Samsca

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/0051	Update of section 4.5 of the SmPC in order to add drug-drug interaction information with St John's wort based on literature and to implement the recommendation from EMA on the risk of drug interactions with Hypericum perforatum (St John's Wort) and antiretroviral medicinal products. The	13/02/2025		SmPC and PL	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).

	Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				
PSUSA/2994/ 202405	Periodic Safety Update EU Single assessment - tolvaptan (indicated for adults with hyponatraemia secondary to syndrome of inappropriate antidiuretic hormone secretion (SIADH))	16/01/2025	n/a		PRAC Recommendation - maintenance
IB/0049	B.II.z - Quality change - Finished product - Other variation	19/09/2024	n/a		
IB/0048	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	24/04/2024	n/a		
IA/0047	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	28/02/2023	n/a		
II/0046/G	This was an application for a group of variations. C.I.3.b - 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 - Change(s) with new additional data submitted by the MAH C.I.3.b - 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	12/05/2022	05/05/2023	SmPC and PL	

	assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH				
PSUSA/2994/ 202105	Periodic Safety Update EU Single assessment - tolvaptan (indicated for adults with hyponatraemia secondary to syndrome of inappropriate antidiuretic hormone secretion (SIADH))	02/12/2021	n/a		PRAC Recommendation - maintenance
IA/0044	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	30/06/2021	n/a		
IA/0043	A.7 - Administrative change - Deletion of manufacturing sites	04/03/2021	25/01/2022	Annex II and PL	
PSUSA/2994/ 202005	Periodic Safety Update EU Single assessment - tolvaptan (indicated for adults with hyponatraemia secondary to syndrome of inappropriate antidiuretic hormone secretion (SIADH))	14/01/2021	n/a		PRAC Recommendation - maintenance
IB/0042	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	22/12/2020	25/01/2022	SmPC	
IA/0040	B.II.e.4.a - Change in shape or dimensions of the container or closure (immediate packaging) - Non-sterile medicinal products	16/01/2020		SmPC, Labelling and PL	
PSUSA/2994/ 201905	Periodic Safety Update EU Single assessment - tolvaptan (indicated for adults with hyponatraemia secondary to syndrome of inappropriate antidiuretic hormone secretion (SIADH))	28/11/2019	n/a		PRAC Recommendation - maintenance

IAIN/0038/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	28/03/2019	n/a		
IAIN/0037	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	22/02/2019	n/a		
PSUSA/2994/201805	Periodic Safety Update EU Single assessment - tolvaptan (indicated for adults with hyponatraemia secondary to syndrome of inappropriate antidiuretic hormone secretion (SIADH))	29/11/2018	n/a		PRAC Recommendation - maintenance
T/0036	Transfer of Marketing Authorisation	11/09/2018	31/10/2018	SmPC, Labelling and PL	
IAIN/0035/G	This was an application for a group of variations. B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g.	23/08/2018	31/10/2018	SmPC, Labelling and PL	

	tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier				
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	17/07/2018	31/10/2018	Annex II and PL	
II/0031	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	31/05/2018	29/06/2018	SmPC and PL	The product information has been updated to add a contraindication for patients with hypersensitivity to benzazepine derivatives using tolvaptan. This corresponds to an existing contraindication in the risk management plan deriving from an exclusion from clinical trials of this group of patients during the development of tolvaptan. A warning has also been added to underline that severe sensitivity reactions or anaphylaxis can occur in patients with benzazepine or benzazepine derivative hypersensitivity.
II/0030	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	21/06/2018	31/10/2018	SmPC and PL	The product information has been updated to add a warning to section 4.4 of the SmPC under 'Idiosyncratic hepatic toxicity' which explains that liver failure requiring liver transplantation has been reported post-marketing in association with the ADPKD indication. Wording in Section 4.8 of the SmPC under 'not known' now mentions 'acute hepatic failure' as a suspected adverse event with a footnote that it was 'observed in post-marketing with tolvaptan in ADPKD. Liver transplantation was necessary'.

					The PL was updated accordingly.
IA/0028	B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	15/02/2018	n/a		
IAIN/0027/G	This was an application for a group of variations. B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary 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.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	25/01/2018	n/a		
IA/0026	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)	14/12/2017	n/a		
PSUSA/2994/ 201705	Periodic Safety Update EU Single assessment - tolvaptan (indicated for adults with hyponatraemia secondary to syndrome of inappropriate antidiuretic hormone secretion (SIADH))	30/11/2017	n/a		PRAC Recommendation - maintenance

X/0024	Annex I_2.(c) Change or addition of a new strength/potency	20/07/2017	18/09/2017	SmPC, Annex II, Labelling and PL	
PSUSA/2994/201605	Periodic Safety Update EU Single assessment - tolvaptan (indicated for adults with hyponatraemia secondary to syndrome of inappropriate antidiuretic hormone secretion (SIADH))	01/12/2016	n/a		PRAC Recommendation - maintenance
PSUSA/2994/201505	Periodic Safety Update EU Single assessment - tolvaptan (indicated for adults with hyponatraemia secondary to syndrome of inappropriate antidiuretic hormone secretion (SIADH))	03/12/2015	n/a		PRAC Recommendation - maintenance
IA/0022	B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits	19/11/2015	n/a		
II/0020	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	24/09/2015	n/a		
PSUV/0019	Periodic Safety Update	04/12/2014	n/a		PRAC Recommendation - maintenance
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	30/07/2014	n/a		
R/0016	Renewal of the marketing authorisation.	25/04/2014	19/06/2014	SmPC, Annex II and PL	During the 5 year renewal period since launch of Samsca (tolvapatan), there has been no additional information on

					efficacy or effectiveness (including information on lack of efficacy) in the authorized indication of treatment of hyponatraemia secondary to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). A number of safety issues have been addressed during this period via type II variations, updates of the product information, and DHCP letter. The risk-benefit balance of Samsca in the treatment of hyponatraemia secondary to the syndrome of inappropriate antidiuretic hormone secretion (SIADH) remains favourable and therefore the renewal of the marketing authorisation with unlimited validity is recommended.
II/0017	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/01/2014	28/02/2014	SmPC, Labelling and PL	
IAIN/0015	A.1 - Administrative change - Change in the name and/or address of the MAH	21/11/2013	28/02/2014	SmPC, Labelling and PL	
IAIN/0014	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	25/07/2013	n/a		
II/0013	Update of sections 4.4 and 4.8 of the SmPC in order to include potential hepatotoxicity information following the results of the study in a non-approved indication. The Package Leaflet was updated accordingly. Furthermore, the MAH took the opportunity to update Annex II in accordance with the QRD template, version 9. The variation proposed amendments to the Summary	25/04/2013	27/05/2013	SmPC, Annex II and PL	A signal of hepatotoxicity was identified in the clinical trial conducted by the MAH in a potentially new indication of ADPKD in the USA. An increased risk of serious liver injury adult patients was associated with receiving tolvaptan (4.4%) compared with placebo (1.0%). Although tolvaptan is not indicated for treatment of ADPKD in the EU, the CHMP considered that this is important safety information also for the EU prescribers and patients and thus, the Product Information of Samsca was amended to reflect this

	of Product Characteristics, Annex II and Package Leaflet. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				data.
IB/0011/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.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 - 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.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	01/03/2013	n/a		

	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation 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.z - Stability of AS - Other variation				
II/0012	Update of sections 4.4, 4.5, and 4.8 of the SmPC with the safety information following a PRAC recommendation of the 31 October 2012, after the identification of a signal regarding the possible risk of more severe dehydration when tolvaptan is administered concomitantly with a diuretic and the risk of more severe dehydration leading to renal dysfunction. The Package Leaflet was updated accordingly. Furthermore, the MAH took the opportunity to update Annex II in accordance with the QRD template. The variation concerned amendments to the Summary of Product Characteristics and Package Leaflet. 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	21/02/2013	27/05/2013	SmPC, Annex II and PL	Sections 4.4, 4.5 and 4.8 of the SmPC were amended after the identification of a signal regarding the possible risk of more severe dehydration when tolvaptan is administered concomitantly with a diuretic and the risk of more severe dehydration leading to renal dysfunction. The Package Leaflet was updated accordingly.

IA/0010	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	12/11/2012	n/a		
IAIN/0009/G	This was an application for a group of variations. A.5.a - Administrative change - Change in the name and/or address of a manufacturer responsible for batch release 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)	22/10/2012	29/10/2012	Annex II and PL	
IA/0008	B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	28/08/2012	n/a		
II/0007	Update of sections 4.4. and 4.5 o the SmPC in order to add a warning and update the information on drug interactions between tolvaptan and other treatments for hyponatremia and medicinal products that increase serum sodium concentration. The Package Leaflet was updated in accordance. This update originates from the review of clinical data and signal detection regarding the possible interaction of tolvaptan with sodium chloride leading to severe neurological complications secondary to hypernatraemia (EPITT reference 14669). Furthermore, the update of the PI concerns the response to the request for information following the assessment of PSUR4. Additionally, minor editorial changes were made in the PI and in the address of	15/03/2012	20/04/2012	SmPC, Labelling and PL	Since rapid correction of hyponatraemia is a potential risk with tolvaptan treatment and the rapid rise in serum sodium is known to be associated with a risk of central pontine myelinolysis and other neurological effects that can be fatal or result in permanent damage, the purpose of this variation was to include relevant warning and update the information on drug interactions between tolvaptan and other treatments for hyponatreamia and medicinal products that increase serum sodium concentration in the product information of Samsca.

	the MAH (postcode) in SmPC, labelling and PIL. This variation proposed amendments to the SmPC, Labelling and Package Leaflet. 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				
II/0006	Update of section 4.5 of the SmPC in order to add information on co-administration of tolvaptan and vasopressin analogues. The Package Leaflet is updated in accordance. This variation is made in response to recommendations made at the conclusion of PSUR 4. 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	15/03/2012	20/04/2012	SmPC and PL	Following the assessment of a case report of drug interaction of tolvaptan with desmopressin and the review of the related clinical information, it is possible that tolvaptan is capable of attenuating the release of von Willebrand factor by dDAVP (1-deamino-8-D-arginine vasopressin) in von Willebrand disease patients. This drug-drug interaction, if unrecognized, may place vWD patients at increased risk of continued bleeding if dDAVP is administered for prevention or treatment of bleeding while continuing to take tolvaptan. And adequate wording was added to the PI in order to reflect this interaction.
II/0005	Update of sections 4.2, 4.4 and 4.8 of the SmPC following assessment of PSUR 3 and of the cumulative case review of case reports of rapid correction of hyponatraemia with the relevant safety information on rapid correction of hyponatraemia. The package leaflet is updated in accordance. In addition, the MAH took the opportunity to include a	15/03/2012	20/04/2012	SmPC and PL	Since rapid correction of hyponatraemia is a potential risk with tolvaptan treatment and the rapid rise in serum sodium is known to be associated with a risk of neurological side effects that can be fatal or result in permanent damage, the purpose of this variation was to include relevant information on the monitoring of fluid and electrolyte balance, especially the levels of sodium. Further

	few minor editorial changes including the update of details of a local representative (Italy) in the Package Leaflet. Furthermore, the MAH introduced minor clarification in section 4 of the PIL. The requested variation proposed amendments to the Summary of Product Characteristics, and Package Leaflet. 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				guidance is given on the management of rapid correction of serum sodium. The common adverse reaction of rapid correction of hyponatraemia sometimes leading to neurological symptoms was also included in the SmPC.
IB/0003	C.I.3.a - 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 - Changes with NO new additional data are submitted by the MAH	12/08/2011	n/a	SmPC and PL	
IA/0004/G	This was an application for a group of variations. C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV 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	22/07/2011	n/a		

IA/0002/G	This was an application for a group of variations. C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV 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	22/03/2011	n/a	Annex II	
N/0001	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	30/09/2010	n/a	PL	