Regulatory Affairs

Piqray®

(Alpelisib)

Summary of the Risk Management Plan (RMP) v1.0 for Piqray®

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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 minimize 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.swissmedicinfo.ch) approved and authorized by Swissmedic.

Novartis Pharma Schweiz AG is fully responsible for the accuracy and correctness of the content of the here published summary RMP of Piqray®.

The medicine and what it is used for

Piqray® is used in combination with fulvestrant for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, advanced breast cancer with a PIK3CA mutation after disease progression when patients have previously received endocrine therapy including an aromatase inhibitor.

It contains alpelisib as the active substance and it is given by oral route.

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 Prescribing information 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.

**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**

<table>
<thead>
<tr>
<th>List of important risk and missing information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Important identified risks:</td>
</tr>
<tr>
<td>Hypersensitivity</td>
</tr>
<tr>
<td>Hyperglycaemia</td>
</tr>
<tr>
<td>Pneumonitis</td>
</tr>
<tr>
<td>Severe cutaneous reactions</td>
</tr>
<tr>
<td>Important potential risks:</td>
</tr>
<tr>
<td>None</td>
</tr>
<tr>
<td>Missing information:</td>
</tr>
<tr>
<td>Safety with long-term use</td>
</tr>
</tbody>
</table>

**Summary of important risks**

**Table 2**  
**Important identified risk: Hypersensitivity**

<table>
<thead>
<tr>
<th>Evidence for linking the risk to the medicine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence for an involvement of the PI3K signalling pathway in</td>
</tr>
</tbody>
</table>
immunological functions has been reported. Hypersensitivity reactions have been reported in subjects receiving alpelisib.

Risk factors and risk groups
There are no identified risk factors for hypersensitivity reactions in alpelisib-treated subjects.

Risk minimization measures
Routine risk communication
Prescribing information sections Contraindications, Special warnings and precautions for use, Undesirable effects

Other routine risk minimization measures beyond the Product Information
None

Table 3 Important identified risk: Hyperglycaemia

<table>
<thead>
<tr>
<th>Evidence for linking the risk to the medicine</th>
<th>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.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk factors and risk groups</td>
<td>Patients with diabetes mellitus or pre-diabetic conditions such as impaired fasting glucose.</td>
</tr>
<tr>
<td>Risk minimization measures</td>
<td>Routine risk communication</td>
</tr>
<tr>
<td></td>
<td>Prescribing information sections Posology and method of administration, Special warnings and precautions for use, Undesirable effects</td>
</tr>
<tr>
<td></td>
<td>Other routine risk minimization measures beyond the Product Information</td>
</tr>
<tr>
<td></td>
<td>None</td>
</tr>
</tbody>
</table>

Additional pharmacovigilance activities
Additional pharmacovigilance activities:
Study CBYL719C2402

See Section postauthorization development plan of this summary for an overview of the postauthorization development plan.
### Table 4  Important identified risk: Pneumonitis

<table>
<thead>
<tr>
<th>Evidence for linking the risk to the medicine</th>
<th>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.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk factors and risk groups</td>
<td>There are no identified risk factors for the occurrence of pneumonitis in alpelisib-treated patients.</td>
</tr>
</tbody>
</table>
| Risk minimization measures                  | **Routine risk communication**  
Prescribing information sections Special warnings and precautions for use, Undesirable effects  
**Other routine risk minimization measures beyond the Product Information**  
None                                                                 |

### Table 5  Important identified risk: Severe cutaneous reactions

<table>
<thead>
<tr>
<th>Evidence for linking the risk to the medicine</th>
<th>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.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk factors and risk groups</td>
<td>There are no identified risk factors for the occurrence of severe cutaneous reactions in alpelisib treated patients.</td>
</tr>
</tbody>
</table>
| Risk minimization measures                  | **Routine risk communication**  
Prescribing information sections Posology and method of administration, Special warnings and precautions for use, Undesirable effects  
**Other routine risk minimization measures beyond the Product Information**  
None                                                                 |

### Table 6  Important identified risk: safety with long-term use
Risk minimization measures

Routine risk minimization measures
None

Additional risk minimization measures
None

Post-authorization development plan

Studies which are conditions of the marketing authorization

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

Other studies in post-authorization development plan

Table 7  Other studies in the post-authorization development plan

<table>
<thead>
<tr>
<th>Study short name</th>
<th>Rationale and study objectives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study CBYL719C2402</td>
<td>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, including the risk in susceptible populations. 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 PIK3CA-mutated advanced breast cancer treated with alpelisib in combination with fulvestrant. The secondary objectives are, 1. To characterize time to hyperglycaemia or hyperglycemic crises since alpelisib initiation among patients who developed such events, and 2. To estimate, if feasible, the incidence (both incidence rate and incidence proportion) of hyperglycaemia in susceptible populations among the cohort of patients treated with alpelisib in combination with fulvestrant, including:</td>
</tr>
</tbody>
</table>
a) Patients diagnosed with diabetes prior to the initiation of alpelisib treatment (i.e. patients with comorbid diabetes)

b) Patients with corticosteroids during anytime of alpelisib treatment.

**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 AI either as (neo)adjuvant or for advanced disease.

**Primary objective:**
To determine whether treatment with alpelisib in combination with fulvestrant prolongs PFS compared to treatment with placebo in combination with fulvestrant for patients with PIK3CA mutant status.

**Key secondary objective:**
To determine whether treatment with alpelisib in combination with fulvestrant prolongs overall survival compared to treatment with placebo in combination with fulvestrant for patients with PIK3CA mutant status.

This is a pivotal submission study which is currently ongoing. The data generated from this study will be utilized to further characterize the missing information 'safety with long-term use'.