EVOTAZ

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/0050	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	27/03/2025	02/05/2025	SmPC and PL	The MAH submitted a Type II variation to update sections 4.3 and 4.5 of the SmPC for Evotaz (atazanavir/cobicistat, ATV/COBI) to add:

[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).

					- a new contraindication for the coadministration of ATV/COBI with the antineoplastic agents apalutamide, encorafenib, or ivosidenib and, - Drug-Drug Interactions (DDIs) information for the coadministration of ATV/COBI with the kinase inhibitor, fostamatinib, and the gonadotropin-releasing hormone receptor antagonist, elagolix. Based on post-marketing safety data and in accordance with the revised Company Core Data Sheet (CCDS) for ATV/COBI FDC tablet version 8.0, Evotaz SmPC sections 4.3 and 4.5 have been updated. The CHMP is of the view that the proposed updates are adequately justified, noting that these amendments are already approved for medicinal products containing atazanavir as a single active substance Based on the above, the table 1 of section 4.5 of the SmPC (entitled "Interactions between EVOTAZ and other medicinal products") has been amended to reflect the DDIs information for the coadministration of ATV/COBI with fostamatinib and elagolix. Additionally, the wording of section 4.3 has been amended as follows (deletions in strikethrough and additions in bold and underlined):" "*(…) Co-administration with ~~the following~~ medicinal products that are strong inducers of the CYP3A4 isoform of cytochrome P450 due to the potential for loss of therapeutic effect* ***and development of possible resistance*** *(see section 4.5);* ***co-administration is contraindicated with, but not limited to, the following*** *~~drugs~~* ***medicines:*** • *carbamazepine, phenobarbital, phenytoin (antiepileptics)*

					• *St John's wort (Hypericum perforatum) (herbal product)* • *rifampicin (antimycobacterial)* • ***apalutamide, encorafenib, ivosidenib (antineoplastics)*** *(…)".* For more information, please refer to the Summary of Product Characteristics. The package leaflet was amended accordingly.
PSUSA/10404 /202401	Periodic Safety Update EU Single assessment - atazanavir / cobicistat	03/10/2024	n/a		PRAC Recommendation - maintenance
IA/0048/G	This was an application for a group of variations. B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information	27/11/2023	n/a		
IA/0047/G	This was an application for a group of variations. 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) B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished	17/10/2023	n/a		

	product formulation - Change that does not affect the product information				
IB/0046/G	This was an application for a group of variations. B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method 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.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)	31/07/2023	n/a		
WS/2498/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a	13/07/2023	n/a		

	re-test period/storage period supported by real time data				
II/0044	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	16/03/2023	22/05/2024	SmPC	Section 4.5 of the SmPC is being updated to include recommendations on the co-administration of Evotaz with antiplatelets and corticosteroids. Such recommendations are included in Table 1 (Interactions between EVOTAZ and other medicinal products). Changes to the Package Leaflet (PL) have been included in this procedure accordingly.
IB/0043	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	10/11/2022	03/02/2023	SmPC and PL	
IB/0042	B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	06/05/2022	n/a		
IAIN/0041	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	16/02/2022	03/02/2023	Annex II and PL	
PSUSA/10404 /202101	Periodic Safety Update EU Single assessment - atazanavir / cobicistat	02/09/2021	n/a		PRAC Recommendation - maintenance
II/0038	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	20/05/2021	21/06/2021	SmPC, Annex II and PL	
IB/0039/G	This was an application for a group of variations. B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other	22/12/2020	n/a		

	variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation				
PSUSA/10404 /202001	Periodic Safety Update EU Single assessment - atazanavir / cobicistat	03/09/2020	n/a		PRAC Recommendation - maintenance
IB/0037/G	This was an application for a group of variations. B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation 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	24/07/2020	n/a		

IG/1223/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/importer responsible for batch release 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	17/04/2020	16/04/2021	Annex II and PL	
R/0031	Renewal of the marketing authorisation.	30/01/2020	27/03/2020	SmPC, Annex II and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of EVOTAZ in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
IG/1193	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	17/01/2020	n/a		
IAIN/0032	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	20/12/2019	n/a		
IAIN/0033	B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site	17/12/2019	n/a		
II/0030	Update of sections 4.3 and 4.5 of the SmPC in order	17/10/2019	14/11/2019	SmPC and PL	

	to add as contraindications the concomitant administration of dabigatran or lomitapide with Evotaz, and to add recommendations on the drug-drug interaction between Evotaz and the direct oral anticoagulants dabitagran, ticagrelor, apixaban and edoxaban, as well as with the lipid modifying agent lomitapide, based on already updated information in other marketing authorisations. Sections 4.2, 4.4 and 4.6 of the SmPC are also updated to reflect the accumulated information on the use of cobicistat during pregnancy, based on published literature. The Package Leaflet is updated accordingly. In addition, the marketing authorisation holder (MAH) took the opportunity 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				
PSUSA/10404 /201901	Periodic Safety Update EU Single assessment - atazanavir / cobicistat	05/09/2019	n/a		PRAC Recommendation - maintenance
IA/0029	A.7 - Administrative change - Deletion of manufacturing sites	31/07/2019	n/a		
IB/0028/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	19/07/2019	n/a		

	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 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				
IG/1059	A.1 - Administrative change - Change in the name and/or address of the MAH	15/02/2019	28/03/2019	SmPC, Labelling and PL	
PSUSA/10404 /201807	Periodic Safety Update EU Single assessment - atazanavir / cobicistat	14/02/2019	n/a		PRAC Recommendation - maintenance
IB/0024/G	This was an application for a group of variations. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation 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	26/11/2018	28/03/2019	SmPC and PL	
PSUSA/10404 /201801	Periodic Safety Update EU Single assessment - atazanavir / cobicistat	06/09/2018	n/a		PRAC Recommendation - maintenance
WS/1292	This was an application for a variation following a worksharing procedure according to Article 20 of	22/02/2018	07/12/2018	SmPC and PL	

	Commission Regulation (EC) No 1234/2008. Update of section 4.3 and 4.5 of the SmPC in order to add a contraindication with lurasidone to reflect this interaction based on literature data. The Package Leaflet is updated accordingly. The RMP of Reyataz/Evotaz versions 14.1 and 6.1 respectively have been submitted. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IG/0889	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	13/02/2018	n/a		
PSUSA/10404 /201707	Periodic Safety Update EU Single assessment - atazanavir / cobicistat	08/02/2018	n/a		PRAC Recommendation - maintenance
IB/0021/G	This was an application for a group of variations. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	12/12/2017	07/12/2018	SmPC and PL	
WS/1193	This was an application for a variation following a worksharing procedure according to Article 20 of	26/10/2017	11/12/2017	SmPC and PL	

	Commission Regulation (EC) No 1234/2008. To update sections 4.3 and 4.5 of the SmPC to include information on the contraindicated co-administration with grazoprevir-containing products, including elbasvir/grazoprevir fixed dose combination (used to treat chronic hepatitis C infection) reflecting the results of interaction studies. The Package Leaflets are updated accordingly. The RMP versions 13.2 and 5.0, for Reyataz and Evotaz respectively have been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to make some editorial changes and typographical corrections in the REYATAZ and EVOTAZ Product Information. The requested worksharing procedure proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
PSUSA/10404 /201701	Periodic Safety Update EU Single assessment - atazanavir / cobicistat	01/09/2017	n/a		PRAC Recommendation - maintenance
IA/0017	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	11/05/2017	n/a		

	intermediate used in the manufacture of the AS or manufacturer of a novel excipient				
IG/0795	B.III.2.z - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Other variation	04/05/2017	n/a		
PSUSA/10404 /201607	Periodic Safety Update EU Single assessment - atazanavir / cobicistat	23/02/2017	20/04/2017	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10404/201607.
IA/0014	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	24/03/2017	n/a		
II/0010	Update of section 5.1 of the SmPC with Week 144 resistance data of study GS-US-216-0114 submitted in the context of the MAA. In addition, for clarification purposes, the MAH proposed to use the specific designation of tenofovir disoproxil fumarate throughout the EVOTAZ Product Information (PI) to differentiate this pharmaceutical entity from the tenofovir alafenamide (for which no studies with EVOTAZ have been conducted). Consequently section 4.5 of the SmPC was updated to reflect the expected pharmacokinetic effects of the concomitant administration of tenofovir alafenamide and EVOTAZ. Finally, the MAH took this opportunity to implement QRD version 10. C.I.4 - Change(s) in the SPC, Labelling or PL due to	16/03/2017	11/12/2017	SmPC, Labelling and PL	

	new quality, preclinical, clinical or pharmacovigilance data				
IAIN/0012	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	20/01/2017	16/02/2017	SmPC and PL	
PSUSA/10404 /201601	Periodic Safety Update EU Single assessment - atazanavir / cobicistat	02/09/2016	n/a		PRAC Recommendation - maintenance
II/0007/G	This was an application for a group of variations. To submit the final study reports for two Category 3 studies: Gilead Studies GS-US-216-114 and GS-US-216-105. An updated RMP (version 2.0) was adopted. There are no recommended changes in the PI. 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	23/06/2016	n/a		As per CHMP request, 192-week efficacy data was submitted for study GS-US-126-114 and show viral suppression rates of 71.6% for ATV/co+TVD of 71.6% (53 of 74 subjects) and of 79.7% for ATV/r+TVD (55 of 69 subjects). The difference between the two treatment groups in the percentage of subjects with virologic success at Week 192 was –8.0% (95% CI:-22.2% to 6.3%), in line with non-inferiority of the two treatments. More than 50% of subjects in each treatment arm rolled over to other studies after week 144 and before the week 192 window. Virologic failure and development of resistant associated mutations to FTC were slightly higher for the COBI-based arm, while the difference was not statistically significant. No differences in the changes of both number and percentage of CD4 over baseline values were observed. The full term 204-week data was submitted for study GS-US-126-105. This extension phase data for study GS-US-126-105 is also in line with the data for the main study.
IA/0009	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	13/05/2016	n/a		

IA/0008	B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier	13/05/2016	n/a		
WS/0889	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	28/01/2016	16/02/2017	SmPC and PL	
IG/0636	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	04/12/2015	n/a		
IB/0002	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	10/11/2015	n/a		
IG/0602	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)	11/09/2015	n/a		