Symkevi

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
IAIN/0048	A.1 - Administrative change - Change in the name and/or address of the MAH	04/10/2024		SmPC, Labelling and PL	
PSUSA/10730 /202402	Periodic Safety Update EU Single assessment - tezacaftor / ivacaftor	05/09/2024	n/a		PRAC Recommendation - maintenance

[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).

IB/0046	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	21/08/2024		SmPC	
IA/0044	A.7 - Administrative change - Deletion of manufacturing sites	13/02/2024	n/a		
IG/1696/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	05/01/2024	n/a		
PSUSA/10730 /202302	Periodic Safety Update EU Single assessment - tezacaftor / ivacaftor	12/10/2023	07/12/2023	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10730/202302.
IAIN/0042	B.II.g.5.a - Implementation of changes foreseen in an approved change management protocol - Requires no further supporting data	08/09/2023	n/a		

R/0038	Renewal of the marketing authorisation.	22/06/2023	23/08/2023	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 Symkevi in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
II/0039	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	06/07/2023	n/a		
IAIN/0040	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	23/03/2023	23/08/2023	Annex II and PL	
WS/2403	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.f.z - Stability of FP - Other variation	26/01/2023	n/a		
IAIN/0037	B.II.g.5.a - Implementation of changes foreseen in an approved change management protocol - Requires no further supporting data	05/12/2022	n/a		
PSUSA/10730 /202202	Periodic Safety Update EU Single assessment - tezacaftor / ivacaftor	01/09/2022	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		
PSUSA/10730	Periodic Safety Update EU Single assessment -	24/03/2022	24/05/2022	SmPC and PL	Refer to Scientific conclusions and grounds recommending

/202108	tezacaftor / ivacaftor				the variation to terms of the Marketing Authorisation(s)' for PSUSA/10730/202108.
IB/0033/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.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS 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	16/02/2022	n/a		
WS/2048	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	27/01/2022	24/05/2022	SmPC	Study VX17-661-116, part A was a Phase 3, multicenter, rollover study designed to evaluate the long-term safety and tolerability of Tezacaftor in combination with Ivacaftor in CF subjects 6 years of age and older, homozygous or

	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				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
IG/1460	A.1 - Administrative change - Change in the name and/or address of the MAH	13/12/2021	24/05/2022	SmPC, Labelling and PL	
PSUSA/10730 /202102	Periodic Safety Update EU Single assessment - tezacaftor / ivacaftor	02/09/2021	n/a		PRAC Recommendation - maintenance
IB/0027/G	This was an application for a group of variations. B.I.d.1.c - Stability of AS - Change in the re-test period/storage period or storage conditions - Change to an approved stability protocol B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a	12/05/2021	n/a		

	re-test period/storage period supported by real time data				
IAIN/0028	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	15/04/2021	n/a		
IA/0026	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	12/03/2021	n/a		
PSUSA/10730 /202008	Periodic Safety Update EU Single assessment - tezacaftor / ivacaftor	11/03/2021	n/a		PRAC Recommendation - maintenance
IB/0025	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	18/02/2021	n/a		
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	04/12/2020	n/a		

	intermediate used in the manufacture of the AS or manufacturer of a novel excipient				
X/0015/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	17/09/2020	25/11/2020	SmPC, Annex II, Labelling and PL	
IA/0023/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.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	20/11/2020	n/a		
IA/0021	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	09/10/2020	n/a		
PSUSA/10730 /202002	Periodic Safety Update EU Single assessment - tezacaftor / ivacaftor	04/09/2020	n/a		PRAC Recommendation - maintenance
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	17/06/2020	n/a		

	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				
IAIN/0019/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.g.5.a - Implementation of changes foreseen in an approved change management protocol - Requires no further supporting data B.II.g.5.a - Implementation of changes foreseen in an approved change management protocol - Requires no further supporting data B.II.g.5.a - Implementation of changes foreseen in an approved change management protocol - Requires no further supporting data	12/06/2020	n/a		
II/0016	Update of sections 4.8 and 5.1 of the SmPC in order to update the information based on final results from study VX14-661-110 (part A) listed as a category 3 study in the RMP; this is a phase 3, multicenter, 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 (Symkevi) treatment for 96 weeks in cystic	14/05/2020	25/11/2020	SmPC	Section 4.8 of the SmPC was updated to amend the information on the safety data based on final results from study VX14-661-110 (part A). Section 5.1 of the SmPC was also updated to reflect that patients who received placebo in both study 1 and study 2 demonstrated improvements in ppFEV1 when treated with Symkevi in combination with ivacaftor in study 3 [Study 1: within group change=2.1(95% CI: 0.8, 3.3) percentage points, study 2:

	fibrosis (CF) subjects 12 years and older, homozygous or heterozygous for the F508del CFTR mutation. In addition, the Marketing authorisation holder (MAH) took the opportunity to bring the PI in line with the latest QRD template version 10.1 and to introduce minor editorial changes. The RMP version 2.3 has also been submitted. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				within group change=4.1 (95% CI: 2.2, 6.0)) percentage points]. Further, patients who received Symkevi in combination with ivacaftor in the parent studies and continued on treatment, showed a slight attenuation in ppFEV1 in the extension study, however the overall treatment effect was still positive through 120 weeks and 104 weeks for study 1 and study 2, respectively. Studies 1, 2 and 3 are further described in section 5.1 of the SmPC.
IB/0017	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)	08/04/2020	25/11/2020	SmPC	
PSUSA/10730 /201908	Periodic Safety Update EU Single assessment - tezacaftor / ivacaftor	12/03/2020	n/a		PRAC Recommendation - maintenance
II/0012/G	This was an application for a group of variations. Update of sections 4.5 and 5.2 of the SmPC in order to provide information on drug-drug interactions and pharmacogenetic data based on final results from two post-authorisation measures (PAMs) studies: VX18-661-011 (an open-label phase 1 study to examine the effects of combination of tezacaftor and ivacaftor on the pharmacokinetics and safety of pitavastatin in healthy subjects) and pharmacokinetics study P088 (pharmacogenetic study of TEZ and IVA exposure with respect to CYP3A4*22 genotype).	12/12/2019	11/02/2020	SmPC	The SmPC sections 4.5 and 5.2 have been updated based on final results from two post-authorisation measures studies with the information that Symkevi in combination with ivacaftor was found to have no clinically relevant effect on the exposure of pitavastatin, an OATP1B1 substrate. No dose adjustment of OATP1B1 substrates is required when co-administered with Symkevi. Furthermore, the effect of the CYP3A4*22 heterozygous genotype on tezacaftor and ivacaftor exposure is consistent with the effect of co-administration of a weak CYP3A4 inhibitor, which is not clinically relevant. Therefore, no dose-adjustment of tezacaftor and ivacaftor is considered necessary. No data are available for CYP3A4*22 homozygous genotype

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				patients.
IA/0013/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 - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits	27/09/2019	n/a		

	B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier				
PSUSA/10730 /201902	Periodic Safety Update EU Single assessment - tezacaftor / ivacaftor	05/09/2019	n/a		PRAC Recommendation - maintenance
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		
IA/0011	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	14/06/2019	n/a		
IAIN/0008/G	This was an application for a group of variations. 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.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS -	15/03/2019	n/a		

	Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place				
II/0002/G	This was an application for a group of variations. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	21/02/2019	11/02/2020	SmPC, Labelling and PL	
IAIN/0007/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 manufacturing site for the FP - Secondary packaging site	07/02/2019	11/02/2020	Annex II and PL	

	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.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				
T/0003	Transfer of Marketing Authorisation	03/12/2018	11/01/2019	SmPC, Labelling and PL	
IB/0005	B.II.c.1.z - Change in the specification parameters and/or limits of an excipient - Other variation	18/12/2018	n/a		
IB/0004	B.II.c.1.z - Change in the specification parameters	18/12/2018	n/a		

	and/or limits of an excipient - Other variation				
IB/0001	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	05/12/2018	n/a		
IA/0006	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	30/11/2018	n/a		