Sivextro

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/0054	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	30/01/2025	28/02/2025	SmPC and PL	Extension of indication to include treatment of paediatric patients aged from birth to less than 12 years for SIVEXTRO, based on final results from studies MK-1986-013, MK-1986-014 and MK-1986-018. MK-1986-013 is a single-dose trial to evaluate pharmacokinetics (PK) and safety of oral and intravenous (IV) administration 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).

					tedizolid phosphate in patients from 2 years to <12 years of age; MK-1986-014 is an open-label, multicentre, 2-part, single and multiple dose study to assess the PK of tedizolid phosphate and its active metabolite, tedizolid, and the safety of tedizolid phosphate following single and multiple dose IV and single oral dose. MK-1986-018 is a randomised, active controlled, investigator-blind, multicentre trial to evaluate safety and efficacy in patients from birth to less than 12 years of age. In addition, changes to the posology for patients ≥12 years of age are proposed. A weight-banded IV dosing regimen is proposed for all paediatric patients <35 kg of body weight, including those ≥12 years of age. To maintain alignment between the IV and oral dosing regimens, the 200 mg tablet dosing regimen is proposed for paediatric patients weighing ≥35 kg only, regardless of age. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.2, 5.3 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. The Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet and to implement minor editorial corrections. Version 8.0 of the RMP is being approved with this procedure. Please refer to Scientific Discussion 'Sivextro-H-C-002846-II-0054
IA/0056	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	06/09/2024	n/a		

	batch control/testing takes place				
IA/0055	B.III.2.z - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Other variation	31/07/2024	n/a		
II/0053	Update of section 5.1 of the SmPC in order to implement the revised EUCAST MIC breakpoints of tedizolid. 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	06/06/2024	28/02/2025	SmPC and PL	Section 5.1 was adapted to include the standard agreed text pointing to where to find the EUCAST MIC breakpoints of tedizolid. For more information, please refer to the Summary of Product Characteristics.
PSUSA/10369 /202306	Periodic Safety Update EU Single assessment - tedizolid phosphate	22/02/2024	19/04/2024	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10369/202306.
IA/0051	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	29/05/2023	n/a		
N/0050	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	27/03/2023	19/04/2024	Labelling	
N/0049	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	01/12/2022	03/02/2023	PL	
IB/0048/G	This was an application for a group of variations.	16/09/2022	n/a		

	B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure 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.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits 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				
WS/2193	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	02/06/2022	n/a		

	B.II.g.2 - Introduction of a post approval change management protocol related to the finished product				
II/0046	B.II.e.1.b.2 - Change in immediate packaging of the finished product - Change in type/addition of a new container - Sterile medicinal products and biological/immunological medicinal products	19/05/2022	n/a		
IA/0047/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	14/03/2022	03/02/2023	Annex II and PL	
IAIN/0045	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	07/02/2022	03/02/2023	Annex II and PL	
IA/0043/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	21/12/2021	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				
N/0042	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	06/12/2021	04/02/2022	PL	
PSUSA/10369 /202006	Periodic Safety Update EU Single assessment - tedizolid phosphate	28/01/2021	22/03/2021	SmPC, Annex II, Labelling and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10369/202006.
II/0037	Submission of final results from study Surveillance of Tedizolid Activity and Resistance (STAR) listed as a category 3 study in the RMP; this is a surveillance study established in January 2014 to monitor tedizolid susceptibility activity and emergence of resistance across the US, 11 European Union countries, Russia and Turkey. The RMP version 7.0 is approved with this variation. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	11/03/2021	n/a		The Risk Management Plan was updated to remove the important potential risk "emergence of drug resistance" from the summary of safety concerns and to change the remaining sections of the RMP accordingly.
IAIN/0041	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	15/02/2021	04/02/2022	Annex II and PL	
IB/0040	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	16/10/2020	22/03/2021	SmPC, Labelling and PL	

IB/0038/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 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	28/07/2020	n/a		
II/0035	Extension of Indication (treatment of ABSSSI in adults) to include adolescent population from 12 years old and older for Sivextro; as a consequence, sections 4.1, 4.2, 4.8 and 5.2 of the SmPC are updated. Sections 1 and 2 of the Package Leaflet are updated in accordance. In addition, the MAH took the opportunity to bring the PI in line with the latest QRD template version 10.1 RMP version 5.1 has been approved with this variation. The variation leads to amendments to the Summary of Product Characteristics, Annex II 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	28/05/2020	26/06/2020	SmPC, Annex II and PL	Please refer to Scientific Discussion 'Sivextro-H-C-2846-II-0035'
IB/0036	B.II.d.2.z - Change in test procedure for the finished product - Other variation	11/06/2020	n/a		

PSUSA/10369 /201906	Periodic Safety Update EU Single assessment - tedizolid phosphate	16/01/2020	n/a		PRAC Recommendation - maintenance
R/0031	Renewal of the marketing authorisation.	14/11/2019	09/01/2020	SmPC and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Sivextro in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
II/0032	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	31/10/2019	n/a		
IA/0033/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites 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)	17/09/2019	n/a		
PSUSA/10369 /201806	Periodic Safety Update EU Single assessment - tedizolid phosphate	17/01/2019	n/a		PRAC Recommendation - maintenance
IAIN/0030/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP -	11/10/2018	13/09/2019	Annex II and PL	

	Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing				
II/0027	Submission of the final results from Bayer study 16099, a prospective, randomised, open-label, active-controlled, multicentre study to evaluate the efficacy and safety of tedlizolid in Japanese patients with MRSA infections (skin and soft tissue infection [SSTI] and SSTI-related bacteraemia) listed as a Post-Authorisation Efficacy Study (PAES) in the RMP. The MAH obligations with regard to this PAES are considered fulfilled. The updated RMP version 5.0, implementing Revision 2 of the RMP template, is adopted. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	04/10/2018	n/a		The MAH submitted the final results from Bayer study 16099, a prospective, randomised, open-label, active-controlled, multicentre study to evaluate the efficacy and safety of tedlizolid in Japanese patients with MRSA infections (skin and soft tissue infection [SSTI] and SSTI-related bacteraemia). Following assessment, the CHMP identified concerns with the robustness of the safety data supporting the implementation of the proposed change to the SmPC, including differences in median body weight between the populations in study 16099 and the phase III studies, the high and relevant number of confounding factors and the relatively small data from study 16099, which has been conducted under conditions other than the ones currently recommended in the EU for the use of the product. As a result, the data is not considered to support changes to the product information.
T/0028	Transfer of Marketing Authorisation	17/07/2018	08/08/2018	SmPC, Labelling and PL	
IB/0026	B.II.f.1.d - Stability of FP - Change in storage conditions of the finished product or the diluted/reconstituted product	28/05/2018	08/08/2018	SmPC and PL	
PSUSA/10369 /201706	Periodic Safety Update EU Single assessment - tedizolid phosphate	11/01/2018	n/a		PRAC Recommendation - maintenance

II/0019	Update of section 4.8 of the SmPC of the concentrate for solution for infusion formulation, in order to add information from BAY119-2631/16121, a Phase 3 randomized, double-blind, multi-centre study comparing the efficacy and safety of intravenous to oral 6-day tedizolid phosphate and intravenous to oral 10 day linezolid for the treatment of acute bacterial skin and skin structure infections (ABSSSI) and change the reported expected frequency of the adverse reaction "infusion site phlebitis" from "uncommon" to "common". The Package Leaflet is updated accordingly. An updated RMP (version 3.2) has also been submitted, proposing to collect safety information regarding tedizolid phosphate by conducting three investigator initiated studies and deleting the original proposed long term safety study. The MAH also took the opportunity to make minor editorial corrections throughout the product information. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	30/11/2017	08/08/2018	SmPC, Annex II and PL	In a Phase 3 study conducted in China, the Philippines, Taiwan, and the US investigating tedizolid phosphate for the treatment of acute bacterial skin and skin structure infections, infusion site reactions (phlebitis) were reported more frequently (2.7%) in tedizolid treated subjects than in the linezolid control group (0%) with the concentrate for solution for infusion formulation, particularly among Asian patients. The frequency of the adverse reaction "infusion site phlebitis" was therefore revised from "uncommon" to "common".
IA/0025	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)	17/11/2017	n/a		
IA/0023	B.III.2.z - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Other variation	21/09/2017	n/a		

II/0021	Submission of the final report for the CANWARD 2016 study, a national population based surveillance system, assessing the prevalence of anti-microbial resistance in pathogens associated with respiratory, skin and soft tissue, urinary and bacteraemic infections in hospitalized patients in Canada, listed as a category 3 study in the RMP. This variation does not propose any changes to the product information. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	21/09/2017	n/a		The MAH submitted data from the final report from the CANWARD 2016 Study: A National Population Based Surveillance System, Assessing the Prevalence of Antimicrobial Resistance in Pathogens Associated with Respiratory, Skin and Soft Tissue, Urinary and Bacteremic Infections in Hospitalized Patients in Canada, which ran from January 2014 until December 2016. A total of 9,504 isolates were evaluated and the results indicated overall persistence of good in-vitro activity against all microbiologic species relevant for the approved indication. No major resistance issues are expected to affect clinical efficacy. The benefit/risk assessment for the product is unchanged by the submitted data and no changes are made to the product information.
IA/0022	B.II.e.4.a - Change in shape or dimensions of the container or closure (immediate packaging) - Non-sterile medicinal products	15/09/2017	n/a		
PSUSA/10369 /201612	Periodic Safety Update EU Single assessment - tedizolid phosphate	06/07/2017	n/a		PRAC Recommendation - maintenance
IA/0020/G	This was an application for a group of variations. B.II.e.2.a - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Tightening of specification limits B.II.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to the specification with its corresponding	16/05/2017	n/a		

	test method				
IAIN/0018	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	21/03/2017	16/06/2017	Annex II and PL	
PSUSA/10369 /201606	Periodic Safety Update EU Single assessment - tedizolid phosphate	12/01/2017	n/a		PRAC Recommendation - maintenance
II/0009	Update of sections 4.4, 4.5 and 5.2 of the SmPC based on the completed Drug-Drug Interaction study MK-1986-004. The Package Leaflet has been updated accordingly. In addition the MAH took the opportunity to implement editorial changes in the annexes and to update the annexes in line with the latest QRD template version 10. A revised RMP version 2.2 was agreed during the procedure. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	10/11/2016	16/06/2017	SmPC, Labelling and PL	In a clinical study comparing the single dose (10 mg) pharmacokinetics of rosuvastatin (Breast Cancer Resistant Protein [BCRP] substrate) alone or in combination with Sivextro (once-daily 200 mg oral dose), rosuvastatin AUC and Cmax increased by approximately 70% and 55%, respectively, when coadministered with Sivextro. Therefore, orally administered Sivextro can result in inhibition of BCRP at the intestinal level. If possible, an interruption of the co-administered BCRP substrate medicinal product (such as imatinib, lapatinib, methotrexate, pitavastatin, rosuvastatin, sulfasalazine, and topotecan) should be considered during the six days of treatment with oral Sivextro. In a clinical study comparing the single dose (2 mg) pharmacokinetics of midazolam (CYP3A4 substrate) alone or in combination with Sivextro (once-daily 200 mg oral dose for 10 days), midazolam AUC and Cmax when co-administered with Sivextro were 81% and 83% of midazolam AUC and Cmax when administered alone, respectively. This effect is not clinically meaningful, and no dose adjustment for co-administered CYP3A4 substrates is

					necessary during Sivextro treatment.
IAIN/0016	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	26/10/2016	16/06/2017	Annex II and PL	
PSUSA/10369 /201603	Periodic Safety Update EU Single assessment - tedizolid phosphate	29/09/2016	n/a		PRAC Recommendation - maintenance
IA/0014/G	This was an application for a group of variations. 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.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits	22/07/2016	n/a		
IAIN/0013	B.II.e.6.a - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that affects the product information	22/07/2016	16/06/2017	SmPC	
IA/0011/G	This was an application for a group of variations. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process	13/05/2016	n/a		

	of the AS B.I.a.3.b - Change in batch size (including batch size ranges) of AS or intermediate - Downscaling down to 10-fold				
IA/0010/G	This was an application for a group of variations. 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.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	25/04/2016	n/a		
PSUSA/10369 /201509	Periodic Safety Update EU Single assessment - tedizolid phosphate	14/04/2016	n/a		PRAC Recommendation - maintenance
IAIN/0008	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	22/02/2016	n/a		
T/0007	Transfer of Marketing Authorisation	16/12/2015	11/01/2016	SmPC, Labelling and PL	
IB/0004/G	This was an application for a group of variations. A.6 - Administrative change - Change in ATC Code/ATC Vet Code C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	21/10/2015	11/01/2016	SmPC, Annex II, Labelling and PL	

IB/0005	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	09/10/2015	n/a		
IAIN/0003	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	16/06/2015	n/a		
IAIN/0002	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	01/06/2015	n/a		
IAIN/0001/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.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	13/05/2015	11/01/2016	Annex II and PL	