Zavicefta

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/0035	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	19/09/2024	21/10/2024	SmPC and PL	Please refer to Scientific Discussion 'Zavicefta-H-C-004027-II-0035'
IB/0037/G	This was an application for a group of variations.	15/10/2024	n/a		Please refer to Scientific Discussion 'Zavicefta-H-C-004027-II-0035'

[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).

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	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one 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.a.2.z - Changes in the manufacturing process of the AS - 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 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.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS				
IA/0036	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	30/04/2024	n/a		
II/0033	Update of section 4.8 of the SmPC in order to add 'Kounis syndrome' to the list of adverse drug	25/01/2024	21/10/2024	SmPC and PL	'Kounis syndrome' is a serious adverse reaction to which healthcare professionals need to be alerted. Inclusion in

	reactions (ADRs). A warning about this syndrome was also added to section 4.4, with a cross-reference to section 4.8. The Package Leaflet was updated accordingly. In addition, the MAH took the opportunity to introduce minor changes to the PI and to update the list of local representatives in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				section 4.8 (under SOC "Cardiac disorders") with a frequency unknown was implemented. Furthermore, information on this ADR was included in section 4.4 of the Zavicefta SmPC. The PL was updated accordingly. For more information, please refer to the Summary of Product Characteristics.
IB/0034/G	This was an application for a group of variations. B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation B.I.z - Quality change - Active substance - Other variation B.I.z - Quality change - Active substance - Other variation 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.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	03/01/2024	n/a		
PSUSA/10513 /202302	Periodic Safety Update EU Single assessment - ceftazidime / avibactam	28/09/2023	n/a		PRAC Recommendation - maintenance
IB/0032/G	This was an application for a group of variations.	04/07/2023	n/a		

	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				
PSUSA/10513 /202202	Periodic Safety Update EU Single assessment - ceftazidime / avibactam	29/09/2022	n/a		PRAC Recommendation - maintenance
IB/0029	B.II.f.1.a.3 - Stability of FP - Reduction of the shelf life of the finished product - After dilution or reconstitution	22/04/2022	26/04/2023	SmPC and PL	
II/0027/G	This was an application for a group of variations. B.II.b.4.z - Change in the batch size (including batch size ranges) of the finished product - Other variation B.II.b.3.b - Change in the manufacturing process of the finished or intermediate product - Substantial changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product 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 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	24/02/2022	n/a		

	B.II.d.2.z - Change in test procedure for the finished product - Other variation B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition) B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition) B.II.d.2.z - Change in test procedure for the finished product - Other variation B.II.b.1.f - Replacement or addition of a manufacturing site for part or all of the manufacturing process of the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for sterile medicinal products (including those that are aseptically manufactured) excluding biological/ immunological medicinal products B.II.b.1.f - Replacement or addition of a manufacturing site for part or all of the manufacturing process of the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for sterile medicinal products (including those that are aseptically manufactured) excluding biological/ immunological medicinal products				
N/0028	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	01/10/2021	26/04/2023	PL	
PSUSA/10513 /202102	Periodic Safety Update EU Single assessment - ceftazidime / avibactam	30/09/2021	n/a		PRAC Recommendation - maintenance

II/0025/G	This was an application for a group of variations. B.II.c.1.b - Change in the specification parameters and/or limits of an excipient - Addition of a new specification parameter to the specification with its corresponding test method 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 test method 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 test method 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 test method 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 test method	15/04/2021	n/a		

	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 test method 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 test method 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 test method 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 test method B.III.2.z - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Other variation B.III.2.a.2 - Change of specification(s) of a former non EU Pharmacopoeial substance to fully comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - Excipient/AS starting material B.II.d.2.z - Change in test procedure for the finished product - Other variation B.II.d.2.z - Change in test procedure for the finished product - Other variation B.II.d.2.z - Change in test procedure for the finished				

	product - Other variation B.II.d.2.z - Change in test procedure for the finished product - Other variation B.II.d.2.z - Change in test procedure for the finished product - Other variation B.II.d.2.z - Change in test procedure for the finished product - Other variation B.II.d.2.z - Change in test procedure for the finished product - Other variation B.II.d.2.z - Change in test procedure for the finished product - Other variation B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range B.II.b.4.z - Change in the batch size (including batch size ranges) of the finished product - Other variation B.II.b.3.b - Change in the manufacturing process of the finished or intermediate product - Substantial changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product 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.1.f - Replacement or addition of a manufacturing site for part or all of the manufacturing process of the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for sterile medicinal products (including those that are aseptically manufactured) excluding biological/				

	immunological medicinal products 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.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 A.7 - Administrative change - Deletion of manufacturing sites B.III.2.z - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Other variation				
R/0024	Renewal of the marketing authorisation.	10/12/2020	11/02/2021	SmPC, Annex II and PL	
II/0023/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites 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	28/01/2021	n/a		

	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.g - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a new manufacturer of the AS that is not supported by an ASMF and requires significant update to the relevant AS section in the dossier B.I.a.1.g - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a new manufacturer of the AS that is not supported by an ASMF and requires significant update to the relevant AS section in the dossier 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.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.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.c.2.b - Change in the specification parameters and/or limits of the immediate packaging of the AS - Addition of a new specification parameter to the				

	specification with its corresponding test method B.I.c.2.b - Change in the specification parameters and/or limits of the immediate packaging of the AS - Addition of a new specification parameter to the specification with its corresponding test method B.I.c.2.b - Change in the specification parameters and/or limits of the immediate packaging of the AS - Addition of a new specification parameter to the specification with its corresponding test method B.I.c.2.b - Change in the specification parameters and/or limits of the immediate packaging of the AS - Addition of a new specification parameter to the specification with its corresponding test method B.I.c.2.b - Change in the specification parameters and/or limits of the immediate packaging of the AS - Addition of a new specification parameter to the specification with its corresponding test method B.I.c.2.b - Change in the specification parameters and/or limits of the immediate packaging of the AS - Addition of a new specification parameter to the specification with its corresponding test method B.I.c.2.b - Change in the specification parameters and/or limits of the immediate packaging of the AS - Addition of a new specification parameter to the specification with its corresponding test method B.I.c.2.b - Change in the specification parameters and/or limits of the immediate packaging of the AS - Addition of a new specification parameter to the specification with its corresponding test method B.I.c.2.b - Change in the specification parameters and/or limits of the immediate packaging of the AS - Addition of a new specification parameter to the				

	specification with its corresponding test method				
II/0015	Extension of indication to include paediatric patients aged 3 months to less than 18 years for Zavicefta (for the treatment of cIAI and cUTI, HAP/VAP and aerobic Gram-negative infections in patients with limited treatment options), based on data from paediatric studies D4280C00014, C3591004 and C3591005 and the population PK modelling/simulation analyses (CAZ-MS-PED-01 and CAZ-MS-PED-02). As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2, 6.3 and 6.6 of the SmPC are updated in order to reflect this additional population, the paediatric posology, paediatric safety information, the description of the clinical trials and handling instructions for paediatric dosing. The Package Leaflet is updated in accordance. A warning was included in section 4.4 of the SmPC, with a cross-reference to section 4.9, to highlight a potential risk of overdosing for the youngest children from 3 months to less than 12 months of age, related to the difficulties to calculate the volume of administration of the dose. In addition, a table with dosing volumes calculated based on different weights was added to section 6.6. The Marketing authorisation holder (MAH) took the opportunity to correct the sodium content to SmPC sections 2 and 4.4 and PL section 2 and the volumes of distribution of ceftazidime and avibactam in SmPC section 5.2. The RMP version 3.2 has been approved with this variation.	17/09/2020	22/10/2020	SmPC and PL	Please refer to Scientific Discussion 'Zavicefta -H-C-4027-II-0015'

	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
PSUSA/10513 /202002	Periodic Safety Update EU Single assessment - ceftazidime / avibactam	01/10/2020	n/a		PRAC Recommendation - maintenance
II/0019	Extension of Indication to include bacteraemia (in association with, or suspected to be associated with, the currently approved indications for complicated intra-abdominal infection (cIAI), complicated urinary tract infection (cUTI) and hospital-acquired pneumonia, including ventilator-associated pneumonia (HAP/VAP)) for Zavicefta; as a consequence, sections 4.1 and 4.2 of the SmPC are updated in order to add this indication and the posology. Furthermore, the PI is brought in line with the latest QRD template version 10.1. The Package Leaflet is updated in accordance. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	25/06/2020	06/08/2020	SmPC, Annex II and PL	Please refer to Scientific Discussion 'Zavicefta-H-C-0004027-II-0019'
IAIN/0021	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	20/02/2020	06/08/2020	Annex II and PL	
N/0020	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	02/12/2019	06/08/2020	PL	

PSUSA/10513 /201902	Periodic Safety Update EU Single assessment - ceftazidime / avibactam	05/09/2019	n/a		PRAC Recommendation - maintenance
IB/0018	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	17/06/2019	n/a		
N/0016	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/04/2019	06/08/2020	PL	
PSUSA/10513 /201808	Periodic Safety Update EU Single assessment - ceftazidime / avibactam	14/03/2019	n/a		PRAC Recommendation - maintenance
N/0013	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/10/2018	25/02/2019	PL	
PSUSA/10513 /201802	Periodic Safety Update EU Single assessment - ceftazidime / avibactam	06/09/2018	n/a		PRAC Recommendation - maintenance
II/0009	The SmPC section 4.2 has been updated as follows: Paediatric population Safety and efficacy in children and adolescents below 18 years of age have not yet been established. Currently available data are described in section 4.8 but no recommendation on a posology can be made. The SmPC section 4.3 has been updated as follows: Controlled sodium diet Each vial contains a total of 6.44 mmol of sodium (approximately 148 mg), equivalent to 7.4% of the WHO recommended maximum daily intake for sodium. The maximum daily dose of this product is equivalent to 22.2% of the WHO recommended	14/06/2018	25/02/2019	SmPC, Labelling and PL	

	maximum daily intake for sodium. The SmPC section 4.8 has been updated as follows: Paediatric population The safety assessment in children is based on the safety data from 1 trial in which 61 paediatric patients aged from 3 months to less than18 years with cIAI received Zavicefta. Overall, the safety profile in these 61 children was similar to that observed in the adult population with cIAI. The PL has been updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
II/0008	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	12/04/2018	n/a		
PSUSA/10513 /201708	Periodic Safety Update EU Single assessment - ceftazidime / avibactam	08/03/2018	n/a		PRAC Recommendation - maintenance
IAIN/0010	A.1 - Administrative change - Change in the name and/or address of the MAH	12/02/2018	25/02/2019	SmPC, Labelling and PL	
PSUSA/10513 /201702	Periodic Safety Update EU Single assessment - ceftazidime / avibactam	28/09/2017	n/a		PRAC Recommendation - maintenance

T/0006	Transfer of Marketing Authorisation	23/06/2017	19/07/2017	SmPC, Labelling and PL	
PSUSA/10513 /201608	Periodic Safety Update EU Single assessment - ceftazidime / avibactam	09/03/2017	n/a		PRAC Recommendation - maintenance
II/0002	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/02/2017	19/07/2017	SmPC, Annex II, Labelling and PL	The MAH has updated: - section 4.4 of the SmPC to reflect that clinical efficacy and safety studies of Zavicefta have been conducted in patients with Hospital Acquired Pneumonia (HAP) including Ventilator-Associated Pneumonia (VAP): 'In a single study in patients with nosocomial pneumonia 280/808 (34.7%) had VAP and 40/808 (5.0%) were bacteraemic at baseline' ; - section 4.8 to change the frequency of thrombocytopenia and pruritus from uncommon to common - section 5.1 to add a new section for HAP/VAP pathogens: 'Hospital-acquired pneumonia including ventilator-associated pneumonia Gram-negative micro-organisms • Enterobacter cloacae • Escherichia coli • Klebsiella pneumoniae • Proteus mirabilis • Serratia marcescens • Pseudomonas aeruginosa'. The Package leaflet has been updated accordingly.
N/0003	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	01/02/2017	19/07/2017	PL	