Teysuno

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
N/0058	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/12/2024		PL	
IB/0056/G	This was an application for a group of variations. B.I.z - Quality change - Active substance - Other	11/09/2024	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).

	variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation				
IB/0057/G	This was an application for a group of variations. B.I.z - Quality change - Active substance - Other variation 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	19/07/2024	n/a		
IB/0055	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	15/01/2024		SmPC and PL	
IB/0054/G	This was an application for a group of variations. B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation 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.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	21/09/2023	n/a		

IB/0053	B.II.c.2.z - Change in test procedure for an excipient - Other variation	19/05/2023	n/a		
IB/0052/G	This was an application for a group of variations. B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation A.4 - Administrative change - Change in the name	03/03/2023	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				
IB/0051	B.II.d.2.e - Change in test procedure for the finished product - Update of the test procedure to comply with the updated general monograph in the Ph. Eur.	15/02/2023	n/a		
II/0045	Extension of indication to include as monotherapy or in combination with oxaliplatin or irinotecan, with or without bevacizumab, for the treatment of patients with metastatic colorectal cancer for whom it is not possible to continue treatment with another fluoropyrimidine due to hand-foot syndrome or cardiovascular toxicity that developed in the adjuvant or metastatic setting. As a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 10.2 of the RMP has also been submitted. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	16/12/2021	24/01/2022	SmPC and PL	Please refer to Scientific Discussion 'Teysuno H/C/001242/II/0045'
IAIN/0050	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	19/11/2021	24/01/2022	Annex II and PL	

PSUSA/2875/ 202101	Periodic Safety Update EU Single assessment - gimeracil / oteracil monopotassium / tegafur	30/09/2021	n/a		PRAC Recommendation - maintenance
IA/0047	B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer	04/12/2020	n/a		
IA/0046/G	This was an application for a group of variations. B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.2 - Submission of a new/updated or	20/11/2020	n/a		

	deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer				
A31/0040	Pursuant to Article 31 of Directive 2001/83/EC, France requested on 13 March 2019 the opinion of the European Medicines Agency to assess the need to take action at EU level regarding the detection of DPD deficient patients (especially through genotyping and/or phenotyping) in patients treated with fluorouracil and related substances (capecitabine, tegafur and flucytosine). The Agency was requested to assess the impact thereof on the benefit-risk balance of fluorouracil and related substances containing products and to give its opinion on whether the marketing authorisation of these products should be maintained, varied, suspended or revoked.	30/04/2020	03/07/2020	SmPC and PL	Please refer to the assessment report: Teysuno EMEA/H/A-31/1481/C/001242/0040
IAIN/0044/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site	08/05/2020	n/a		

II/0042	C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	17/04/2020	n/a		
IAIN/0043/G	This was an application for a group of variations. A.1 - Administrative change - Change in the name and/or address of the MAH A.7 - Administrative change - Deletion of manufacturing sites 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 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	12/12/2019	03/07/2020	SmPC, Annex II, Labelling and PL	
IB/0041	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	23/07/2019	08/08/2019	SmPC, Labelling and PL	
IB/0037/G	This was an application for a group of variations.	10/01/2019	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 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.7 - Administrative change - Deletion of manufacturing sites B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)				
IB/0039/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.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)	08/01/2019	n/a		

IB/0038/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.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	08/01/2019	n/a		
PSUSA/2875/ 201801	Periodic Safety Update EU Single assessment - gimeracil / oteracil monopotassium / tegafur	06/09/2018	n/a		PRAC Recommendation - maintenance
IAIN/0035/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site	28/03/2018	n/a		
IB/0034	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)	07/03/2018	07/02/2019	SmPC and Labelling	

IAIN/0033	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	16/02/2018	07/02/2019	Annex II and PL	
PSUSA/2875/ 201701	Periodic Safety Update EU Single assessment - gimeracil / oteracil monopotassium / tegafur	14/09/2017	10/11/2017	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2875/201701.
IA/0032	A.7 - Administrative change - Deletion of manufacturing sites	20/07/2017	n/a		
N/0030	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/03/2017	10/11/2017	PL	
II/0029	Submission of the final clinical study report for SALTO - A phase III randomized, multicentre study comparing the safety of Teysuno versus capecitabine, as monotherapy or in combination with bevacizumab, as first line treatment in patients with metastatic colorectal cancer. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	16/03/2017	n/a		In fulfillment of MEA 001 (post authorization measure) the Marketing Authorisation Holder has submitted the final results of SALTO, a phase III randomized, multicentre study comparing the safety of Teysuno versus capecitabine, as monotherapy or in combination with bevacizumab, as first line treatment in patients with metastatic colorectal cancer; a safety evaluation of oral fluoropyrimidines by the Dutch Colorectal Cancer Group. The results of the study showed non-inferiority between the two study arms in terms of overall survival and progression-free survival. The results of this study suggested a potential reduction in incidence of hand-foot syndrome (HFS) associated with treatment with Teysuno compared with capecitabine. The open-label design of the study might have introduced relevant bias in the evaluation of the results. Moreover, treatment compliance was not systematically checked

					during the study. Overall, the results of the SALTO study did not warrant changes to the Product Information for Teysuno. Teysuno is currently approved in the EU in adults for the treatment of advanced gastric cancer when given in combination with cisplatin. It is not approved in the EU for treatment of metastatic colorectal cancer. The benefit-risk balance of Teysuno for the approved indication remains positive.
PSUSA/2875/ 201601	Periodic Safety Update EU Single assessment - gimeracil / oteracil monopotassium / tegafur	15/09/2016	11/11/2016	SmPC	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2875/201601.
IB/0028	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	02/09/2016	n/a		
IAIN/0027	C.I.12 - Inclusion or deletion of black symbol and explanatory statements for medicinal products in the list of medicinal products that are subject to additional monitoring	11/05/2016	11/11/2016	SmPC and PL	
II/0025	Submission of study S1119, a phase I, open-label, nonrandomized, dose-finding, safety and tolerability study of orally administered Teysuno in combination with epirubicin and oxaliplatin in patients with advanced solid tumors. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	01/04/2016	n/a		

R/0022	Renewal of the marketing authorisation.	24/09/2015	19/11/2015	SmPC, Annex II, Labelling and PL	Based on the review of the available information the CHMP is of the opinion that the quality, the safety and the efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considers that the benefit/risk profile of Teysuno continues to be favourable. The CHMP is of the opinion that the renewal can be granted with unlimited validity.
PSUSA/2875/ 201501	Periodic Safety Update EU Single assessment - gimeracil / oteracil monopotassium / tegafur	24/09/2015	19/11/2015	SmPC	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2875/201501.
IAIN/0024	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	12/11/2015	n/a		
IA/0023	A.7 - Administrative change - Deletion of manufacturing sites	29/06/2015	19/11/2015	Annex II and PL	
IB/0020	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	13/05/2015	n/a		
PSUV/0017	Periodic Safety Update	09/10/2014	n/a		PRAC Recommendation - maintenance
II/0016	C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	22/05/2014	n/a		

PSUV/0015	Periodic Safety Update	10/04/2014	n/a		PRAC Recommendation - maintenance
IB/0011	B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF	17/12/2013	n/a		
IAIN/0014	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	26/11/2013	n/a		
IAIN/0013/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing	24/10/2013	22/08/2014	Annex II and PL	
IAIN/0012	C.I.12 - Inclusion or deletion of black symbol and explanatory statements for medicinal products in the list of medicinal products that are subject to additional monitoring	24/09/2013	22/08/2014	SmPC and PL	
IB/0010	B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	06/09/2013	22/08/2014	SmPC	

N/0008	Update the list of Local Representatives in the Package Leaflet; Correct the pharmaceutical form of the medicinal product in the blister in line with the common text in the BG, DA, LT, NO, PL and SK languages; Change the INN name of the medicinal product in the blister to Latin or English for BG, DA, EL, ET, FI, HU, IS, LT, LV, NO, PL, RO, SK, SL and SV languages; Correct and get the Slovenian leaflet in line wit the common leaflet. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	15/11/2012	26/07/2013	Labelling and PL	
IAIN/0007	A.5.a - Administrative change - Change in the name and/or address of a manufacturer responsible for batch release	08/08/2012	29/10/2012	Annex II and PL	
IAIN/0006	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	08/08/2012	29/10/2012	SmPC, Labelling and PL	
II/0005	C.I.8.a - Introduction of a new Pharmacovigilance system - which has not been assessed by the relevant NCA/EMA for another product of the same MAH	16/02/2012	16/02/2012		Following the transfer of the marketing authorisation to Nordic Group B.V. (Commission Decision 12 October 2011) a Detailed Description of Pharmacovigilance System was introduced by the new MAH.
II/0002	Update of SmPC sections 4.2, 4.3, 4.4, 4.8, 5.1 and 5.2 with regard to the use in patients with severe renal impairment further to the request of the CHMP following the assessment of the results of a renal	15/12/2011	31/01/2012	SmPC, Annex II and PL	Study TPU-S1111 was a Phase 1, open-label study evaluating the pharmacokinetics of components of Teysuno in patients with varying degrees of renal function. Based on the data from TPU-S1111 study and in accordance with the

	impairment study (FUM 002). Section 2 of the Package leaflet is updated accordingly. Furthermore, the MAH took the opportunity to add the list of local representatives in the Package Leaflet. Annex II has been updated in accordance with the latest QRD template. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH				CHMP assessment and conclusions, the following updates to the SmPC were included. The pharmacodynamic and pharmacokinetic results from Study TPU-S1111 have been summarized in SmPC sections 5.1 and 5.2. Furthermore, it has been mentioned in SmPC section 4.2 that, although roughly similar 5-FU exposure was obtained in severe renally impaired patients at a dose of 20 mg/m2 QD, treatment is not recommended due to possibly higher incidence of Adverse Events of the blood and lymphatic system disorders System Organ Class, unless the benefits clearly outweigh the risks. Therefore the contraindication of severe renal impairment has been deleted and in SmPC section 4.4 a warning has been included for patients with severe renal impairment. A contraindication for end stage renal patients requiring dialysis has been added to SmPC section 4.3 as no data is available for patients requiring haemodialysis because they were excluded from the TPU-S1111 study. The section 2 of the package leaflet has been updated accordingly.
IAIN/0004	B.II.b.2.b.1 - Change to batch release arrangements and quality control testing of the FP - Not including batch control/testing	07/12/2011	31/01/2012	Annex II and PL	
T/0003	Transfer of Marketing Authorisation	12/09/2011	12/10/2011	SmPC, Labelling and PL	n/a
IA/0001/G	This was an application for a group of variations. 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	19/04/2011	n/a		

	the pharmacovigilance system C.I.9.e - Changes to an existing pharmacovigilance 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				