Kaftrio

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/10868 /202204	Periodic Safety Update EU Single assessment - ivacaftor / tezacaftor / elexacaftor	01/12/2022	n/a		PRAC Recommendation - maintenance
II/0024	Update of sections 4.8 and 5.1 of the SmPC in order to update efficacy and safety information based on interim results from clinical study VX17-445-105	01/12/2022		SmPC and PL	The MAH submitted with this variation the interim results of the open-label clinical study VX17-445-105 (Study 105), designed to evaluate the long-term safety and efficacy of

[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).

	(Study 105) listed as a category 3 study in the RMP; this is a Phase III, open label extension study to evaluate the long-term safety and efficacy of ELX/TEZ/IVA in CF subjects homozygous for F508del (F/F genotype) or heterozygous for F508del and a minimal function (MF) mutation (F/MF genotypes). The RMP version 6.1 has also been submitted. In addition, the MAH took the opportunity to implement minor corrections (section 5.3 and 6.5); as well as editorial changes to the SmPC. The requested variation proposed amendments to the Summary of Product Characteristics and to the Risk Management Plan (RMP). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				Kaftrio treatment for 192 weeks in cystic fibrosis (CF) subjects, 12 years of age and older and homozygous or heterozygous for the F508del mutation. Overall, the interim analysis of 506 patients showed a clinically relevant and durable treatment effect in CF subjects throughout the first 96 weeks of treatment. Patients from the control arms as well as patients who received IVA/TEZ/ELX in combination with IVA in the parent studies 445-102 and 445-103, showed sustained or continued improvements in percent predicted Forced Expiratory Volume in 1 second (ppFEV1), Sweat Chloride (SwCl), Cystic Fibrosis Questionnaire – Revised Respiratory Domain (CFQ-R RD) score, Body Mass Index (BMI), BMI z-score, and weight over 96 weeks of treatment. No new safety concerns were identified with extended ELX/TEZ/IVA treatment. For more information, please refer to the Summary of Product Characteristics.
IB/0031	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	24/10/2022	n/a		
II/0017/G	This was an application for a group of variations. C.I.4 Update of section 5.3 of the SmPC in order to update the non-clinical information based on final results from a 2-year oral carcinogenicity study in rats (VX-445-TX-015) evaluating the carcinogenic potential of up to 10 mg/kg/day of elexacaftor. An updated RMP	29/09/2022	02/12/2022	SmPC	This variation concerns the submission of the final study reports from 2 non-clinical studies. In the 2-year oral carcinogenicity study in rats (VX-445-TX-015), administration of elexacaftor up to 10mg/kg/day by oral gavage did not reveal carcinogenic potential. The juvenile toxicity study (VX-661-TX-038) aimed to determine the potential effects of once-daily oral (gavage) administration of tezacaftor alone or in combination with

	(version 6.0) has also been submitted to include the completion of the 2-year carcinogenicity study in rats as well as to update the post-market pregnancy safety information collection form following EMEA/H/C/WS2048. C.I.13 To submit the final report of Tezacaftor Juvenile Toxicity study (VX-661-TX-038). 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				ivacaftor on growth and development in juvenile rats. Rats exposed during postnatal day 7 to 35 (PND 7-35) showed mortality and moribundity, even at low doses. Findings were dose related and generally more severe when dosing with tezacaftor was initiated earlier in the postnatal period. Exposure in rats from PND 21-49 did not show toxicity at the highest dose which was approximately two times the intended human exposure. Tezacaftor and its metabolite, M1-TEZ, are substrates for P glycoprotein. Lower brain levels of P-glycoprotein activity in younger rats resulted in higher brain levels of tezacaftor and M1-TEZ. These findings are not relevant for the indicated paediatric population 6 to 11 years of age, for whom levels of P-glycoprotein activity are equivalent to levels observed in adults. For more information, please refer to the Summary of Product Characteristics.
IB/0029	C.I.3.z - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Other variation	20/08/2022	02/12/2022	SmPC	Sections 4.8 and 5.1 of the SmPC have been updated to implement the wording agreed by the CHMP following the outcome of the assessment done under Articles 45 or 46 of Regulation 1901/2006 in procedure EMEA/H/C/005269/P46/008.
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		
PSUSA/10868 /202110	Periodic Safety Update EU Single assessment - ivacaftor / tezacaftor / elexacaftor	10/06/2022	n/a		PRAC Recommendation - maintenance
IA/0026	B.I.b.2.a - Change in test procedure for AS or	26/04/2022	n/a		

	starting material/reagent/intermediate - Minor changes to an approved test procedure				
IA/0025/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 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	22/04/2022	n/a		
IAIN/0023	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	21/03/2022	n/a		
IB/0020	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)	22/02/2022	02/12/2022	SmPC	To extend the shelf-life of the finished product Kaftrio 75/50/100 film-coated tablets, EU/1/20/1468/001, as packaged for sale from 24 months to 36 months when stored in the intended container closure system.
IAIN/0022	B.II.g.5.a - Implementation of changes foreseen in an approved change management protocol - Requires no further supporting data	17/02/2022	n/a		
IB/0021/G	This was an application for a group of variations. B.I.a.2.a - Changes in the manufacturing process of	17/02/2022	n/a		

	the AS - Minor change in the manufacturing process of the AS 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.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 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 B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size				
X/0008/G	This was an application for a group of variations. 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	11/11/2021	07/01/2022	SmPC, Annex II, Labelling and PL	Please refer to the Scientific Discussion: Kaftrio EMEA/H/C/005269/X/0008/G
IG/1460	A.1 - Administrative change - Change in the name	13/12/2021	02/12/2022	SmPC,	

	and/or address of the MAH			Labelling and PL	
PSUSA/10868 /202104	Periodic Safety Update EU Single assessment - ivacaftor / tezacaftor / elexacaftor	02/12/2021	n/a		PRAC Recommendation - maintenance
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. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	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 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.
II/0011/G	This was an application for a group of variations. B.II.b.1.d - Replacement or addition of a manufacturing site for the FP - Site which requires an initial or product specific inspection 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.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	07/10/2021	n/a		
IB/0015	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)	26/05/2021	n/a		
IB/0013/G	This was an application for a group of variations. 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 B.I.d.1.c - Stability of AS - Change in the re-test	10/05/2021	n/a		

	period/storage period or storage conditions - Change to an approved stability protocol				
II/0001	Extension of indication of Kaftrio to patients with CF aged 12 years and older 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). Changes were also made to the PI to bring it in line with the current Agency/QRD template. As a consequence of this new indication and QRD changes, sections 4.1, 4.2, 4.4, 4.5, 4.6, 4.7, 4.8, 5.1 and 5.2, 5.3 and 6.6 of the SmPC have been updated. The Package Leaflet has been updated accordingly. The RMP is updated to version 2. 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 the Scientific Discussion: Kaftrio EMEA/H/C/005269/II/0001
IAIN/0012	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	15/04/2021	n/a		
IAIN/0007/G	This was an application for a group of variations. B.II.g.5.a - Implementation of changes foreseen in	05/03/2021	n/a		

	an approved change management protocol - Requires no further supporting data 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				
IB/0004	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	22/02/2021	n/a		
IAIN/0006/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.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 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 A.4 - Administrative change - Change in the name	11/02/2021	n/a		

	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				
IA/0005/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 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.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.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.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	11/02/2021	n/a		

	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/0003	C.I.13: Submission of the final clinical study report for study VX18-445-007 (study 007), listed as a category 3 study in the RMP with the aim to evaluate the pharmacokinetics of Kaftrio (elexacaftor/tezacaftor/ivacaftor) in subjects with moderate hepatic impairment. The RMP version 1.2 has also been submitted. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	11/02/2021	n/a		Kaftrio is not recommended in patients with moderate hepatic impairment and should only be considered, when there is a clear medical need and the benefits are expected to outweigh the risks. In these patients, a recommendation to apply a reduced dose was agreed during the initial marketing authorisation as follows: In case of moderate hepatic impairment, a possible 25% reduction of the elexacaftor and tezacaftor dose, 62.5% reduction of the ivacaftor dose over a 48 hour period should be considered. Data from the Study VX18-445-007 provide further support for the current dose-advice in patients with moderate hepatic impairment. The dose-reduction (i.e. a 25% reduction in the doses of elexacaftor, tezacaftor, and their respective metabolites and a 62.5% reduction in the dose of ivacaftor over a 48-hour period) is expected to lead to comparable exposure to elexacaftor and M23-elexacaftor, to a 40% reduction in ivacaftor exposure and to a 10% decrease in tezacaftor exposure. In conclusion, the current recommendation in the product information does not need to be amended. The RMP (version 1.2) is updated to reflect the submission of this category 3 study and fulfilment of this post approval commitment.

N/0002	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	04/11/2020	26/04/2021	PL	