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 2 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. Cases of severe hyperglycaemia, in some cases associated with Hyperglycaemic Hyperosmolar Non-Ketotic Syndrome (HHNKS) or ketoacidosis have been reported in post-marketing setting.
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 CBYL719C2404 Study CBYL719C2005 See Section 2.3 of this summary for an overview of the post-authorization development plan.

Table 3 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 4 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 PL Section 2 Warnings and precautions PL Section 4 Possible side effects **Other routine risk minimization measures beyond the Product Information** None

Table 5 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 CBYL719C2404 See Section 2.3 of this summary for an overview of the post-authorization development plan.

Table 6 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

There are no studies which are conditions of the marketing authorization or specific obligation of Piqray.

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

CBYL719C2404	The purpose of the study is to further evaluate the safety of Piqray in the real world setting in European countries.
	
	The study will focus on two of the important identified risks hyperglycaemia and osteonecrosis of the jaw.
	
	The primary objective is to assess the incidence of hyperglycemia.
	
	The secondary objectives are as follows:
	• To assess the risk factors for hyperglycemia including following:
	  • Patient characteristics – age, body mass index, sex.
	  • Medical history of diabetes mellitus (including gestational diabetes), tobacco use, or baseline diabetic status per laboratory values for HbA1c and fasting glucose (normal, pre-diabetes, and diabetes).
	  • Concomitant medications known to affect blood glucose levels (systemic corticosteroids, statins, quinolones, thiazides and thiazide-like diuretics, beta blockers, atypical antipsychotics, protease inhibitors and calcineurin inhibitors)
	  • Family history of diabetes mellitus
	• To describe the safety and tolerability of Piqray in combination with fulvestrant in a non-interventional setting.
	• To assess the incidence of osteonecrosis of the jaw, and the risk factors for ONJ including the following:
	  • Patient characteristics – age, body mass index, sex.

Study short name	Rationale and study objectives
	• Prior and/or concomitant use of bisphosphonates (e.g. zoledronic acid) (Yes/No). • Prior and/or concomitant use of RANK-ligand inhibitors (e.g. denosumab) (Yes/No). • To estimate the incidence of complications of a non-compensated hyperglycaemic state such as ketoacidosis and hyperglycemic hyperosmolar non-ketotic syndrome (HHNKS) under real-life conditions. • To describe other AESIs of alpelisib in combination with fulvestrant observed during follow-up of treated patients. • GI toxicity (nausea, vomiting and diarrhea) • Rash • Hypersensitivity (e.g. anaphylactic reaction) • Pancreatitis • Pneumonitis • SCARs
CBYL719C2005	In order to assess effectiveness of additional risk minimization measures for hyperglycemia (prescriber's/HCP guide), Novartis will conduct the survey 12 to 18 months post Piqray (alpelisib) reimbursement among oncologists/ HCPs prescribing Piqray. The primary objective of this study is to measure physician knowledge and understanding of the key information included in the educational material. The following objectives will be addressed • Investigate whether physicians have received any educational material related to Piqray (alpelisib) • Assess physicians' knowledge and understanding of key safety information pertaining to the educational material • Assess physicians' knowledge and understanding of key safety information pertaining to the following areas: • Risk factors for hyperglycemia • Signs and symptoms of hyperglycemia • Management of hyperglycemia prior to starting and during treatment with Piqray (alpelisib).

Study short name	Rationale and study objectives
	Secondary objective: The survey will assess as secondary objectives HCPs' self-reported risk minimization behaviors.