of changes foreseen in an approved change management protocol - Requires no further supporting data	01/09/2021	n/a		

	B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size B.II.b.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				
IA/0105	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	24/08/2021	n/a		
IB/0103/G	This was an application for a group of variations. 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	09/08/2021	n/a		
IA/0102/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 A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	14/06/2021	n/a		

	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)				
IAIN/0100	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	28/04/2021	n/a		
II/0089	Extension of indication for Kalydeco (ivacaftor) tablets in combination regimen with Kaftrio (ivacaftor/tezacaftor/elexacaftor) tablets for the treatment of adults and adolescents aged 12 years and older with cystic fibrosis (CF) who have at least one F508del mutation in the CFTR gene, regardless of the second allele, based on the results of Study VX18-445-104 in CF patients 12 years and older. This is an 8-week randomized, double-blind, controlled study in subjects heterozygous for the F508del mutation and a gating or residual function mutation (F/G and F/RF genotypes). As a consequence, sections 4.1, 5.1, and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. The RMP is updated to Version 11.0. Furthermore, the PI is brought in line with the latest QRD template version 10.1. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	25/03/2021	26/04/2021	SmPC and PL	Please refer to Scientific Discussion 'Kalydeco EMEA/H/C/002494/II/0089'

II/0093	B.II.g.2 - Introduction of a post approval change management protocol related to the finished product	15/04/2021	n/a		
IA/0097	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	13/04/2021	n/a		
II/0094	Submission of the final report from study VX15-770-122 listed as a category 3 study in the RMP. This is a study in US Cystic Fibrosis Patients with the R117H-CFTR mutation to confirm the long-term safety and effectiveness of Kalydeco, including patients <18 Years of age, combining data captured in the Cystic Fibrosis Foundation Patient Registry from an interventional cohort and a non-interventional cohort. In addition, the MAH took the opportunity to propose a change of due date for Study 126, listed as a category 3 in the RMP. The RMP version 10.1 is acceptable. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	11/03/2021	n/a		The results from study VX15-770-122, a Phase 4 study to confirm the long-term safety and effectiveness of Kalydeco in cystic fibrosis patients who have the R117H mutation, were in line with the known safety profile of ivacaftor and no new relevant safety concerns have emerged. Nevertheless, it should be noted that the analyses were primarily descriptive in nature and focused on evaluation of observed patterns over time and thus no robust conclusions could be made.
IB/0095	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	26/02/2021	n/a		
N/0090	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	15/12/2020	26/04/2021	PL	

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		
IA/0091/G	This was an application for a group of variations. B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure 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.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	02/12/2020	n/a		
X/0083/G	This was an application for a group of variations. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or	17/09/2020	25/11/2020	SmPC, Labelling and PL	

	modification of an approved one Annex I_2.(c) Change or addition of a new strength/potency				
II/0086	Please refer to the Recommendations section above. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	17/09/2020	03/11/2020	SmPC and PL	Please refer to Scientific Discussion 'Kalydeco-H-C-002494-II-Var.86.
PSUSA/9204/202001	Periodic Safety Update EU Single assessment - ivacaftor	04/09/2020	n/a		PRAC Recommendation - maintenance
II/0085	Extension of indication to include the combination regimen of the ivacaftor 150 mg tablets with elexacaftor/tezacaftor/ivacaftor fixed dose combination (FDC) tablets for the treatment of adults and adolescents aged 12 years and older with cystic fibrosis who who are homozygous for F508del mutation in the CFTR gene or heterozygous for F508del in the CFTR gene with a minimal function (MF) mutation; as a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. The RMP is updated to version 8.8. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	23/07/2020	21/08/2020	SmPC and PL	Please refer to Scientific Discussion 'Kalydeco-H-C-002494-II-0085'
IG/1180/G	This was an application for a group of variations.	17/06/2020	n/a		

	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				
II/0082	Extension of indication to include treatment of cystic fibrosis in children aged 6 years and older and weighing 25 kg or more for Kalydeco 150 mg tablets and in children aged 6 months and older and weighing 5 kg to less than 25 kg for Kalydeco granules 25 mg, 50 mg and 75 mg who have an R117H mutation in the CFTR gene. As a consequence, sections 4.1, 4.2, 4.4 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. The RMP version 8.7 has also been submitted. The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP). C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	30/04/2020	09/06/2020	SmPC and PL	Please refer to Scientific Discussion 'Kalydeco-H-C-002494-II-Var.No 0082'
II/0084	Update of section 5.1 of the SmPC in order to update the information based on results from study VX14-	14/05/2020	21/08/2020	SmPC	Update of section 5.1 of the SmPC to reflect that final data from study 110; a phase 3, multicentre, open label, rollover

	661-110 (Part A) which is a phase 3, multicentre, open label, rollover study for studies 103, 106, 107, 108, 109, 111, 112, and 114 designed to evaluate the long-term safety and tolerability of tezacaftor/ivacaftor treatment in combination with ivacaftor for 96 weeks in cystic fibrosis (CF) subjects 12 years and older, homozygous or heterozygous for the F508del CFTR mutation. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				study for studies 103, 106, 107, 108, 109, 111, 112, and 114 designed to evaluate the long-term safety and tolerability of tezacaftor/ivacaftor treatment in combination with ivacaftor for 96 weeks in cystic fibrosis (CF) subjects 12 years and older, homozygous or heterozygous for the F508del CFTR mutation, are now available.
II/0080	B.II.g.2 - Introduction of a post approval change management protocol related to the finished product	12/12/2019	n/a		
X/0075/G	This was an application for a group of variations. Annex I_2.(c) Change or addition of a new strength/potency C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	17/10/2019	09/12/2019	SmPC, Labelling and PL	
IA/0081/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.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS -	02/10/2019	n/a		

	Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier				
IA/0079	B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits	13/08/2019	n/a		
WS/1595	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	18/07/2019	n/a		
II/0076	Update of sections 4.4, and 5.1 of the SmPC to clarify the classification of the G970R-CFTR mutation as a splicing mutation, based on data from the Study 770-112 G970R substudy (previously submitted in procedure II/54) and an additional mRNA analysis (report N052). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/04/2019	09/12/2019	SmPC	Results of substudy of 770-112 G970R study and of additional mRNA analysis (report N052) were reflected in the SmPC of Kalydeco (tablets and granules), which clarified the classification of the G970R CFTR mutation as a splicing defect resulting in little-to-no CFTR protein at the cell surface.

IAIN/0077/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.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 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.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing	08/03/2019	09/12/2019	Annex II and PL	
IAIN/0074/G	This was an application for a group of variations. B.II.b.2.a - Change to importer, batch release	14/12/2018	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.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.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 B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing				
IAIN/0073/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.2.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	14/12/2018	n/a		

	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				
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/0071	Transfer of Marketing Authorisation	26/10/2018	26/11/2018	SmPC, Labelling and PL	
II/0069	Extension of Indication to include treatment of cystic fibrosis in children age 12 to less than 24 months who have one of the currently approved gating mutations in the CFTR gene for Kalydeco 50 mg & 75 mg Granules; as a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. Relevant consequential changes are made to the Kalydeco 150 mg film-coated tablet Product Information. The Package Leaflet is updated in accordance. The RMP version 8.1 has also been submitted.	18/10/2018	22/11/2018	SmPC, Labelling and PL	Please refer to Scientific Discussion 'Kalydeco-H-C-2494-II-69'

	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
II/0063/G	This was an application for a group of variations. 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 C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	26/07/2018	10/10/2018	SmPC, Annex II, Labelling and PL	
SW/0070	Post Authorisation Safety Study results - EMEA/H/C/PSR/S/0014	28/06/2018	23/08/2018	Annex II	The final study report submitted by the MAH complies with their obligation to perform a PASS to evaluate the long-term safety of ivacaftor in patients with cystic fibrosis as imposed at the time of the initial marketing authorisation. Therefore, in view of available data regarding the PASS final study report, the PRAC considered that changes to the conditions of the marketing authorisation were warranted.
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		
IG/0881	B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP -	11/01/2018	n/a		

	Replacement/addition of a site where batch control/testing takes place				
IB/0064	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	14/11/2017	n/a		
IA/0065	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	27/10/2017	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		
IB/0062/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	08/09/2017	23/08/2018	SmPC	

	stability protocol				
PSUSA/9204/201701	Periodic Safety Update EU Single assessment - ivacaftor	01/09/2017	n/a		PRAC Recommendation - maintenance
IA/0060/G	This was an application for a group of variations. 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.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	12/07/2017	n/a		
R/0052	Renewal of the marketing authorisation.	23/02/2017	28/04/2017	SmPC and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Kalydeco in the approved indication remains favourable, but recommended that one additional five-year renewal be required based on the following pharmacovigilance grounds: There is a PASS category 1 ongoing. The fourth annual analysis will be completed by December 2016, with the final report submitted by December 2017. Long term safety is considered a key element to evaluate the benefit-risk balance of the product and therefore a second renewal is required.
II/0057	B.II.d.1.f - Change in the specification parameters and/or limits of the finished product - Deletion of a	27/04/2017	n/a		

	specification parameter which may have a significant effect on the overall quality of the finished product				
IB/0058	B.II.g.5.b - Implementation of changes foreseen in an approved change management protocol - Requires further supporting data	10/04/2017	n/a		
II/0053/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.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.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.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.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.f.1.e - Stability of FP - Change to an approved	09/03/2017	n/a		

	stability protocol B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation				
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 elsewhere in this Annex which involve the submission of studies to the competent authority	26/01/2017	n/a		
II/0054	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	26/01/2017	n/a		
IB/0056	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	11/01/2017	n/a		
II/0049	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	10/11/2016	n/a		
II/0046	B.II.g.2 - Introduction of a post approval change management protocol related to the finished product	10/11/2016	n/a		
II/0050	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	13/10/2016	16/02/2017	SmPC, Labelling and PL	

PSUSA/9204/201601	Periodic Safety Update EU Single assessment - ivacaftor	02/09/2016	n/a		PRAC Recommendation - maintenance
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/0044	B.II.g.2 - Introduction of a post approval change management protocol related to the finished product	23/06/2016	n/a		
IB/0045	B.II.g.5.b - Implementation of changes foreseen in an approved change management protocol - Requires further supporting data	04/05/2016	n/a		
IA/0048/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 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	15/04/2016	n/a		

IB/0043	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)	01/02/2016	16/02/2017	SmPC and Labelling	
X/0034/G	This was an application for a group of variations. 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 Annex I_2.(c) Change or addition of a new strength/potency	24/09/2015	16/11/2015	SmPC, Annex II, Labelling and PL	Please refer to the scientific discussion Kalydeco-H-C-002494-X-0034-G
II/0027	Extension of indication to include the treatment of cystic fibrosis in patients aged 18 years and older who have a R117H mutation in the CFTR gene. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated and the Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to implement minor editorial changes in the annexes and to align the product information with the latest QRD template. An updated RMP version 4.9 was agreed as part of this procedure. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	24/09/2015	16/11/2015	SmPC and PL	For further information please refer to the published Assessment Report: Kalydeco H-2494-II-27-AR.

PSUSA/9204/201501	Periodic Safety Update EU Single assessment - ivacaftor	10/09/2015	n/a		PRAC Recommendation - maintenance
T/0040	Transfer of Marketing Authorisation	23/07/2015	20/08/2015	SmPC, Labelling and PL	
IA/0042	B.II.e.4.a - Change in shape or dimensions of the container or closure (immediate packaging) - Non-sterile medicinal products	04/08/2015	n/a		
IAIN/0041	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	20/07/2015	n/a		
II/0032	Submission of the final population PK report (including data from all completed studies that had enrolled patients aged 6-11 years [including study 110 and study 111]) to fulfil post-authorisation measure MEA 010. 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		
IB/0039	B.II.c.1.z - Change in the specification parameters and/or limits of an excipient - Other variation	29/05/2015	n/a		
IA/0038/G	This was an application for a group of variations. B.I.c.1.a - Change in immediate packaging of the AS	13/05/2015	n/a		

	- Qualitative and/or quantitative composition B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure				
II/0035	Submission of the final Clinical Study Report of VX08-770-105 in order to fulfil the post-authorisation measure (ANX 002.1) including the updated RMP version 4.3; Annex II has been amended accordingly. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	23/04/2015	20/08/2015	Annex II	
II/0031	Update of sections 4.8 and 5.1 of the SmPC in order to reflect the results of Part 2 of Study VX12-770-111 as fulfilment of the post-authorisation measure (PAM) MEA 007. In addition the MAH also took the opportunity to include minor editorial changes in the Product Information. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/04/2015	20/08/2015	SmPC and PL	Results of part 2 of study VX12-770-111 have been reflected in the Summary of Product characteristics to update pharmacological properties and safety aspects of the product. In part 2, all patients received ivacaftor for 16 additional weeks. The duration of continuous ivacaftor treatment was 24 weeks for patients randomised to part 1 placebo/ivacaftor treatment sequence and 16 weeks for patients randomised to part 1 ivacaftor/placebo treatment sequence. Similar results to part 1 were seen in part 2 of the study. At the 4 week follow up visit (4 weeks after dosing with ivacaftor ended), mean sweat chloride values for each group were trending to pre-treatment levels. The mean (SD) absolute change in percent predicted FEV1 following 16 weeks (patients randomised to ivacaftor/placebo treatment sequence in part 1) of continuous ivacaftor treatment was 10.4% (13.2%). At the follow up visit, 4 weeks after ivacaftor dosing had ended,

					the mean (SD) absolute change in percent predicted FEV1 from part 2 week 16 was -5.9% (9.4%). For patients randomised to placebo/ivacaftor treatment sequence in part 1 there was a further mean (SD) change of 3.3% (9.3%) in percent predicted FEV1 after the additional 16 weeks of treatment with ivacaftor. At the follow up visit, 4 weeks after ivacaftor dosing had ended, the mean (SD) absolute change in percent predicted FEV1 from part 2 week 16 was -7.4% (5.5%).
II/0036/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 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	26/03/2015	n/a		
PSUSA/9204/201407	Periodic Safety Update EU Single assessment - ivacaftor	12/02/2015	n/a		PRAC Recommendation - maintenance
II/0029	B.II.g.2 - Introduction of a post approval change management protocol related to the finished product	22/01/2015	n/a		

II/0026	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	18/12/2014	20/08/2015	SmPC	
II/0030	Update of section 4.5 of the SmPC in order to add information on drug-drug interaction of Ivacaftor and ciprofloxacin after finalisation of study VX13-770-017. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	20/11/2014	20/08/2015	SmPC	New data from the ciprofloxacin drug-drug interaction study (VX13-770-017) identified that ciprofloxacin (750 mg q12h) had no clinically relevant effect on the exposure of ivacaftor and metabolites. As such, Section 4.5 of the SmPC has been updated indicating that no dose adjustment is necessary for ivacaftor during concomitant dosing with ciprofloxacin.
PSUV/0021	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/0021.
N/0028	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	28/08/2014	19/11/2014	Labelling	
IA/0024	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	29/07/2014	n/a		
II/0009	Extension of Indication to include additional gating (class III) mutations in the CFTR gene: G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N and S549R. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated.	26/06/2014	28/07/2014	SmPC and PL	For further information please refer to the published Assessment Report: Kalydeco H-2494-II-09-AR.

	Particularly, a new warning with regard to lack of clinically relevant improvement from treatment in patients with G970R mutation in the CFTR gene has been added to the product information. The Package Leaflet has been updated accordingly. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
II/0020/G	This was an application for a group of variations. To change the test method and specification limit of an impurity present in the ivacaftor active substance. B.I.b.1.f - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Change outside the approved specifications limits range for the AS 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.a.z - Change in manufacture of the AS - Other variation	24/07/2014	n/a		
IA/0023	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	30/06/2014	n/a		

II/0015/G	This was an application for a group of variations. Group of variations consisting of the submission of the following RMP commitments: final study reports for studies VX08-770-102 and VX08-770-104 covering results from the post-treatment, 2-year, observational long-term follow up. 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	26/06/2014	n/a		Overall, the safety profile of ivacaftor observed during the 2-year, post-treatment, observational follow-up period in two studies in patients with cystic fibrosis was consistent with the expectations in patients with this disease. However, the high number of disease exacerbations in the ivacaftor group compared to placebo reported in one of the two studies is unexpected. Overall, the rates of CF exacerbations in the Ivacaftor group show a lack of efficacy upon off-label use since the enrolled subjects were patients without an approved CFTR mutation. The off-label use in patients without an approved CFTR mutation is an important potential risk in the ivacaftor RMP and the potential consequences of off-label use will be evaluated in each PSUR.
II/0013	Update of section 5.1 of the Summary of Product Characteristics (SmPC) to reflect the interim analysis at week 96 of study VX08-770-105, an open-label extension of studies VX08-770-102 and 103. Sections 4.4 and 4.8 are also updated regarding the maximum length of treatment and the adverse reactions tables, respectively, based on these new available data. 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	26/06/2014	28/07/2014	SmPC and PL	In an open-label study comparing patients switched from placebo to ivacaftor vs patients who continued on ivacaftor treatment, patients in the ivacaftor/ivacaftor group maintained the improvement seen at week 48 of the initial study (day 0 through week 48) in percent predicted FEV1 through week 144. No new safety information was found relevant for inclusion in section 4.8 of the SmPC, however the adverse reaction tables were updated regarding frequencies for a number of events (dizziness, vestibular disorder, and breast mass). Within the paediatric sub-population, the frequency categories for dizziness, tinnitus, sinus congestion, diarrhoea, breast mass, and bacteria in sputum were also updated.
IB/0022/G	This was an application for a group of variations. B.I.a.1.z - Change in the manufacturer of AS or of a	11/06/2014	n/a		

	starting material/reagent/intermediate for AS - Other variation 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				
IAIN/0018	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	08/05/2014	n/a		
IAIN/0017	B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer	15/04/2014	n/a		
IB/0016	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	28/03/2014	n/a		
II/0014/G	This was an application for a group of variations. Update of sections 4.4 and 4.5 of the SmPC in order to include information from study VX12-770-016, a drug drug interaction (DDI) study with digoxin in order to fulfil MEA 006. Section 4.2 of the SmPC clarified by replacing "potent" by "strong" when	20/03/2014	28/07/2014	SmPC	The effect of Kalydeco on the PK of digoxin has been assessed in a phase 1, open-label, single-centre, non-randomized study of multiple-dose oral ivacaftor (150 mg every 12 hours [q12h]) in combination with single-dose oral digoxin (0.25 mg) in healthy subjects. It can be agreed that the administration of Kalydeco increases digoxin exposure by 1.3-fold, consistent with weak inhibition of P-

	referring to inhibitors of CYP3A (ketoconazole, (itraconazole, posaconazole, voriconazole, telithromycin and clarithromycin). In addition the MAH has submitted the following RMP commitments: report on modelling and simulation of reduced ivacaftor strength dosing to inform on the potential daily dosing recommendations in patients receiving strong CYP3A4 inhibitors and in patients with moderate hepatic impairment to inform on potential daily dosing recommendations in patients with severe hepatic impairment, and two years follow-up of subjects who prematurely discontinued in study VX08-770-103. 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 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				gp. The MAH's proposed changes to sections 4.2, 4.4 and 4.5 of the SmPC are supported by the CHMP. The potential daily dosing of ivacaftor in patients receiving strong CYP3A4 inhibitors, simulations of ivacaftor plasma concentrations after the administration of different ivacaftor daily dose with ketoconazole have also been provided. At present, no further investigations will be requested to the MAH and the authorised posology (150 mg twice weekly) is considered acceptable. In relation to the potential daily dose of ivacaftor in patients with severe hepatic impairment, data provided by the MAH refer to moderate hepatic impairment patients but they are not informative for patients with severe hepatic impairment. As for the case of concomitant administration of CYP3A4 inhibitors no further investigations are requested to the MAH as ivacaftor strengths other than 150 mg are not currently marketed and no safety concerns have been identified with the use of ivacaftor at the authorised posology (150 mg every other day). Finally, an update is provided by the MAH regarding on discontinuations from study VX08-770-103. Results show that all patients on ivacaftor completed the study and that all patients discontinuing were on placebo.
PSUV/0010	Periodic Safety Update	06/02/2014	n/a		PRAC Recommendation - maintenance
IB/0011	To align the PI with the latest QRD template vs. 9, including the black symbol and additional monitoring statements, and amendment of the Braille text.	02/12/2013	28/07/2014	SmPC, Annex II, Labelling	

	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation			and PL	
IA/0012	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	21/11/2013	n/a		
PSUV/0008	Periodic Safety Update	19/09/2013	20/11/2013	SmPC	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUV/0008.
IB/0005/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.2.z - Changes in the manufacturing process of the AS - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	15/08/2013	n/a		
IA/0004/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 of the finished product, including quality control sites (excluding manufacturer for batch release) 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	04/06/2013	n/a		

	the product information				
II/0002	To address Annex II condition on Design Space verification protocol. B.I.e.1.z - Design Space - Introduction of a new design space or extension of an approved design space for the AS - Other variation	30/05/2013	20/11/2013	Annex II	
II/0001	Update of section 5.3 (preclinical safety data) of the SmPC to include information on 'cataracts' in juvenile rats following the CHMP assessment of study VX-770-TX-025 (MEA 004). In addition the MAH has taken the opportunity to make editorial changes to the PI and to include the Marketing Authorisation date in the SmPC and the Marketing Authorisation numbers in the SmPC and in the Labelling. Furthermore, the PI is being brought in line with the latest QRD template version 8.3. C.I.3.z - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Other variation	21/02/2013	20/11/2013	SmPC, Annex II and Labelling	The assessment of the study VX-770-TX-025 in juvenile rats when dosed from postnatal day 7 through postnatal day 35 has shown that cataracts were observed in juvenile rats dosed with ivacaftor at dose levels of 10 mg/kg/day (0.12 times the recommend human dose) and higher. Information regarding the results of this study was therefore added to the product information.
IAIN/0003/G	This was an application for a group of variations. C.I.9.d - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the safety database C.I.9.e - Changes to an existing pharmacovigilance	06/02/2013	n/a		

	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				