Regulatory Affairs

# Alpelisib

## Summary of the EU Safety Risk Management Plan

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| Active substance(s) (INN or common name): | *Alpelisib* |
| Product concerned (brand name): | *Piqray®* |
| Document status: | *Final* |
| Version number of the RMP Public Summary: | *4.0* |
| Date of final sign off of the RMP Public Summary | *15-07-2021* |



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# Summary of the risk management plan for Piqray® (Alpelisib)

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Piqray® is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Piqray® in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Novartis Pharma Schweiz AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Piqray®.

## 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: link to the EPAR summary landing page.

## 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 risk and missing information** | |
|---|---|
| Important idenitified 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**

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| 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 | **Routine risk communication** |

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| measures | Prescribing information sections Posology and method of administration, Special warnings and precautions for use, Undesirable effects<br>Information for patients sections Warnings and precautions, How to take Piqray, Possible side effects<br>**Additional risk minimization measures**<br>Prescriber's guide<br>**Other routine risk minimization measures beyond the Product Information**<br>none |
| Additional pharmacovigilance activities | **Additional pharmacovigilance activities:**<br>Study CBYL719C2404<br>Study CBYL719C2005<br>See Section 2.3 of this summary for an overview of the postauthorization development plan. |

**Table 3 Important identified risk: Pneumonitis**

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| 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**<br>Prescribing information sections Special warnings and precautions for use, Undesirable effects<br>Information for patients sections Warnings and precautions, Possible side effects<br>**Other routine risk minimization measures beyond the Product Information**<br>None |

**Table 4 Important identified risk: Severe cutaneous reactions**

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| 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**<br>Prescribing information sections Posology and method of administration, Special warnings and precautions for use, Undesirable effects<br>**Other routine risk minimization measures beyond the Product Information**<br>None |

**Table 5 Important identified risk: Osteonecrosis of the jaw**

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| 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**<br>Prescribing information sections Special warnings and precautions for use, Undesirable effects<br>Information for patients sections Warnings and precautions, Possible side effects<br>**Other routine risk minimization measures beyond the Product Information**<br>None |
| Additional pharmacovigilance activities | **Additional pharmacovigilance activities:**<br>Study CBYL719C2404<br>See Section “Post-authorisation development plan” of this summary for an overview of the post-authorization development plan. |

| **Table 6** | **Important identified risk: safety with long-term use** |
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| Risk minimization measures | **Routine risk minimization measures**<br>None<br>**Additional risk minimization measures**<br>None |

## II C: Post-authorization development plan

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

**Table 7 Studies which are conditions of the marketing authorization**

| **Study short name** | **Purpose of the study:** |
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| 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.<br>**Primary objective:**<br>To determine whether treatment with alpelisib + fulvestrant prolongs PFS vs. treatment with placebo + fulvestrant for patients with PIK3CA mutant status.<br>**Secondary objectives:**<br>• To determine whether treatment with alpelisib +fulvestrant prolongs OS vs. treatment with placebo + fulvestrant for patients with PIK3C mutation<br>• To establish proof of concept of treatment benefit with alpelisib + fulvestrant with respect to PFS for patients without a PIK3CA non- mutant status<br>• To evaluate the two treatment arms with respect to OS for patients with PIK3CA non-mutant status<br>• To evaluate the two treatment arms and cohorts of interest with respect to ORR, CBR.<br>• To evaluate the two treatment arms and cohorts of interest with respect to time to deterioration of ECOG performance status. |

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| | • To evaluate the safety and tolerability of alpelisib +fulvestrant<br>• To evaluate change in global health status/QOL in the two treatment arms and cohorts of interest<br>• To characterize the PK of fulvestrant, and alpelisib + fulvestrant.<br>• 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 8 Other studies in the post-authorization development plan**

| Study short name | Rationale and study objectives |
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| Study CBYL719C2404 | The purpose of the study is to further evaluate the safety of Piqray in the real world setting in European countries.<br>The study will focus on two of the important identified risks<br>hyperglycaemia and osteonecrosis of the jaw.<br>The primary objective is to assess the incidence of hyperglycemia.<br>The secondary objectives are as follows:<br>• To assess the risk factors for hyperglycemia including following:<br>o Patient characteristics – age, body mass index, sex.<br>o Medical history of diabetes mellitus or baseline laboratory values for HbA1c and fasting glucose (normal, pre-diabetes, and diabetes).<br>o 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)<br>o Family history of diabetes mellitus<br>o Tobacco use (never, prior, current) |

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| | • To describe the safety and tolerability of Piqray in combination with fulvestrant in a non-interventional setting.<br>• To assess the incidence of osteonecrosis of the jaw, and the risk factors for ONJ including the following:<br>o Prior and/or concomitant use of bisphosphonates (e.g. zoledronic acid) (Yes/No).<br>o Prior and/or concomitant use of RANK-ligand inhibitors (e.g. denosumab) (Yes/No).<br>• 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. |
| BYL719C2005 | 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.<br><br>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<br><br>• Investigate whether physicians have received any educational material related to Piqray (alpelisib).<br>• Assess physicians' knowledge and understanding of key safety information pertaining to the educational material<br>• Assess physicians' knowledge and understanding of key safety information pertaining to the following areas:<br>o Risk factors for hyperglycemia<br>o Signs and symptoms of hyperglycemia<br>o Management of hyperglycemia prior to starting and during treatment with Piqray (alpelisib).<br><br>Secondary objective:<br><br>The survey will assess as secondary objectives HCPs' self-reported risk minimization behaviors. |