Summary of the risk management plan for PIQRAY® (alpelisib)

This is a summary of the risk management plan (RMP) for Piqray®. The RMP details important risks of Piqray, how these risks can be minimized, and how more information will be obtained about Piqray's risks and uncertainties (missing information).

Piqray's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Piqray should be used.

This summary of the RMP for Piqray should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Piqray*'s* RMP.

I. The medicine and what it is used for

Piqray is indicated in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor positive, HER2-negative, locally advanced or metastatic breast cancer with PIK3CA mutation after disease progression following endocrine-therapy as monotherapy. It contains alpelisib as the active substance and it is given by oral route.

Further information about the evaluation of the benefits of Piqray can be found in the EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/piqray

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Piqray, together with measures to minimize such risks and the proposed studies for learning more about the risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;

- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In the case of Piqray, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Piqray is not yet available, it is listed under 'missing information' below.

II.A: List of important risks and missing information

Important risks of Piqray are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Piqray. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table 1 List of important risks and missing information

List of important risks and missing information	
Important identified risks	Hyperglycaemia
	Pneumonitis
	Severe cutaneous reactions
	Osteonecrosis of the jaw
Important potential risks	None
Missing information	Safety with long-term use

II B: Summary of important risks

Table 1 Important identified risk: Hyperglycaemia

Evidence for linking the risk to the medicine	Hyperglycaemia is a reversible, on-target effect of PI3K inhibition. Preclinical study data indicate that alpelisib has the potential to interfere with the glucose and insulin homeostasis. Hyperglycaemia has been observed both in preclinical and clinical studies with alpelisib.
Risk factors and risk groups	Patients with diabetes mellitus or pre-diabetic conditions such as impaired fasting glucose and other conditions such as BMI ≥30 and age ≥75.
Risk minimization measures	**Routine risk communication** SmPC Section 4.2 Posology and method of administration SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects PL Section 2 Warnings and precautions PL Section 3 How to take Piqray PL Section 4 Possible side effects **Additional risk minimization measures** Prescriber's guide **Other routine risk minimization measures beyond the Product Information** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Study CBYL719C2402 Study BYL719A0IC02 See Section II C of this summary for an overview of the post-authorization development plan.

Table 2 Important identified risk: Pneumonitis

Evidence for linking the risk to the medicine	Pneumonitis is a known toxicity of PI3K/mTOR pathway inhibitors. Serious cases of pneumonitis/acute interstitial pneumonitis/ interstitial lung disease have been reported with alpelisib across all studies.
Risk factors and risk groups	There are no identified risk factors for the occurrence of pneumonitis in alpelisib-treated patients.
Risk minimization measures	**Routine risk communication** SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects PL Section 2 Warnings and precautions PL Section 4 Possible side effects **Other routine risk minimization measures beyond the Product Information** None

Table 3 Important identified risk: Severe cutaneous reactions

Evidence for linking the risk to the medicine	Skin and subcutaneous tissue disorders including severe cutaneous reactions are a known effect of PI3K/mTOR pathway inhibitors. Cases of severe cutaneous reactions have been reported in clinical studies.
Risk factors and risk groups	There are no identified risk factors for the occurrence of severe cutaneous reactions in alpelisib treated patients.
Risk minimization measures	**Routine risk communication** SmPC Section 4.2 Posology and method of administration SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects **Other routine risk minimization measures beyond the Product Information** None

Table 4 Important identified risk: Osteonecrosis of the jaw

Evidence for linking the risk to the medicine	Osteonecrosis of the jaw was reported in clinical studies, in different populations and combination treatment.
Risk factors and risk groups	Subjects receiving bisphosphonates and/or denosumab before or during treatment with alpelisib are at a higher risk of developing ONJ.
Risk minimization measures	**Routine risk communication** SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects PL Section 2 Warnings and precautions PL Section 4 Possible side effects **Other routine risk minimization measures beyond the Product Information** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Study BYL719A0IC02 See Section II C of this summary for an overview of the post-authorization development plan.

Table 5 Missing information: Safety with long-term use

Risk minimization measures	**Routine risk minimization measures** None **Additional risk minimization measures** None

II C: Post-authorization development plan

II.C.1 Studies which are conditions of the marketing authorization

Table 6 Studies which are conditions of the marketing authorization

Study short name	Purpose of the study:
Study CBYL719C2301 (SOLAR-1)	The purpose of this study is to determine whether treatment with alpelisib plus fulvestrant prolongs progression-free survival (PFS) compared to fulvestrant and placebo in men and postmenopausal women with hormone receptor positive (HR+), HER2-negative advanced breast cancer, who received prior treatment with an aromatase inhibitor either as (neo)adjuvant or for advanced disease. **Primary objective:** To determine whether treatment with alpelisib + fulvestrant prolongs PFS vs. treatment with placebo + fulvestrant for patients with PIK3CA mutant status. **Secondary objectives:** • To determine whether treatment with alpelisib +fulvestrant prolongs OS vs. treatment with placebo + fulvestrant for patients with PIK3C mutation • To establish proof of concept of treatment benefit with alpelisib + fulvestrant with respect to PFS for patients without a PIK3CA non-mutant status • To evaluate the two treatment arms with respect to OS for patients with PIK3CA non-mutant status • To evaluate the two treatment arms and cohorts of interest with respect to ORR, CBR. • To evaluate the two treatment arms and cohorts of interest with respect to time to deterioration of ECOG performance status. • To evaluate the safety and tolerability of alpelisib +fulvestrant • To evaluate change in global health status/QOL in the two treatment arms and cohorts of interest • To characterize the PK of fulvestrant, and alpelisib + fulvestrant. • To evaluate the association between PIK3CA mutation status as measured in ctDNA at baseline with PFS upon treatment with alpelisib.

II.C.2. Other studies in post-authorization development plan

Table 7 Other studies in the post-authorization development plan

Study short name	Rationale and study objectives
Study CBYL719C2402	Hyperglycaemia is an identified risk for alpelisib. The purpose of the study is to further characterize the risk of hyperglycaemia in the real world setting.

Study short name	Rationale and study objectives
	The **primary objective** is to estimate the incidence of hyperglycemia (any severity, and severe hyperglycemia) in a cohort of men and postmenopausal women with HR-positive HER2-negative advanced or metastatic breast cancer treated with alpelisib in combination with fulvestrant, following treatment with an endocrine-based regimen. The **secondary objectives** are, • To characterize time to hyperglycemia (any severity, and severe hyperglycemia) since alpelisib initiation among patients who developed such events. • To evaluate the impact of known risk factors of hyperglycemia in the real world setting.

BYL719A0IC02	The purpose of this study is to evaluate the overall safety and tolerability of alpelisib in combination with fulvestrant in a population according to SmPC of European patients with HR+, HER2- ABC harboring PIK3CA mutation(s) whose disease has progressed on or after endocrine based therapy.
	Primary objective:
	To evaluate the safety and tolerability of alpelisib plus fulvestrant.
	Secondary objective:
	• To assess the overall response rate (ORR) in patients with measurable disease
	• To assess alpelisib dose changes due to adverse events
	• To assess clinical benefit rate (CBR)
	• To assess duration of response (DOR) in patients with confirmed complete response (CR) or partial response (PR)
	• To assess risk factors for hyperglycemia
	• To assess the time to tumor progression (TTP) as per RECIST 1.1
	• To assess the treatment discontinuation rate
	• To evaluate change in global health status/QOL and pain (only in selected countries)
	• To evaluate effectiveness of additional risk minimization measures for hyperglycaemia
	  • Analyzing all hyperglycaemia AESI events (serious and non-serious)
	  • Assessing HCP awareness of the content of educational material via HCP questionnaire