Senshio

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/10340 /202402	Periodic Safety Update EU Single assessment - ospemifene	03/10/2024	n/a		PRAC Recommendation - maintenance
R/0048	Renewal of the marketing authorisation.	25/07/2024	01/10/2024	SmPC, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Senshio in the approved indication remains favourable and

[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).

					therefore recommended the renewal of the marketing authorisation with unlimited validity.
IB/0047	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	31/05/2024	n/a		
IB/0046/G	This was an application for a group of variations. 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 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	30/08/2023	n/a		
IA/0045	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	06/06/2023	n/a		
IAIN/0044/G	This was an application for a group of variations. 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	07/03/2023	16/02/2024	SmPC, Annex II, Labelling and PL	

	A.1 - Administrative change - Change in the name and/or address of the MAH				
IA/0043	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	31/01/2023	n/a		
II/0042/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.b - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a manufacturer of the AS supported by an ASMF	19/05/2022	n/a		
II/0041	Extension of indication by lifting the second line treatment restriction. This is supported by the submission of the final study report of the imposed non-interventional post-authorisation safety study. As mentioned in Annex IID, this is an observational retrospective cohort study of ospemifene to assess the incidence of venous thromboembolism and other safety concerns as agreed in the Risk Management Plan (RMP), in vulvar and vaginal atrophy (VVA) patients treated with ospemifene compared to 1) patients newly prescribed SERMs for oestrogen-	27/01/2022	24/02/2022	SmPC, Annex II and PL	Please refer to Scientific Discussion 'Senshio-H-C-002780-II-0041

	deficiency conditions or breast cancer prevention, and 2) the incidence in untreated VVA patients. As a consequence, section 4.1 of the SmPC is updated. The Package Leaflet and Annex IID are updated in accordance. Version 2 of the RMP has also been submitted. In addition, the Marketing authorisation holder took the opportunity to update the list of local representatives in the Package Leaflet. The variation leads to amendments to the Summary of Product Characteristics, Annex II D 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				
PSUSA/10340 /202102	Periodic Safety Update EU Single assessment - ospemifene	30/09/2021	n/a		PRAC Recommendation - maintenance
IB/0039	B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation	28/05/2021	n/a		
IA/0038	A.7 - Administrative change - Deletion of manufacturing sites	10/03/2021	24/02/2022	Annex II and PL	
IA/0037	A.7 - Administrative change - Deletion of manufacturing sites	10/12/2020	23/07/2021	Annex II and PL	
IAIN/0036/G	This was an application for a group of variations. B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP -	07/10/2020	n/a		

	Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing 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				
PSUSA/10340 /202002	Periodic Safety Update EU Single assessment - ospemifene	01/10/2020	n/a		PRAC Recommendation - maintenance
IB/0035/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation	24/07/2020	n/a		
IAIN/0033/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.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.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging	18/03/2020	23/07/2021	Annex II and PL	

	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				
IA/0032/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.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.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)	21/01/2020	n/a		
PSUSA/10340 /201902	Periodic Safety Update EU Single assessment - ospemifene	19/09/2019	22/11/2019	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for

					PSUSA/00010340/201902
R/0028	Renewal of the marketing authorisation.	25/07/2019	21/10/2019	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 Senshio in the approved indication remains favourable, but recommended that one additional five-year renewal be required based on the following pharmacovigilance grounds: There is an imposed category 1 Post Authorisation Safety Study (PASS) ongoing. This study evaluates the risk of various side effects in a cohort of post-menopausal women newly prescribed ospemifene relative to 1) a cohort of patients diagnosed but not treated for vulvar and vaginal atrophy and 2) a cohort of postmenopausal women newly prescribed other SERM therapies utilised for oestrogen-deficiency conditions or breast cancer prevention. The primary objective of the study is to compare the incidence of venous thromboembolic events in a real-world patient population. Secondary objectives includes e.g. assessment of off label use among ospemifene patients in the EU. The MAH is obliged to submit yearly interim reports for this 5-year study. The estimated date of submission of final report is 31 March 2021. Currently, the third PASS annual report (dated 26 October 2018) has been submitted and assessed. However, the comparative analysis cannot be completed until the target sample size has been achieved. The final results of this study may yield important safety data that could have impact on the benefit-risk balance of the product. Therefore, a recommendation for a second renewal of the marketing authorisation based on pharmacovigilance grounds is warranted.

					Therefore, based upon the safety profile of Senshio, which requires the submission of 1-yearly PSURs, the CHMP concluded that the MAH should submit one additional renewal application in 5 years' time.
IA/0031	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	05/09/2019	n/a		
IA/0030	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	08/08/2019	n/a		
IA/0027	A.7 - Administrative change - Deletion of manufacturing sites	21/03/2019	n/a		
T/0026	Transfer of Marketing Authorisation	18/01/2019	11/03/2019	SmPC, Labelling and PL	
IB/0024	B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF	28/09/2018	n/a		
IAIN/0025	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	21/09/2018	n/a		
PSUSA/10340 /201802	Periodic Safety Update EU Single assessment - ospemifene	06/09/2018	n/a		PRAC Recommendation - maintenance

IB/0023	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)	23/07/2018	11/03/2019	SmPC, Labelling and PL	
PSUSA/10340 /201708	Periodic Safety Update EU Single assessment - ospemifene	22/03/2018	28/05/2018		The MAH conducted a review of headache cases and identified 167 individual case safety reports, of which there were reports of headache (n=147), migraine (n=15), sinus headache (n=2) and single reports for head discomfort, migraine with aura and exertional headache. There were 11 cases that included a positive dechallenge, with 5 of the cases also showing a positive rechallenge. A strong temporal relationship between ospemifene and headache was seen in many of the cases, which suggests a causal relationship between ospemifene and headache. The MAH has proposed to update Section 4.8 of the Summary of Product Characteristics and Section 4 of the Patient Information Leaflet to include headache as an adverse event for ospemifene, with a frequency of common which was agreed by the PRAC Committee.
IB/0020/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.z - Stability of AS - Change in the re-test period/storage period or storage conditions - Other variation	10/01/2018	n/a		
IA/0019/G	This was an application for a group of variations.	12/10/2017	n/a		

	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.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure				
PSUSA/10340 /201702	Periodic Safety Update EU Single assessment - ospemifene	28/09/2017	n/a		PRAC Recommendation - maintenance
IAIN/0018/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.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	13/09/2017	19/02/2018	Annex II and PL	
IA/0017	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	18/07/2017	n/a		
IB/0015	B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g.	27/04/2017	19/02/2018	SmPC, Labelling and	

	tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes			PL	
PSUSA/10340 /201608	Periodic Safety Update EU Single assessment - ospemifene	09/03/2017	n/a		PRAC Recommendation - maintenance
II/0010	B.I.a.1.b - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a manufacturer of the AS supported by an ASMF	02/03/2017	n/a		
II/0012/G	This was an application for a group of variations. - Update of section 4.5 of the SmPC in relation to CYP3A4 based on the results of study E1508I0242and in fulfilment of PAM 008. - Update of section 5.2 of the SmPC with information on ospemifene metabolism and excretion based on the results of study E1508I0242 in fulfilment of PAM 013 and PAM 014. - Update of section 5.2 of the SmPC with information on ospemifene distribution based on the results of studies OSP-PF-046-N and OSP-PF-047-N in fulfilment of PAM 006 and PAM 007. - Update of section 5.2 of the SmPC based on the results of the bile salt export pump (BSEP) transporter study OSP-PF-041-N in fulfilment of PAM 009. As a consequence, an updated RMP version 1.2 is provided accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to	02/02/2017	19/02/2018	SmPC	Drug interaction studies were performed with probe substrates for CYP2C9 (warfarin), CYP3A4 (midazolam), CYP2C19, and CYP3A4 (omeprazole) and CYP2B6 (bupropion). Ospemifene did not cause a clinically meaningful change in the exposure to the substrates, indicating that ospemifene does not affect those enzyme activities in vivo to a clinically significant extent. Ospemifene and 4-hydroxyospemifene are highly (both >99%) bound to serum proteins. Plasma/blood cell partitioning of [14C]-Ospemifene (<3%) and [14C]-4-hydroxyospemifene (<2%) is low. The apparent volume of distribution is 448 l. In in vitro studies, ospemifene and 4 hydroxyospemifene did not inhibit bile salt export pump (BSEP) transporters at clinically relevant concentrations. Following oral administration of [3-H]-ospemifene in the fasted state, approximately 75% and 7% of the dose was excreted in faeces and urine respectively. Less than 0.2% of the ospemifene dose was excreted unchanged in urine. Following a single oral administration of 60 mg ospemifene in the fed state, 17.9%, 10.0% and 1.4% of the

	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				administered dose was excreted in faeces as ospemifene, 4-hydroxyospemifene and 4'-hydroxyospemifene, respectively. The fate of remaining fraction is unknown but can probably be explained by formation of glucuronide metabolites.
PSUSA/10340 /201602	Periodic Safety Update EU Single assessment - ospemifene	29/09/2016	n/a		PRAC Recommendation - maintenance
IB/0013	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	22/09/2016	n/a		
IAIN/0011	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	24/06/2016	n/a		
IB/0008	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)	16/06/2016	13/02/2017	SmPC	
PSUSA/10340 /201508	Periodic Safety Update EU Single assessment - ospemifene	17/03/2016	n/a		PRAC Recommendation - maintenance
II/0004	Update of sections 4.5 and 5.2 of the SmPC as a consequence to new preclinical data submitted to fulfil the post-authorisation measures PAM 010 and	17/03/2016	13/02/2017	SmPC	Glucuronidation is an important metabolic pathway in Humans. UGT1A3, UGT2B7, and UGT1A1 are the responsible enzymes for glucuronidation of ospemifene and

	011. In addition, the MAH took the opportunity to make minor corrections and to implement minor editorial changes in the SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				UGT1A8, UGT2B7, and UGT1A1 are the responsible enzymes for glucuronidation of M-1. The contribution of each isozyme is concentration dependent. Inhibition of UGT1A3, UGT2B7, UGT1A1, or UGT1A8 may potentially affect the glucuronidation of ospemifene and/or 4-hydroxyospemifene. Ospemifene and its major metabolite M-1 both are direct inhibitors of the human UGT enzymes UGT1A3, and UGT1A9 at clinically relevant concentration. Further also UGT1A4, UGT1A6, UGT2B7, and UGT2B15 are affected. The pharmacokinetics of drugs that are mainly metabolised by UGT1A3 and UGT1A9 could be affected when administered concomitantly with ospemifene and co-administration should be made with caution.
IAIN/0005	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	21/10/2015	n/a		
II/0002	B.I.a.2.b - Changes in the manufacturing process of the AS - Substantial change to the manufacturing process of the AS which may have a significant impact on the quality, safety or efficacy of the medicinal product	24/09/2015	n/a		
IB/0003/G	This was an application for a group of variations. B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.4.b - Change in the batch size (including batch	10/09/2015	n/a		

	size ranges) of the finished product - Downscaling down to 10-fold				