Piqray

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
R/0028	Renewal of the marketing authorisation.	12/12/2024	07/02/2025	SmPC and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Piqray in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.

[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).

PSUSA/10871 /202405	Periodic Safety Update EU Single assessment - alpelisib	16/01/2025	n/a		PRAC Recommendation - maintenance
II/0024	Update of the RMP (version 8.1) in order to remove the PASS CBYL719C2404 (Cat. 3) RMP commitment (MEA 002). 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	05/09/2024	n/a		
IA/0026	A.7 - Administrative change - Deletion of manufacturing sites	12/07/2024	n/a		
II/0025	Update of sections 4.2, 4.4 and 4.8 of the SmPC in order to update the frequency of some Adverse Drug Reactions (ADRs) as well as safety information based on the final results from study CBYL719C2301 (SOLAR-1), a randomized, double-blind, placebo-controlled, international, multicenter, Phase III study to determine the efficacy and safety of treatment with alpelisib plus fulvestrant versus placebo plus fulvestrant in men and postmenopausal women with hormone receptor-positive, HER2-negative advanced breast cancer which progressed on or after AI (Aromatase Inhibitor) treatment. The Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to	11/07/2024	07/02/2025	SmPC and PL	The MAH has provided with this type II variation the final cumulative safety results after all subjects randomized in study C2301 (SOLAR-1) and who received at least one dose of study treatment (in both cohorts), had discontinued the study and up to the last patient last visit, with a data cut-off date of 09 June 2023. Sections 4.2, 4.4 and 4.8 of the SmPC are updated accordingly. For more information, please refer to the Summary of Product Characteristics.

	new quality, preclinical, clinical or pharmacovigilance data				
II/0022/G	This was an application for a group of variations. Update of section 4.8 of the SmPC in order to add "uveitis" to the list of adverse drug reactions (ADRs) with a frequency "Not known" based on a cumulative review of the MAH safety database and literature. The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to correct the spelling of the active substance 'alpelisib' in the SmPC. The RMP version 7.2 has also been submitted. 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	30/05/2024	19/07/2024	SmPC and PL	N/A
IAIN/0023/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	21/03/2024	n/a		
PSUSA/10871 /202305	Periodic Safety Update EU Single assessment - alpelisib	11/01/2024	n/a		PRAC Recommendation - maintenance

II/0018	Update of sections 4.5 and 5.2 of the SmPC in order to update drug-drug interaction information, based on final results from study BYL719A2111; this is a phase 1, open-label, fixed-sequence, two-period drug-drug interaction (DDI) study evaluating the PK probe substrates for CYP3A4, CYP2B6, CYP2C8, CYP2C9, and CYP2C19 when administered either alone or in combination with repeated doses of alpelisib. The Annex II and Package Leaflet are updated accordingly. The RMP version 6.0 has also been submitted. In addition, the MAH took the opportunity to update the list of local representatives and to introduce minor editorial changes to the PI. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	14/09/2023	19/07/2024	SmPC, Annex II and PL	SmPC new text: No dose adjustment is required when co administering Piqray with CYP3A4 substrates (e.g. everolimus, midazolam), CYP2C8 substrates (e.g. repaglinide), CYP2C9 substrates (e.g. warfarin), CYP2C19 substrates (e.g. omeprazole). For CYP2B6 substrate, no relevant changes in the exposure were observed when co-administered with Piqray however the results should be considered with caution due to limited data. Metabolic interaction CYP3A4, CYP2C8, CYP2C9, CYP2C19 and CYP2B6 substrates In a drug-drug interaction study, co administration of repeated doses of alpelisib 300 mg with a single dose of sensitive substrates of CYP3A4 (midazolam), CYP2C8 (repaglinide), CYP2C9 (warfarin), CYP2C19 (omeprazole) and CYP2B6 (bupropion), administered as a cocktail, showed that there is no clinically signficant pharmacokinetic interaction. The data from CYP2B6 substrate (bupropion) should be interpreted with caution due to the small sample size. In healthy subjects, co administration of a CYP2C9 substrate (S-warfarin) with repeated doses of 300 mg alpelisib at steady state, increased S warfarin exposure on average by 34% and 19% for AUCinf and Cmax respectively, compared to administration of S warfarin alone. This indicates that alpesilib is a mild inhibitor of CYP2C9.

					For more information, please refer to the Summary of Product Characteristics.
IAIN/0021/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 or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient 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.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	25/08/2023	19/07/2024	Annex II and PL	
PSUSA/10871 /202211	Periodic Safety Update EU Single assessment - alpelisib	08/06/2023	n/a		PRAC Recommendation - maintenance
II/0017	Update of section 5.3 of the SmPC in order to update non-clinical information based on data from two skin toxicology studies conducted in rats: Study 1770766 and Study 1870156.	12/01/2023	07/07/2023	SmPC	In exploratory rat studies evidence of inflammatory changes of the skin was found. For more information, please refer to the Summary of Product Characteristics.

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
PSUSA/10871 /202205	Periodic Safety Update EU Single assessment - alpelisib	12/01/2023	n/a		PRAC Recommendation - maintenance
II/0013	Update of the SmPC sections 4.6 and 5.3 in order to add fertility data based on studies 2070119 "BYL719: Oral (Gavage) Study of Fertility in the Male Rat" and 2070120 "BYL719: Oral (Gavage) Study of Fertility and Early Embryonic Development in the Female Rat". C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	20/10/2022	07/07/2023	SmPC	There are no clinical data available on the effects of alpelisib on fertility. Based on repeated dose toxicity and fertility studies in animals, alpelisib may impair fertility in males and females of reproductive potential. For more information, please refer to the Summary of Product Characteristics.
PSUSA/10871 /202111	Periodic Safety Update EU Single assessment - alpelisib	23/06/2022	17/08/2022	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10871/202111.
II/0012	Update of sections 4.5 and 5.2 of the SmPC in order to add drug-drug interaction information with CYP3A4 inducers based on Study BYL719A2110, a drug-drug interactions study that evaluated the PK of alpelisib when administered alone or with rifampin, a strong CYP3A4 inducer, in healthy participants. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance	21/07/2022	07/07/2023	SmPC	Once daily administration of 600 mg rifampin (a strong CYP3A4 inducer) for 7 days followed by co administration with a single 300 mg oral dose of alpelisib on day 8, decreased alpelisib Cmax by 38% and AUC by 57% in healthy adults (N=25). Co-administration of rifampin 600 mg once daily for 15 days with alpelisib 300 mg once daily starting from day 8 to day 15 decreased the steady state alpelisib Cmax by 59% and AUC by 74%.

	data				Co-administration with a strong CYP3A4 inducer decreases alpelisib AUC, which may reduce alpelisib efficacy. Co-administration of alpelisib with strong CYP3A4 inducers (e.g. apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort) should be avoided and selection of an alternative concomitant medicinal product, with no or minimal potential to induce CYP3A4, should be considered. For more information, please refer to the Summary of Product Characteristics.
IG/1521	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	23/06/2022	n/a		
IB/0014	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	06/06/2022	n/a		
IAIN/0011/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 batch control/testing takes place 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	02/05/2022	n/a		

	manufacturer				
IA/0010/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 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 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	30/03/2022	n/a		
II/0008/G	This was an application for a group of variations. Update of section 5.1 of the SmPC based on final results from study CBYL719C2301 (SOLAR-1) listed as a PAES in the Annex II; this is a phase III, randomized, double-blind, placebo controlled study of alpelisib in combination with fulvestrant for men and postmenopausal women with hormone receptor positive, HER2-negative advanced breast cancer which progressed on or after aromatase inhibitor treatment; the Annex II is updated accordingly. In addition, the MAH is updating the ATC code in the	24/03/2022	17/08/2022	SmPC and Annex II	The table in Module 8b of the EPAR will be updated as follows: Scope Please refer to the Recommendations section above Summary SmPC new text The study met its primary objective at the final PFS analysis (cut off date 12 Jun 2018), demonstrating a statistically significant improvement in PFS per investigator assessment in the PIK3CA mutant cohort for patients receiving alpelisib plus fulvestrant, compared to patients receiving placebo plus fulvestrant with an estimated 35%

	SmPC. The RMP version 5.0 has also been submitted. A.6 - Administrative change - Change in ATC Code/ATC Vet Code C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				risk reduction of disease progression or death in favour of treatment with alpelisib plus fulvestrant. At the time when the final OS analysis was conducted (data cut off date of 23 Apr 2020) a descriptive follow-up efficacy analysis for PFS data was performed. With a median duration from randomisation to data cut off of approximately 42 months, the reported PFS results were consistent with those from the primary PFS analysis. There was an estimated 36% risk reduction of progression or death in favour of treatment with alpelisib plus fulvestrant (HR=0.64; 95% CI: 0.50, 0.81) At the final OS analysis, the study did not meet its key secondary objective. As of the data cut off date of 23 Apr 2020, a total of 87 (51.5%) deaths were reported in the alpelisib plus fulvestrant arm and 94 (54.7%) in the placebo plus fulvestrant arm. The HR was 0.86 (95% CI: 0.64, 1.15; p=0.15, one sided) and the pre specified O'Brien Fleming efficacy boundary of p ≤0.0161 was not crossed. Median OS was 39.3 months (95% CI: 34.1, 44.9) in the alpelisib plus fulvestrant arm and 31.4 months (95% CI: 26.8, 41.3) in the placebo plus fulvestrant arm. In patients with prior CDK4/6i treatment (n=20), the median OS in the alpelisib plus fulvestrant arm was 29.8 months (95% CI: 6.7, 38.2) compared to 12.9 months (95% CI: 2.5, 34.6) in the placebo plus fulvestrant arm (HR=0.67; 95% CI: 0.21, 2.18). For more information, please refer to the Summary of Product Characteristics.
PSUSA/10871 /202105	Periodic Safety Update EU Single assessment - alpelisib	13/01/2022	n/a		PRAC Recommendation - maintenance

N/0006	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/09/2021	17/08/2022	PL	
PSUSA/10871 /202011	Periodic Safety Update EU Single assessment - alpelisib	10/06/2021	n/a		PRAC Recommendation - maintenance
II/0005/G	This was an application for a group of variations. C.1.4 Update of sections 4.4 and 4.8 of the SmPC in order to add hyperglycaemic hyperosmolar non-ketotic syndrome to the list of adverse drug reactions (ADRs) with frequency "unknown" and to update the warning on hyperglycaemia and ketoacidosis based on a review of the safety database. The Package leaflet and Annex II are updated accordingly. The RMP version 4.0 is approved. C.1.4 Update of sections 4.2 and 4.8 of the SmPC to modify the management of hyperglycaemia, rash and diarrhoea and add information about osteonecrosis of the jaw based on the pivotal trial SOLAR-1. The MAH also took the opportunity to make minor editorial changes to the SmPC. 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	22/04/2021	21/05/2021	SmPC, Annex II and PL	Severe hyperglycaemia, in some cases associated with hyperglycaemic hyperosmolar nonketotic syndrome (HHNKS) or ketoacidosis, has been observed in patients treated with Piqray. Some cases of ketoacidosis with fatal outcome have been reported in the post-marketing setting. HHNKS has been included to the list of adverse drug reactions (ADRs) with frequency "unknown". Recommendations for dose modification and management of hyperglycaemia, rash and diarrhoea have been updated as part of this group of variations based on the protocol of SOLAR-1 study. For further information please refer to the Summary of Product Characteristics (SmPC), section 4.2.
II/0001	Submission of an updated RMP version 2.0 in order to replace the category 3 studies CBYL719C2402 and	11/03/2021	n/a		

	CBYL719A0IC02 with a new non interventional safety study (CBYL719C2404). Additionally, a separated Health Care Professional Survey (CBYL719A0IC02) is proposed as part of the pharmacovigilance plan. 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				
IAIN/0003/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 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.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	07/01/2021	21/05/2021	Annex II and PL	
IB/0002	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	27/11/2020	n/a		