SIRTURO

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/10074 /202209	Periodic Safety Update EU Single assessment - bedaquiline	14/04/2023	n/a		PRAC Recommendation - maintenance
II/0051	Update of section 4.6 of the SmPC in order to update information on breastfeeding based on new literature. In addition, the MAH took the opportunity	23/02/2023		SmPC and PL	For more information, please refer to the Summary of Product Characteristics.

[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).

	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				
R/0050	Renewal of the marketing authorisation.	10/11/2022	20/12/2022		The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for SIRTURO, subject to the Specific Obligations and Conditions as laid down in Annex II to the opinion.
IB/0049/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 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.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	06/05/2022	n/a		

PSUSA/10074 /202109	Periodic Safety Update EU Single assessment - bedaquiline	07/04/2022	n/a		PRAC Recommendation - maintenance
R/0045	Renewal of the marketing authorisation.	11/11/2021	06/01/2022		
IA/0048	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	16/12/2021	n/a		
II/0043	Update of section 4.2 of the SmPC to revise the information on the use of bedaquiline in combination with other medicinal products and to amend the information regarding treatment duration. In addition, the MAH took the opportunity to include an editorial correction in section 5.1 of the SmPC and to update the contact details for the local representative for UK in the package leaflet, in line with QRD version 10.2. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	14/10/2021	15/11/2021	SmPC and PL	The CHMP endorsed the following updates to the Product Information: Consideration should be given to WHO guidelines when selecting the appropriate combination regimen. Only use SIRTURO in combination with other medicinal products to which the patient's MDR-TB isolate has been shown to be susceptible in vitro, or is likely to be susceptible. The total duration of treatment with SIRTURO is 24 weeks. Data on longer treatment duration is very limited. When treatment with SIRTURO is considered necessary beyond 24 weeks to obtain a curative treatment, a longer duration of therapy may be considered under close safety surveillance. For more information, please refer to the Summary of Product Characteristics.
IAIN/0046	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	21/09/2021	n/a		

IB/0044	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)	02/09/2021	15/11/2021	SmPC	
PSUSA/10074 /202009	Periodic Safety Update EU Single assessment - bedaquiline	09/04/2021	n/a		PRAC Recommendation - maintenance
X/0036/G	This was an application for a group of variations. Annex I_2.(c) Change or addition of a new strength/potency C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	28/01/2021	26/03/2021	SmPC, Annex II, Labelling and PL	
II/0042	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	11/02/2021	n/a		
R/0040	Renewal of the marketing authorisation.	12/11/2020	11/01/2021	Annex II	The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for SIRTURO, subject to the Specific Obligations and Conditions as laid down in Annex II to the opinion
PSUSA/10074 /201909	Periodic Safety Update EU Single assessment - bedaquiline	17/04/2020	n/a		PRAC Recommendation - maintenance

IB/0039	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	08/04/2020	n/a		
II/0038	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	13/02/2020	n/a		
II/0033/G	This was an application for a group of variations. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	12/12/2019	23/01/2020	SmPC and PL	
R/0035	Renewal of the marketing authorisation.	14/11/2019	09/01/2020		The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for SIRTURO, subject to the Specific Obligations and Conditions as laid down in Annex II to the opinion.
PSUSA/10074 /201809	Periodic Safety Update EU Single assessment - bedaquiline	14/03/2019	n/a		PRAC Recommendation - maintenance

II/0028	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	14/02/2019	09/01/2020	SmPC and PL	
R/0031	Renewal of the marketing authorisation.	15/11/2018	11/01/2019		The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for SIRTURO, subject to the Specific Obligations and Conditions as laid down in Annex II to the opinion.
II/0030	B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range	13/12/2018	n/a		
N/0032	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/10/2018	11/01/2019	PL	
PSUSA/10074 /201709	Periodic Safety Update EU Single assessment - bedaquiline	12/04/2018	n/a		PRAC Recommendation - maintenance
IB/0027/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	04/04/2018	n/a		

	intermediate used in the manufacture of the AS or manufacturer of a novel excipient B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS 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.III.2.b - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State				
R/0024	Renewal of the marketing authorisation.	25/01/2018	05/03/2018	SmPC, Annex II and PL	The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional marketing authorisation for SIRTURO, subject to the Specific Obligations and Conditions as laid down in Annex II to the Opinion. The CHMP also agreed that the changing treatment landscape has prompted changes to the timelines in providing the interim results and ultimately final study report of the phase III STREAM study (specific obligation) to Q4 2023. In addition, the MAH took the opportunity to bring the SmPC, labelling and package leaflet in line with the QRD template version 10.0; and update the local representative in Lithuania and

					Slovenia.
II/0026	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	08/02/2018	n/a		
PSUSA/10074 /201703	Periodic Safety Update EU Single assessment - bedaquiline	28/09/2017	n/a		PRAC Recommendation - maintenance
II/0021	Update of section 4.4 of the SmPC in order to add delamanid and levofloxacin as examples of drugs that prolong the QT interval following the review of the global safety database for all serious cases received from 28 December 2012 to 30 September 2016. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	29/06/2017	05/03/2018	SmPC and PL	The cumulative review of QT prolongation events with the use of bedaquiline (BDQ) from 28 December 2012 to 30 September 2016 suggest that when co administered with other medicinal products that prolong the QTc interval (including delamanid and levofloxacin), an additive or synergistic effect on QT prolongation cannot be excluded. Caution is recommended when prescribing bedaquiline concomitantly with medicinal products with a known risk of QT prolongation. In the event that co administration of such medicinal products with bedaquiline is necessary, clinical monitoring including frequent electrocardiogram assessment is recommended. Section 4.4 of the SmPC under “Cardiovascular safety” was updated accordingly.
PSUSA/10074 /201609	Periodic Safety Update EU Single assessment - bedaquiline	21/04/2017	16/06/2017	SmPC	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)’ for PSUSA/10074/201609.
IA/0022	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)	28/04/2017	n/a		

R/0017	Renewal of the marketing authorisation.	10/11/2016	23/12/2016		The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for SIRTURO, subject to the Specific Obligations and Conditions as laid down in Annex II to the Opinion.
IA/0020	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)	22/12/2016	n/a		
IB/0018	B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation	09/11/2016	23/12/2016	SmPC and Labelling	
PSUSA/10074 /201603	Periodic Safety Update EU Single assessment - bedaquiline	29/09/2016	n/a		PRAC Recommendation - maintenance
N/0015	Update of the package leaflet with revised contact details of the local representatives for Estonia, Lithuania, Latvia, Romania and Sweden. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	22/04/2016	23/12/2016	PL	
PSUSA/10074 /201509	Periodic Safety Update EU Single assessment - bedaquiline	17/03/2016	n/a		PRAC Recommendation - maintenance

IB/0014	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)	19/02/2016	23/12/2016	SmPC	
IB/0013	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	07/01/2016	23/12/2016	SmPC, Annex II, Labelling and PL	
R/0010	Renewal of the marketing authorisation.	19/11/2015	07/01/2016		The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for SIRTURO, subject to the Specific Obligations and Conditions as laid down in Annex II to the Opinion.
IA/0012/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	22/12/2015	n/a		
II/0008/G	This was an application for a group of variations. Update of sections 5.1 and 5.2 of the SmPC in order to update information on mechanisms of resistance and drug-drug interactions of bedaquiline based on the results from non-clinical studies. In addition, the	22/10/2015	07/01/2016	SmPC and PL	In this variation the MAH updated the Product Information with data related to the mechanisms of resistance. Target-based mutations generated in preclinical studies lead to 8- to 133 fold increases in bedaquiline MIC, resulting in MICs ranging from 0.25 to 4.0 mg/l. Efflux-based mutations have been seen in preclinical and clinical isolates. These lead to

	Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, minor editorial changes have been introduced throughout the PI. 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				2- to 8 fold increases in bedaquiline MICs, resulting in bedaquiline MICs ranging from 0.25 to 0.50 mg/l. However no clear relationship between increased post-baseline bedaquiline MICs and microbiologic outcomes was observed in the phase 2 trials where bedaquiline was given for 24 weeks, followed by continuation of the background regimen. Furthermore the MAH included the information from in vitro study which indicated a potential for bedaquiline to inhibit BCRP at the concentrations achieved in the intestine after oral administration. The clinical relevance is unknown.
PSUSA/10074 /201503	Periodic Safety Update EU Single assessment - bedaquiline	08/10/2015	n/a		PRAC Recommendation - maintenance
IB/0007/G	This was an application for a group of variations. B.II.e.1.b.1 - Change in immediate packaging of the finished product - Change in type/addition of a new container - Solid, semi-solid and non-sterile liquid pharmaceutical forms B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	30/04/2015	07/01/2016	SmPC, Labelling and PL	
PSUSA/10074 /201409	Periodic Safety Update EU Single assessment - bedaquiline	10/04/2015	n/a		PRAC Recommendation - maintenance
IG/0531	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging	05/03/2015	n/a		

	site				
R/0003	Renewal of the marketing authorisation.	20/11/2014	19/01/2015		The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for SIRTURO, subject to the Specific Obligations and Conditions as laid down in Annex II to the Opinion.
II/0002/G	This was an application for a group of variations. Update of section 5.3 of the SmPC (non-clinical information) is updated following the results of the final rat carcinogenicity study (see present/proposed table). No revision is proposed based on the data of the transporter studies. With this submission the applicant fulfils the pre-clinical PAMs (Additional Pharmacovigilance activities in the risk management plan) listed as category 3 in the current approved RMP v 1.6 (dd 14 Jan 2014). The requested variation proposed amendments to the Summary of Product Characteristics. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	18/12/2014	07/01/2016	SmPC and Annex II	

	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
II/0004/G	This was an application for a group of variations. 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	20/11/2014	19/01/2015	SmPC	
N/0001	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	27/03/2014	19/01/2015	Labelling	