

Date: 20 May 2020

Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Piqray

International non-proprietary name: alpelisib

Pharmaceutical form: film-coated tablets

Dosage strength: 200 mg, 200 mg + 50 mg, 150 mg

Route(s) of administration: oral

Marketing Authorisation Holder: Novartis Pharma Schweiz AG

Marketing Authorisation No.: 67359

Decision and Decision date: approved on 24 March 2020

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

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- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
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- In addition to the actual SwissPAR, a concise version of SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, Distribution, Metabolism, Elimination
ALAT	Alanine aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC0-24h	Area under the plasma concentration-time curve for the 24-hour dosing interval
BCRP	Breast cancer resistance protein
BIRC	Blinded independent review committee
CDK	Cyclin-dependent kinase
CI	Confidence interval
Cmax	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ER	Oestrogen receptor
ERA	Environmental Risk Assessment
GLP	Good Laboratory Practice
HER2	Human epidermal growth factor receptor 2
hERG	Human ether-à-go-go-related gene
HR	Hazard ratio
HR	Hormone receptor
ICH	International Council for Harmonisation
IC ₅₀	Half-maximal inhibitory concentration
Ig	Immunoglobulin
INN	International Nonproprietary Name
LDPE	Low-density polyethylene
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MRP	Multidrug resistance-associated proteins
mTOR	mammalian target of rapamycin
N/A	Not applicable
NCI	National Cancer Institute
NO(A)EL	No Observed (Adverse) Effect Level
OAT	Organic anion transporter
OATP	Organic anion-transporting polypeptide
OS	Overall survival
PD	Pharmacodynamics
PFS	Progression-free survival
P-gp	P-glycoprotein
PI3K	Phosphatidylinositol 3-kinase
PIK3CA	Gene which encodes the p110- α catalytic subunit of PI3K
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population PK
PSP	Pediatric Study Plan (US-FDA)
QD	Once daily
RMP	Risk Management Plan
SwissPAR	Swiss Public Assessment Report
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices

TPO (SR 812.21)
UGT Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
Uridine 5'-Diphospho-Glucuronosyltransferase

2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status

The applicant requested the status of a new active entity for the active substance (alpelisib) of the medicinal product mentioned above.

2.2 Indication and Dosage

2.2.1 Requested Indication

Piqray is indicated for the treatment of postmenopausal women and men with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, advanced breast cancer with a PIK3CA mutation in combination with fulvestrant after disease progression following an endocrine-based therapy.

2.2.2 Approved Indication

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.

2.2.3 Requested Dosage

The recommended starting dose of alpelisib is 300 mg once daily. To allow management of adverse events, a maximum of two dose reductions by 50 mg each is allowed (250 mg once daily or 200 mg once daily).

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	06 March 2019
Formal control completed	15 March 2019
List of Questions (LoQ)	17 June 2019
Answers to LoQ	9 August 2019
Predecision	15 November 2019
Answers to Predecision	13 January 2020
Final Decision	24 March 2020
Decision	approval

2.4 Medical Context

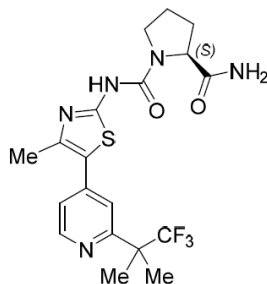
The phosphatidylinositol-3-kinase PI3K-AKT- mammalian target of rapamycin mTOR pathway is one of the most frequently dysregulated pathways in cancer, and PIK3CA is one of the most frequently altered genes in metastatic breast cancer^{1 2 3}.

PIK3CA mutations are more likely to be observed in HR-positive HER2-negative tumours.

3 Quality Aspects

3.1 Drug Substance

INN: Alpelisib
 Chemical name: (2*S*)-*N*1-{4-Methyl-5-[2-(1,1,1-trifluoro-2-methylpropan-2-yl)pyridin-4-yl]-1,3-thiazol-2-yl}pyrrolidine-1,2-dicarboxamide
 Molecular formula: C₁₉H₂₂F₃N₅O₂S
 Molecular mass: 441.47 g/mol
 Molecular structure:



Physico-chemical properties:

Alpelisib is a white to almost white crystalline powder. It contains one stereogenic centre and is manufactured as a single enantiomer.

Synthesis:

The drug substance is manufactured by a multiple-step chemical synthesis with final crystallisation resulting in the anhydrous form A. The synthesis of the drug substance and the necessary in-process controls are described in detail.

Specification:

In order to ensure a consistent quality of alpelisib, the specifications include all relevant test parameters as recommended by the relevant ICH guidelines.

Stability:

The bulk drug substance is packaged in LDPE bags. Appropriate stability data have been presented. Based on the results, a satisfactory retest period was established.

¹ Janku F: Targeting the PI3K pathway in cancer: are we making headway?, Nature Reviews Clinical Oncology 2018; 15, 273–291

² Bertucci F: Genomic characterization of metastatic breast cancers, Nature 2019; 569, 560–564

³ Mukohara T: PI3K mutations in breast cancer: prognostic and therapeutic implications, Breast Cancer 2015; 7: 111-123

3.2 Drug Product

Description and composition:

Alpelisib film-coated tablets are presented as immediate release round tablets. The edges are bevelled. The film-coated tablets containing 50 mg drug substance are imprinted with “L7” on one side and “NVR” on the other side. The film-coated tablets containing 150mg drug substance are imprinted with “UL7” on one side and “NVR” on the other side. The film-coated tablets containing 200mg alpelisib are imprinted with “YL7” on one side and “NVR” on the other side.

The excipients of the tablet core are: microcrystalline cellulose, mannitol, sodium starch glycolate, hypromellose, magnesium stearate and water.

The film coating of the tablet is composed of hypromellose, black iron oxide (E 172), red iron oxide (E 172), titanium dioxide (E 171) and talc.

Pharmaceutical development:

Alpelisib film-coated tablets were developed as immediate release tablets to be administered orally once daily in order to achieve the appropriate pharmacokinetic profile.

Manufacture:

Alpelisib film-coated tablets are manufactured using a wet granulation process. The manufacturing process is described with a sufficient level of detail. In order to achieve consistent tablet quality, appropriate in-process controls are applied.

Specification:

For the control of the finished product, adequate tests and criteria for release and a shelf-life are established. The specifications include the parameters appearance, identity, purity, dissolution, uniformity of dosage units, assay, degradation products and microbial enumeration tests. The test methods are adequately validated according to the recommendations of the current scientific guidelines.

Container-Closure System:

Alpelisib film-coated tablets are packaged in PVC/PCTFE blisters with push-through aluminium foil lidding.

Stability:

Appropriate stability data are presented. Based on these data, a shelf life was established for the film-coated tablets. The storage recommendation is “Do not store above 30° C”.

3.3 Quality Conclusions

Satisfactory and consistent quality of drug substance and drug product has been demonstrated.

4 Nonclinical Aspects

The applicant provided a comprehensive study package that was based on the ICH S9 guideline. Pivotal safety pharmacology and toxicology studies with alpelisib were conducted in compliance with GLP.

Pharmacology

Primary pharmacology studies demonstrated that alpelisib is an inhibitor of phosphatidylinositol-3-kinase (PI3K)/Akt signalling. In biochemical assays, alpelisib inhibited human PI3K α wild type and mutants E545K and H1047R at low nanomolar concentrations (IC_{50} 4.0-4.8 nM). Alpelisib also inhibited other class I PI3Ks and the related phosphatidylinositol 4-kinase beta (PI4K β), albeit with lower potency (IC_{50} values between 64 and 1156 nM). The activities of class III PI3K/Vps34 and the mammalian target of rapamycin (mTOR) were not impaired at clinically relevant concentrations ($IC_{50} > 9.1 \mu M$). The inhibition of Akt phosphorylation (pAkt) and downstream effectors by alpelisib was demonstrated *in vitro* in cells with constitutively activating forms of class IA PI3Ks. Alpelisib did not interfere with signalling pathways associated with class IV PI3Ks. Potential interactions of alpelisib with class II PI3Ks were not investigated. Based on *in vitro* studies with the major human metabolite M4 (BZG791), this metabolite has no relevant pharmacological activity.

Alpelisib inhibited *in vitro* the proliferation of several human breast cancer cell lines carrying PIK3CA mutations with IC_{50} values ranging from 139 nM to 2331 nM. *In vivo*, oral administration of alpelisib showed significant antitumour activity in different xenograft models in mice and rats, including models with overexpression of PI3K α and tumours of breast cancer origin bearing PI3K mutations H1047R, E545K, and K111N(+erbB2 amplification). There was dose- and time-dependent inhibition of pAkt in tumour tissue that correlated with the plasma concentration. In studies with mice bearing tumours derived from fulvestrant-sensitive oestrogen receptor (ER)+ human breast cancer cell lines with aberrant PI3K/Akt signalling, treatment with alpelisib alone (50 mg/kg/day) led to significant reduction in tumour growth; the combination treatment alpelisib+fulvestrant was more effective vs. fulvestrant treatment alone in two of the three models. In ER+ breast cancer models with resistance against the mTOR inhibitor everolimus or cyclin-dependent kinase 4/6 (CDK4/6) inhibitors, co-treatment of alpelisib with fulvestrant was generally more effective than treatment with the compounds alone.

Alpelisib inhibited glucose uptake into *in vitro* differentiated 3T3-L1 adipocytes with an IC_{50} value of 169 nM. This effect is related to the pharmacological activity and was also seen *in vivo* in preclinical species and in the clinical trials (see *Toxicology*). Alpelisib inhibited angiogenesis and vessel leakage in mice at low oral doses (≥ 3.0 mg/kg/day), which is also related to the pharmacological activity on PI3K/Akt signalling.

Alpelisib inhibited proliferation and/or activation of B- and T-cells in mouse models *in vitro* and *in vivo* at low concentration/doses, probably by interference with PI3K δ and/or PI3K γ signalling. Thus, alpelisib may affect the function of the immune system.

The results of binding and/or activity studies with other protein kinases or potential cellular targets indicate a low potential for systemic effects due to off-target interactions of alpelisib.

Alpelisib inhibited *in vitro* the human ether-à-go-go-related gene (hERG) channel current with an IC_{50} of 9.4 μM (13-fold clinical $C_{max, free}$). *In vivo* in dogs, alpelisib did not cause QTc prolongation in single oral dose studies with up to 180 mg/kg (maximum exposure ~4-fold clinical C_{max}), and no effects on electrocardiogram parameters were observed in the repeated-dose toxicity studies. Slight increases in blood pressure and concomitant decreases in heart rate as well as minimal QTc shortening occurred in a single-dose study in dogs at an exposure below the clinical C_{max} . Thus, the preclinical data do not indicate a risk for QT prolongation, although cases of QT prolongation were reported in the clinical trials. Hypertension was a common finding in the clinical trials with alpelisib.

No adverse effects on central nervous system or respiratory function were observed in rats treated once with 80 mg/kg, which corresponds to an exposure slightly above the clinical C_{max} .

Pharmacokinetics

The pharmacokinetics (PK) of alpelisib was characterised in the mouse, rat, and dog. In all species, absorption after oral administration was fast (T_{max} 0.5-2 h), similar to that in humans. Plasma elimination was faster ($t_{1/2}$ 1.5-3.6 h) than in humans (8.6 h). In rats, exposure was slightly higher in females than in males; in dogs, there was no gender-related effect on exposure. There was no significant accumulation of alpelisib in plasma after repeated oral administration of alpelisib to rats and dogs.

Plasma protein binding of alpelisib was similar in mice (91%), rats (91%), dogs (89%), and humans (89%). Alpelisib did not preferentially distribute to blood cells *in vitro*.

Studies with oral administration of [^{14}C]-labelled alpelisib to albino and pigmented rats showed rapid and wide tissue distribution. Tissue $t_{1/2}$ values were generally less than 24 h; longer persistence of drug-related radioactivity was seen for example in hair follicles, skin, and oesophagus, correlating with the adverse findings in these tissues (see *Toxicology*). There was specific binding to melanin-containing tissues, but levels declined within one week after treatment. Only a minimal amount of drug-related radioactivity crossed the blood-brain barrier.

Metabolism of alpelisib *in vitro* in hepatocytes was low across species (mice, rats, dogs, and humans). The main metabolite was the amide hydroxylation product M4 (BZG791). M4 was a main circulating metabolite in both rats and dogs, but the plasma exposure was significantly lower than in humans. The metabolite showed no genotoxic potential *in vitro* in bacterial and mammalian test systems; additional studies are not required (ICH S9).

As in humans, most of the drug-related radioactivity was excreted via bile/faeces (84% in rats and 90% in dogs).

Toxicology

Studies to characterise the toxicological profile of alpelisib were conducted in rats, dogs, and rabbits. Based on the PK data and the observed pharmacological effects (see below), the species selection is considered acceptable. Animals were treated once daily via the oral route, consistent with the proposed clinical setting.

Alpelisib induced similar toxicities in rats and dogs in the repeated-dose studies with duration of up to 13 weeks. Due to mortality or other dose-limiting toxicity, doses were decreased for studies with longer duration. In the 13-week studies, doses were 2, 6, and 20 mg/kg/day in rats and 0.2, 1.0, and 5.0 mg/kg/day in dogs. Most relevant in-life findings at tolerated doses were body weight loss, transient increases in insulin and glucose serum levels, and haematology changes related to adverse effects on haematopoietic and lymphoid tissues. In dogs, lesions in oral cavity and gastrointestinal tract, vomiting, and faecal changes (mucoïd, diarrhoea) were observed at higher doses (≥ 15 mg/kg/day). The main target organs of alpelisib in rats and dogs were bone marrow, lymphoid organs/tissues, skin, epithelial/mucosal surfaces in the oral cavity and gastrointestinal system (mainly dogs), pancreas, and male and female reproductive organs. Microscopic changes were reversible or showed a tendency to reverse during treatment-free recovery periods. Most of the alpelisib-related effects are considered to be related to its pharmacological activity on cell proliferation and glucose homeostasis. The exposure (AUC) of animals at the NOAELs in the 13-week studies (rat: 2 mg/kg/day, dog: 1 mg/kg/day) was below the clinical exposure, i.e. there are no safety margins. Severe findings in skin (including ulceration/erosion, degeneration, and inflammation) from Brown Norway rats treated with 50 mg/kg/day alpelisib for 4 weeks were associated with changes indicative of a T-cell mediated hypersensitivity reaction. The findings in the toxicity studies correlate with adverse findings in the clinical trials. Hyperglycaemia and severe cutaneous reactions are important identified risks of alpelisib treatment.

Alpelisib was tested negative for genotoxicity in the bacterial reverse mutation assay and in mammalian test systems *in vitro* and *in vivo*. Carcinogenicity studies were not conducted and are not required (ICH S9).

Based on microscopic changes in male and female reproductive organs in the repeat-dose studies, an impact of alpelisib treatment on fertility cannot be excluded. This is described in the information for healthcare professionals.

Administration of alpelisib to pregnant rats and rabbits led to embryotoxicity and teratogenic effects at clinically relevant exposures. These effects are likely related to the pharmacological activity of alpelisib on angiogenesis and glucose homeostasis. This needs to be considered for possible future indications in women of child-bearing potential; the current indication is only for postmenopausal women.

Juvenile toxicity was not assessed. Alpelisib is intended only for the treatment of adults.

Alpelisib was tested negative for phototoxicity in the *in vitro* 3T3 Neutral Red Uptake assay. The risk of phototoxic effects under treatment is therefore considered to be low.

There are no concerns regarding excipients and impurities. All excipients are known and impurities are adequately controlled.

The description and evaluation of the findings in the nonclinical studies in the RMP are considered sufficient.

Based on the ERA, the risk for the environment posed by the introduction of Piqray to the market is considered to be low.

Nonclinical Conclusions

Overall, the submitted nonclinical documentation is considered sufficient to support the approval of Piqray with the new active substance alpelisib in the proposed indication. The pharmacological properties as well as the PK and toxicity profiles of alpelisib were adequately characterised. All nonclinical data that are relevant for safety are included in the information for healthcare professionals. Most of the findings in the preclinical studies correlate with findings in clinical studies.

5 Clinical and Clinical Pharmacology Aspects

5.1 Clinical Pharmacology

Biopharmaceutical Development

In order to investigate the effect of food and gastric pH on the bioavailability of apelisib, one pivotal biopharmaceutical study in healthy subjects was conducted. A low-fat, low-calorie meal increased the absorption, and thus the bioavailability, of apelisib (C_{max} +145%, AUC_{inf} +77%). Whereas fat intake and calorie content did not have an impact on the increase in exposure (AUC_{inf} +73%), the C_{max} increase was less pronounced (+84%) and t_{max} was delayed following a high-fat, high-calorie meal. Since *in vitro* studies showed that the solubility of apelisib is pH-dependent, i.e. decreasing solubility at higher pH values, the effect of ranitidine on the bioavailability of apelisib was investigated. Co-administration with ranitidine led to reduced apelisib exposure and absorption (C_{max} -51%, AUC_{inf} -30%), whereas its effect was partially compensated when administered with a light meal (C_{max} -36%, AUC_{inf} -21%). These findings are reflected in the recommended administration immediately after a meal.

ADME

After a single dose of the proposed dose of 300 mg apelisib following a light meal in healthy subjects, the peak plasma concentrations of 2680 ng/mL were reached after 2.45 h, which resulted in AUC_{last} values of 17,400 ng*h/mL. After multiple QD dosing of 300 mg apelisib alone and with fulvestrant (as part of the proposed indication), the maximal plasma concentrations of 2,970 ng/mL and 2,330 ng/mL, respectively, were reached after 2 h to 4 h, leading to AUC_{0-24h} values of 33,200 ng*h/mL and 30,500 ng*h/mL. The accumulation ratio ranged from 1.1 to 1.5, suggesting an appropriate dosing interval regarding the half-life. Time to steady-state was estimated at two to three days. Based on the population PK analysis using the Phase III data, the steady-state PK parameters following the proposed 300 mg QD dosing regimen co-administered with fulvestrant were estimated as follows: AUC : 32,680 ng*h/mL; C_{max} : 2,400 ng/mL; and C_{min} : 516 ng/mL.

AUC_{0-t} and C_{max} at steady-state increased proportionally to the dose within the range of 30 mg to 450 mg.

Protein binding of apelisib and its main metabolite BZG791 was 89.2% and 96.4%, respectively, as shown in *in vitro* experiments. Apelisib and its metabolites were mainly distributed to the plasma compartment, as shown by a C_p/C_b of approximately 0.8, and the fraction of the total radioactivity in plasma of 41.1% indicated a rather low binding to red blood cells.

Based on the population PK analysis, the apparent volumes of distribution were estimated at 123 L and 114 L, respectively, using the Phase I and III data.

The primary metabolic pathway of apelisib was amide hydrolysis leading to the formation of BZG791, which is the major metabolite in plasma. BZG791 was shown to be pharmacologically inactive. The parent compound apelisib was the predominant entity in plasma, whereas BZG791 accounted for 26.7% of the measured radioactivity in plasma. To a lesser extent, the metabolism of apelisib was liver-mediated via CYP3A4, whereas glucuronidation via UGT1A9 was negligible. The total recovery was 94.5% of the administered dose with 13.5% (2% parent compound, 7.1% BZG791) and 81% (36% parent compound, 32% BZG791) being excreted via urine and faeces, respectively. Faecal excretion occurs most likely through intestinal secretion and hepatobiliary export.

Based on the population PK analyses, the clearance of apelisib was estimated at 9.5 L/h and 9.2 L/h, respectively, using the Phase I and III data. The terminal half-lives derived from these analyses were 8.4 h and 8.6 h.

Special Populations

Following a single dose of 300 mg apelisib, C_{max} decreased by 17% in subjects with moderate hepatic impairment, whereas it remained unchanged in the severe group. AUC_{last} and AUC_{inf} were reduced by 27% in subjects with moderate hepatic impairment and were 26% and 25% higher, respectively, in subjects with severe hepatic impairment. Of note, the unbound fraction (f_u) of apelisib and BZG791, as well as the metabolic ratio of BZG79, were increased in subjects with severe hepatic impairment. Furthermore, hepatic impairment based on bilirubin and aspartate transaminase baseline

values and National Cancer Institute (NCI) severity grading was not identified as a significant covariate in the context of the population PK analysis using the Phase I data including 27% and 0.8% of cancer subjects with mild and moderate hepatic impairment, respectively.

Mild and moderate renal impairment was not identified as a significant covariate in the context of the population PK analyses using the Phase I data. No subjects with severe renal impairment were analysed.

Based on the population PK analysis, no dose adjustments are required for weight, age, gender, or ethnicity.

Interactions

In vitro studies revealed that alpelisib was a strong substrate for BCRP and a weak substrate for P-gp, whereas BZG791 was subject to BCRP- and MRP2-modulated efflux. Alpelisib was shown to be an inducer of CYP2B6, CYP2C9, and CYP3A and an inhibitor of CYP2C8, CYP2C9, CYP2C19, CYP3A4/5 (strongly time-dependant), and SULT (sulfation), while BZG791 was an inducer of CYP2B6, CYP2C8, and CYP2C9. Whereas the K_i values of alpelisib for the evaluated transporters were of no concern, BZG791 was shown to be a moderate inhibitor of OATP1B1 and a strong inhibitor of OAT3. Once absorbed, the inhibition potential of alpelisib for P-gp is not problematic; however, it may have unfavourable effects in the intestine considering the high luminal alpelisib concentrations. Lastly, a potential interaction with UGT and CYP inducers and inhibitors is of no concern since the metabolism of alpelisib occurs mainly via hydrolysis.

The co-administration of alpelisib and the CYP3A4/P-gp substrate everolimus resulted in increased maximal everolimus concentrations (C_{max} : cycle 1, +12%; cycle 2, +11%) and reduced everolimus exposures (AUC_{0-24} : cycle 1 \pm 0; cycle 2, -11.2%).

In the context of the population PK analysis using the Phase I data, fulvestrant co-administration was identified as a significant covariate, leading to an alpelisib exposure decreased by 25%. Interestingly, the predicted steady-state alpelisib exposures using the Phase III data were comparable to those in the Phase I studies when administered alone.

It was shown that co-administration with ranitidine led to reduced alpelisib exposure and absorption in healthy subjects (C_{max} -51%, AUC_{inf} -30%), whereas its effect was partially compensated when administered with a light meal (C_{max} -36%, AUC_{inf} -21%). In the context of the population PK analysis using the Phase I data, the covariates proton pump inhibitor intake, H2 blocker intake, and antacid intake were not statistically significant.

Pharmacodynamics

Alpelisib is an oral α -specific class I phosphatidylinositol-3-kinase (PI3K) inhibitor. In biochemical assays, alpelisib specifically inhibited wild-type PI3K α and its two most frequent mutants.

5.2 Dose Finding and Dose Recommendation

The applicant mentions that 400 mg alpelisib is the maximum tolerated dose if used in combination with 500 mg fulvestrant, according to the results of the phase 2 study X2101. 300 mg of alpelisib were as effective as 400 mg, whereas the incidence of adverse events was much reduced with 300 mg. Modelled analyses also showed that there is an increased risk of hyperglycaemia and rash between 300 and 400 mg alpelisib.

5.3 Efficacy

Alpelisib is a PI3-kinase inhibitor for which approval is sought for the treatment of hormone receptor-positive HER2-negative breast cancer harbouring a mutation in PIK3CA (catalytic subunit α of PI3K kinase). Alpelisib is to be used in combination with the approved oestrogen receptor antagonist fulvestrant as second-line treatment of women with tumours progressing during, or after, endocrine therapy (aromatase inhibitors in all patients in the pivotal trial C2301/SOLAR-1).

Study C2301

The pivotal study in this application is the phase 3 study C2301. This is a double-blind randomised study comparing 300 mg/day alpelisib and placebo as add-on therapy to fulvestrant in postmenopausal women (only one male patient was included in this study) with progression during or after a previous treatment with an aromatase inhibitor. The patients had hormone receptor-positive, HER2-negative tumours and were divided into two separate cohorts (which were also separately analysed at different time points) based on the presence or absence of PIK3CA mutations at exons 7, 9, and 20. Patients with *symptomatic* visceral metastases and patients with an ECOG Performance Score (PS) of 2 or more were excluded from the study.

The primary endpoint was the progression-free survival (PFS) per local investigator radiology review, supported by a random sample of audited tumour assessments read by a blinded central review committee (BIRC). Overall survival (OS) was the key secondary endpoint. These two endpoints PFS and OS in the cohort of patients with PIK3CA mutations were the main analyses of the study. The comparison between alpelisib and placebo in patients *without* mutation tumours was only a secondary comparison in the study C2301 and is not further discussed in this summary.

Overall 243 progression events were needed in the main cohort with PIK3CA mutations to show a 40% reduction in the progression risk with alpelisib, with a power of 83.8% and an alpha level of 2%.

In total 341 patients with PIK3CA mutations and 231 patients without mutations were enrolled in the two cohorts of the study.

PFS and OS results in the cohort with PIK3CA mutations

In the main cohort with PI3CA mutations the mean age was 63.3 years, two thirds of the patients were white, 73.9% had bone metastases and 56.6% visceral metastases. Only 20 patients had previously received a treatment with CDK 4/6 inhibitors. All but two patients had ER-positive tumours, and 73.9% had PR-positive tumours.

The primary analysis of PFS according to the investigators in the patients with mutations after a total of 232 progression events showed that, with 103 events in the alpelisib group and 129 in the control group, there was a significant difference in favour of the alpelisib patients, with a 35% reduction in the risk of tumour progression (HR = 0.65, 95%CI 0.50-0.85, p= 0.00065, with a difference between the median PFS values of 5.3 months).

Similar results were seen in the *audited* sample of 163 tumour assessments reviewed by the blinded independent review committee (BIRC), thus amounting to approximately 50% of the randomised patients (HR = 0.48 compared to 0.50 according to the local assessment in the same sample of audited patients). The overall concordance rate between local and central review ranged from 75 to 80%. The applicant concluded that there was no need for a full assessment of all study patients by the BIRC.

The subgroup analyses of PFS showed consistent results in all tested subgroups, with the exception of the smaller subgroups of non-white/non-Asian patients and the few patients recruited in Latin America. Asians seem to benefit from alpelisib somewhat less than whites (Hazard Ratio (HR) 0.76 versus HR of 0.56 in the latter group).

The effect of alpelisib depending on the mutation location was similar in exons 9 and 20 (exon 7 not shown).

Only 20 patients in the pivotal alpelisib study C2301 had been previously treated with CDK4/6 inhibitors. The 95%CI for the observed subgroup HR-value of 0.48 is very wide (0.17-1.36).

The overall survival (OS) was the key secondary endpoint of this study C2301. At the time of the main analysis, however, only 40 patients in the alpelisib group and 52 in the placebo group had died (HR 0.73, 95% CI 0.48-1.10). According to the planned statistical analyses, a maximum sample of 178 death events were to be assessed at the final analysis of the pivotal study C2301, provided that the two planned interim analyses failed to show superiority for alpelisib on OS.

5.4 Safety

Even if the daily dose of 300 mg alpelisib proposed by the applicant is somewhat lower than the maximum tolerated dose of 400 mg alpelisib, the reported adverse events under the combination of alpelisib and fulvestrant show a broad spectrum of organ system adverse events. Both mutant and non-mutant cohorts of C2301 were included in the safety evaluation. Adverse events mainly involve the gastrointestinal system, including mucosal inflammation/stomatitis, the skin, with rashes affecting a significant proportion of the body surface, the metabolic system, mainly due to hyperglycaemia, the liver and pancreas, hypersensitivity and an anaphylactic reaction. Alpelisib prolongs the QTc interval, but not to a relevant level according to the mean value analyses, even if relevant QTc prolongations were reported in isolated cases.

Hyperglycaemia is a frequent and serious safety concern with alpelisib. In cases exceeding 27.8 mmol/L glucose (500 mg/dL), the treatment should be stopped according to the proposed information for healthcare professionals. Hyperglycaemia led to the prescription of oral antidiabetic drugs in 57% of the patients in study C2301, this in spite of the exclusion from trial participation of patients with fasting glucose levels above 7.7 mmol/L or with HbA1c levels above 6.4%.

There were a few cases of pneumonitis with alpelisib.

Serious adverse events were reported for 34.9% of the alpelisib patients and 16.7% of the placebo patients. These included cases of acute kidney injury, in isolated cases associated with diarrhoea, pyrexia and dehydration, osteonecrosis of the jaw, associated with previous or concurrent exposure to bisphosphonates, dehydration, erythema multiforme and one case of Stevens-Johnson syndrome, as well as cases of hypersensitivity with alpelisib. Isolated cases of pneumonitis were also reported with alpelisib.

An analysis of the notable ECG values showed more prolongations of the QTc interval by 30-60 msec, more prolongations by >60 msec and extending to 450-480 msec in the alpelisib group.

5.5 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

The benefit of a treatment with Piqray has been established in terms of progression-free survival. There is a non-significant trend towards reduced mortality with Piqray. The final analysis of overall survival is awaited and will be provided by the applicant as a post-approval commitment.

The safety profile for Piqray shows a wide range of adverse events. Relevant warnings and precautions as well as adverse events are described in the attached information for healthcare professionals.

Piqray offers a new alternative for the treatment of postmenopausal women with hormone receptor-positive, human epidermal growth factor receptor 2-negative (HR⁺/Her2⁻) advanced breast cancer

harbouring a PIK3CA mutation in combination with fulvestrant after disease progression, in patients with a previous endocrine treatment including an aromatase inhibitor.

Since there was only one male patient in C2301, the indication is restricted to female patients only until more data from male patients with a PIK3CA mutation become available

5.6 Approved Indication and Dosage

See information for healthcare professionals in the Appendix.

6 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.

The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

7 Appendix

7.1 Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Piqray was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals approved and authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:

The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

▼ This medicinal product is subject to additional monitoring. This allows quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse effects. See “Adverse effects” for information on reporting adverse effects.

PIQRAY

Composition

Active substances

Alpelisib

Excipients

Film-coated tablet core: Microcrystalline cellulose, mannitol, sodium starch glycolate type A corresponding to max. 0.21 mg, 0.63 mg and 0.84 mg sodium per 50 mg, 150 mg and 200 mg tablet, respectively, hypromellose, magnesium stearate.

Tablet coating: Hypromellose, titanium dioxide, macrogol 4000, talc, iron oxide red, iron oxide black.

Pharmaceutical form and quantity of active substance per unit

50 mg, 150 mg and 200 mg film-coated tablets.

- 50 mg: Light pink, round, curved, unscored tablet with bevelled edges, imprinted with “L7” on one side and “NVR” on the other side.
- 150 mg: Pale red, ovaloid, curved, unscored tablets with bevelled edges, imprinted with “UL7” on one side and “NVR” on the other side.
- 200 mg: Light red, ovaloid, curved, unscored tablets with bevelled edges, imprinted with “YL7” on one side and “NVR” on the other side.

Indications/Potential uses

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.

Dosage/Administration

Treatment with Piqray must be initiated by a physician experienced in anticancer therapy.

Patients with diabetes mellitus should consult a diabetologist prior to initiation of therapy with Piqray (see also Table 2 under “Dosage/Administration” and “Warnings and precautions”).

Detection of PIK3CA mutation

The PIK3CA mutation can be detected in tumour or plasma specimens with a test validated for Piqray (see “Properties/Actions”). Due to the lower sensitivity of plasma detection PIK3CA-negative patients must be retested using a tumour specimen.

Usual dosage

The recommended dose of Piqray is 300 mg (2 x 150 mg film-coated tablets) and is taken orally once daily without treatment interruption. Piqray should be taken immediately following food, at approximately the same time each day (see “Pharmacokinetics” and “Interactions”). The maximum recommended daily dose of Piqray is 300 mg.

If fulvestrant is co-administered with Piqray, the recommended dose of fulvestrant is 500 mg administered intramuscularly on days 1, 15 and 29 and once monthly thereafter. Please refer to the full prescribing information for fulvestrant.

Treatment duration

Treatment should continue as long as a clinical benefit is observed or until unacceptable toxicity occurs. Dose modifications may be necessary to improve tolerability.

Dose modification due to adverse effects/interactions

The maximum recommended daily dose of Piqray is 300 mg. Management of severe or intolerable adverse drug reactions may require temporary interruption, dose reduction and/or discontinuation of treatment with Piqray. Recommendations for dose reduction in the event of adverse drug reactions (ADRs) are listed in Table 1. A maximum of 2 dose reductions are recommended, after which the patient should be discontinued from treatment with Piqray. Dose reduction should be based on the worst preceding intolerance.

Table 1: Recommendations on dose reduction of Piqray for adverse drug reactions¹

Piqray dose level	Dose and schedule	Number and strength of tablets
Starting dose	300 mg/day continuously	2 x 150 mg tablets
First dose reduction	250 mg/day continuously	1 x 200 mg tablet and 1 x 50 mg tablet
Second dose reduction	200 mg/day continuously	1 x 200 mg tablet

¹ Only one dose reduction is permitted for pancreatitis.

Table 2, Table 3 and Table 4 contain recommendations on treatment interruption, dose reduction or discontinuation of treatment with Piqray in the management of specific ADRs. A clinical assessment by the treating physician, including confirmation of laboratory values if necessary, should support the Piqray treatment plan of each patient based on the individual benefit/risk assessment.

Hyperglycaemia

Table 2: Dose modification and management for hyperglycaemia¹

Fasting plasma glucose (FPG)/blood glucose level ²	Recommended action
Dose adjustments should be based exclusively on fasting blood glucose levels.	
>Upper limit of normal (>ULN)	<p>Consultation with a specialist (diabetologist/endocrinologist) experienced in the treatment of hyperglycaemia should always be considered prior to initiation of therapy for pre-diabetic patients or patients with FPG >250 mg/dl (13.9 mmol/l).</p> <p>Consultation with a diabetologist/specialist experienced in the treatment of hyperglycaemia should take place for patients with diabetes. Patients should be informed on how hyperglycaemia can be reduced by lifestyle changes (e.g. change in diet and physical activity).</p>
>ULN-160 mg/dl or >ULN-8.9 mmol/l	<p>No Piqray dose adjustment required.</p> <p>Initiate or intensify oral antidiabetic treatment³.</p>
>160-250 mg/dl or >8.9-13.9 mmol/l	<p>No Piqray dose adjustment required.</p> <p>Initiate or further intensify oral antidiabetic treatment³.</p> <p>If FPG does not decrease to ≤160 mg/dl or 8.9 mmol/l within 21 days despite appropriate oral antidiabetic treatment, reduce the Piqray dose by 1 dose level and follow the specific recommendations for the FPG value.</p>
>250-500 mg/dl or >13.9-27.8 mmol/l	<p>Interrupt treatment with Piqray.</p> <p>Initiate or further intensify oral antidiabetic treatment³ and consider administering additional antidiabetics (such as insulin³) for 1-2 days until hyperglycaemia resolves.</p> <p>Administer intravenous hydration and consider appropriate treatment (e.g. intervention for electrolyte/ketoacidosis/hyperosmolar disturbances).</p> <p>If FPG decreases to ≤160 mg/dl or 8.9 mmol/l within 3 to 5 days with appropriate antidiabetic treatment, resume Piqray at the next lower dose level.</p> <p>If FPG does not decrease to ≤160 mg/dl or 8.9 mmol/l within 3 to 5 days despite appropriate antidiabetic treatment, consultation with a specialist in the treatment of hyperglycaemia is recommended.</p> <p>If FPG does not decrease to ≤160 mg/dl or 8.9 mmol/l within 21 days despite appropriate antidiabetic treatment³, permanently discontinue Piqray treatment.</p>
>500 mg/dl or >27.8 mmol/l	<p>Interrupt treatment with Piqray.</p> <p>Initiate appropriate antidiabetic treatment³ (administer intravenous hydration or increase the dose of antidiabetics and consider appropriate treatment [e.g. intervention for electrolyte/ketoacidosis/hyperosmolar disturbances]). Re-check values within 24 hours and as clinically indicated.</p> <p>If FPG decreases to (≤500 mg/dl) or (≤27.8 mmol/l), follow the specific recommendations for the FPG value (<500 mg/dl).</p> <p>If FPG is confirmed at >500 mg/dl or (≤27.8 mmol/l), permanently discontinue Piqray treatment.</p>
<p>Determine the FPG and/or HbA1c value before initiating treatment with Piqray. Glucose levels should be corrected in patients with abnormal glucose levels which are in the pre-diabetic (FPG >100-126 mg/dl [5.6-6.9 mmol/l] and/or HbA1c 5.7-6.4%) or diabetic (FPG ≥126 mg/dl [≥7.0 mmol/l] and/or HbA1c ≥6.5%) range before initiating Piqray treatment and closely monitored to enable early detection and treatment of hyperglycaemia.</p>	

Fasting plasma glucose (FPG)/blood glucose level ²	Recommended action
Dose adjustments should be based exclusively on fasting blood glucose levels.	
<p>After the start of treatment with Piqray blood glucose levels and/or FPG must be monitored at least once per week in the first 2 weeks and then every 4 weeks and as clinically indicated. The HbA1c value should be monitored every 3 months as clinically indicated.</p>	
<p>If the patient experiences hyperglycaemia after initiating treatment with Piqray, monitor blood glucose values and/or FPG as clinically indicated and at least twice weekly until blood glucose levels and/or FPG decreases to ≤ 160 mg/dl. During treatment with antidiabetics blood glucose levels and/or FPG must continue to be determined at least once a week in the first 8 weeks and then once every 2 weeks and as clinically indicated.</p>	
<p>¹ For FPG/blood glucose levels: Hyperglycaemia is graded according to CTCAE Version 4.03. CTCAE = Common Terminology Criteria for Adverse Events.</p>	
<p>² Treatment with suitable antidiabetics such as metformin and insulin sensitisers (e.g. thiazolidinediones or dipeptidyl peptidase-4 inhibitors) should be initiated. The relevant prescribing information should be consulted for dosing and dose titration recommendations, including local diabetic treatment guidelines. The following treatment recommendation was given for metformin in the phase III clinical study: Treatment with metformin should be initiated at 500 mg once daily. Based on tolerability the metformin dose may be increased to 500 mg twice daily followed by 500 mg with breakfast and 1000 mg with the evening meal, followed by a further increase to 1000 mg twice daily if needed (see “Warnings and precautions”).</p>	
<p>³ As recommended in the phase III clinical study, insulin may be used for 1-2 days until hyperglycaemia resolves. However, this is not necessary in the majority of cases of alpelisib-induced hyperglycaemia as the half-life of alpelisib is short and blood glucose levels should normalise rapidly following interruption of treatment with Piqray.</p>	

Rash

Prophylactic administration of oral antihistamines may be considered at the time of initiation of treatment with Piqray. Based on the severity of rash, interruption of treatment with Piqray, dose reduction or treatment discontinuation may be required as described in Table 3 (see “Adverse effects”).

Table 3: Dose modification and management for rash¹

Grade	Recommended action
All grades	Consultation with a dermatologist should always be considered.
Grade 1 ($<10\%$ body surface area (BSA) affected by active skin toxicity)	<p>No Piqray dose adjustment required.</p> <p>Initiate topical corticosteroid treatment.</p> <p>Consider additional oral antihistamine treatment to manage symptoms.</p>
Grade 2 ($10\text{-}30\%$ BSA affected by active skin toxicity)	<p>No Piqray dose adjustment required.</p> <p>Initiate or intensify topical corticosteroid and oral antihistamine treatment.</p> <p>Consider low-dose oral corticosteroid treatment.</p>
Grade 3 (e.g. severe rash not responsive to medical management). ($>30\%$ BSA affected by active skin toxicity)	<p>Interrupt treatment with Piqray until rash resolves to grade ≤ 1.</p> <p>Initiate or intensify topical/oral corticosteroid and antihistamine treatment.</p> <p>Once the rash has resolved to grade ≤ 1, resume treatment with Piqray at the same dose for the first occurrence of rash or at the next lower dose level in case of recurrence.</p>

Grade	Recommended action
Grade 4 (e.g. severe bullous, blistering or exfoliating skin conditions). (any % BSA associated with extensive superinfection, with intravenous antibiotics indicated; life-threatening consequences)	Permanently discontinue Piqray.
¹ Grading according to CTCAE Version 5.0	

Other toxicities

Table 4: Dose modification and management for other toxicities (excluding hyperglycaemia and rash)¹

Grade	Recommended action
Grade 1 or 2	No Piqray dose adjustment required. Initiation of appropriate medical therapy and monitoring as clinically indicated ^{2,3} .
Grade 3	Interrupt treatment with Piqray until improvement to grade ≤ 1 , then resume treatment with Piqray at the next lower dose level ² .
Grade 4	Permanently discontinue Piqray ³ .
¹ Grading according to CTCAE Version 5.0. ² For grade 2 and 3 pancreatitis interrupt treatment with Piqray until pancreatitis has resolved to grade ≤ 1 , then resume treatment at the next lower dose level. Only one dose reduction is permitted. If toxicity recurs, permanently discontinue Piqray treatment. ³ For grade 2 diarrhoea interrupt treatment with Piqray until diarrhoea has resolved to grade ≤ 1 . Then resume treatment at the same dose level. For grade 4 diarrhoea interrupt treatment with Piqray until diarrhoea has resolved to grade ≤ 1 . Then resume treatment at the next lower dose level.	

Refer to the prescribing information for fulvestrant for dose modification recommendations in the event of toxicity and other relevant safety information.

Patients with hepatic impairment

Based on a hepatic impairment study in non-cancer subjects with hepatic impairment no dose adjustment is necessary in patients with mild, moderate or severe hepatic impairment (Child-Pugh class A, B or C, respectively) (see “Pharmacokinetics”).

Refer to the prescribing information for fulvestrant for dose modification recommendations for hepatic impairment.

Patients with renal impairment

Based on a population pharmacokinetic analysis no dose adjustment is necessary in patients with mild or moderate renal impairment (see “Pharmacokinetics”). Caution is required in patients with severe renal impairment as there is no experience with the use of Piqray in this population.

Elderly patients

No dose adjustment is required in patients aged 65 years or above (see “Clinical efficacy”).

Children and adolescents

The safety and efficacy of Piqray in children and adolescents have not been established.

Late administration

If a dose of Piqray is forgotten, it can be taken immediately following food and within 9 hours after the time it is usually taken. If more than 9 hours have passed, the dose should be skipped for that day. On the next day Piqray should be taken at the usual time. If the patient vomits after taking the Piqray dose, the patient should not take an additional dose on that day and should take the next dose on the next day at the usual time.

Method of administration

Piqray tablets are swallowed whole (tablets must not be chewed, crushed or split prior to ingestion). Tablets that are broken, cracked or otherwise damaged must not be taken.

Contraindications

Piqray is contraindicated in patients with hypersensitivity to the active substance or any of the excipients.

Warnings and precautions

QTc prolongation

Piqray treatment is associated with QTc prolongation (see “Interactions” and “Properties/Actions”).

Hypersensitivity (including anaphylactic reactions)

Serious hypersensitivity reactions (including anaphylactic reaction and anaphylactic shock), manifested by symptoms such as dyspnoea, sensation of heat, rash, fever or tachycardia were reported in patients treated with Piqray in clinical studies (see “Adverse effects”). Piqray should be permanently discontinued and should not be re-introduced in patients with serious hypersensitivity reactions. Appropriate treatment should be promptly initiated.

Severe cutaneous reactions

Piqray treatment must not be started in patients with a history of severe cutaneous reactions. Cases of severe cutaneous reactions have been reported in patients treated with alpelisib. In the phase III clinical study Stevens-Johnson syndrome (SJS) and erythema multiforme (EM) occurred in 1 (0.4%) and 3

(1.1%) patients, respectively. Piqray treatment must not be initiated in patients with SJS, EM, DRESS syndrome (drug rash with eosinophilia and systemic symptoms) or toxic epidermal necrolysis.

Cases of DRESS syndrome (drug rash with eosinophilia and systemic symptoms) have been reported in the post-marketing setting (see “Adverse effects”).

Patients should be advised of the signs and symptoms of severe cutaneous reactions (e.g. a prodrome of fever, flu-like symptoms, mucosal lesions or progressive skin rash). If signs or symptoms of severe cutaneous reactions are present, treatment with Piqray must be interrupted until the aetiology of the reaction is determined. Furthermore, suitable medical treatment/monitoring must be initiated as clinically indicated. A consultation with a dermatologist is recommended. If a severe cutaneous reaction is confirmed, Piqray must be permanently discontinued. Piqray must not be re-introduced in patients who have experienced previous severe cutaneous reactions. If a severe cutaneous reaction is not confirmed, interruption of treatment with Piqray, dose reduction or treatment discontinuation may be required as described in Table 3 Dose modification and management for rash (see “Dosage/Administration”).

Hyperglycaemia

Prior to initiation of therapy patients who are pre-diabetic or have increased blood glucose levels should consult a diabetologist.

Patients with known diabetes mellitus must be optimally controlled prior to initiation of treatment.

Patients with glucose values above 7.7 mmol/l were excluded from pivotal study C2301. Hyperglycaemia was reported in 64.8% of patients treated with Piqray in this phase III clinical study. Grade 2 (FPG >160-250 mg/dl), 3 (FPG >250-500 mg/dl) or 4 (FPG >500 mg/dl) hyperglycaemia was reported in 15.8%, 33.1% and 3.9% of patients, respectively, in a phase III clinical study. Patients should be advised of the signs and symptoms of hyperglycaemia (e.g. excessive thirst, urinating more often than usual or greater amount of urine than usual, increased appetite with simultaneous weight loss).

In the phase III clinical study, based on baseline FPG and HbA1c values 56% of patients were considered pre-diabetic (FPG >100-126 mg/dl (5.6 to 6.9 mmol/l) and/or HbA1c 5.7-6.4%) and 4.2% of patients were considered diabetic (FPG ≥126 mg/dl (≥7.0 mmol/l) and/or HbA1c ≥6.5%). There were no patients with type 1 diabetes mellitus based on reported medical histories. Among those patients with a pre-diabetic baseline value 74.2% experienced hyperglycaemia (any grade) during treatment with Piqray. Among the patients with grade ≥2 (FPG >160-250 mg/dl) hyperglycaemia the median time to first occurrence of grade ≥2 (FPG >160-250 mg/dl) hyperglycaemia was 15 days (range: 5 days to 517 days) (based on laboratory findings). The median duration of grade 2 (FPG >160-250 mg/dl) or higher hyperglycaemia (based on laboratory findings) was 10 days (95% CI: 8 to 13 days).

In the phase III clinical study, among the 284 patients on alpelisib, 163 (87.2%) of the 187 patients with hyperglycaemia were treated with antidiabetics and 142 of these patients (75.9%) received metformin as monotherapy or in combination with other antidiabetics such as thiazolidinediones or DPP-4 inhibitors. The maximum dose of metformin recommended in the phase III clinical study was 2000 mg per day.

In patients with hyperglycaemia of grade 2 (FPG >160-250 mg/dl) or higher the median time from the first occurrence to improvement of the first event by at least one toxicity level (i.e. 1 grade) was 8 days (95% CI: 8 to 10 days). In all patients with elevated FPG values who continued fulvestrant treatment after discontinuing treatment with Piqray, FPG values returned to baseline (normal).

In the phase III clinical study patients with a history of diabetes mellitus intensified antidiabetic treatment during treatment with Piqray; therefore, these patients require monitoring and possibly intensified antidiabetic treatment. Patients with insufficient control of blood glucose levels may be at a higher risk of developing severe hyperglycaemia and associated complications.

The safety of Piqray in patients with type 1 and uncontrolled type 2 diabetes has not been established as these patients were excluded from the phase III clinical study. Patients with a history of type 2 diabetes were included in the study. Patients with a history of diabetes mellitus may require intensified treatment with antidiabetics and should be monitored closely.

Based on the severity of the hyperglycaemia interruption of treatment with Piqray, dose reduction or discontinuation of treatment may be required as described in Table 2 Dose modification and management for hyperglycaemia (see “Dosage/Administration”).

Pneumonitis

Pneumonitis, including serious cases of pneumonitis/acute interstitial lung disease, have been reported in Piqray-treated patients in clinical studies. Patients should be advised to report promptly any new or worsening respiratory symptoms. In patients with new or worsening respiratory symptoms or suspected pneumonitis Piqray treatment should be interrupted immediately and the patient evaluated for pneumonitis. A diagnosis of non-infectious pneumonitis should be considered in patients with non-specific clinical respiratory signs and symptoms such as hypoxia, cough, dyspnoea or interstitial infiltrates in radiological examinations when infectious or neoplastic diseases and other causes have been excluded by appropriate investigations. Piqray should be permanently discontinued in all patients with confirmed pneumonitis.

This medicinal product contains less than 1 mmol (23 mg) of sodium per film-coated tablet, making it practically “sodium-free”.

Interactions

The elimination of alpelisib occurs primarily through non-hepatic hydrolysis (45%) mediated by multiple enzymes (esterases, amidases, choline esterase) and excretion by hepatobiliary export and intestinal

secretion (40%). The overall contribution of CYP3A4 and glucuronidation to the overall metabolism and clearance of alpelisib was shown to be low in humans ($\leq 15\%$).

Hormonal contraceptives

It is currently unknown whether alpelisib may reduce the effectiveness of systemically acting hormonal contraceptives.

Effect of Piqray on other medicinal products

CYP3A4 substrates

No dose adjustment is required when co-administering Piqray with CYP3A4 substrates (e.g. everolimus, midazolam).

Close observation is required when Piqray is administered in combination with CYP3A4 substrates that also possess an additional time-dependent inhibition and induction potential on CYP3A4 that affects their own metabolism (e.g. rifampicin, ribociclib, encorafenib).

CYP2C9 substrates

Co-administration of Piqray with CYP2C9 substrates (e.g. warfarin) may decrease the plasma concentration of these medicinal products. Monitor such patients closely when Piqray is administered in combination with CYP2C9 substrates; a decrease in plasma concentration may reduce the clinical efficacy of these medicinal products.

CYP2B6 substrates

Co-administration of Piqray with CYP2B6 substrates (e.g. bupropion) may reduce the plasma concentration of these medicinal products. When using Piqray in combination with CYP2B6 substrates, where a decrease in plasma concentration may reduce the clinical efficacy of these medicinal products, precise dosing is required.

P-gp and QAT3 substrates

In vitro tests have shown that alpelisib (and/or its metabolite, BZG791) may inhibit the activity of the active substance transporters OAT3 and P-gp. Due to the high alpelisib concentrations in the intestinal lumen an effect on intestinal P-gp cannot be completely ruled out.

Effect of other medicinal products on Piqray

CYP3A4 inducers

Co-administration of Piqray with a potent CYP3A4 inducer may decrease the concentration of alpelisib, which may reduce the clinical efficacy of alpelisib. Avoid co-administration of Piqray with potent CYP3A4 inducers.

BCRP inhibitors

Alpelisib is a sensitive substrate for the breast cancer resistance protein (BCRP) *in vitro*, which is predominantly expressed in the liver, intestine and at the blood-brain barrier. Absorption of alpelisib is not affected by BCRP inhibition due to saturation of the transporter in the intestine. Due to the involvement of BCRP in the hepatobiliary export and intestinal secretion of alpelisib, co-administration of Piqray with BCRP inhibitors may increase the concentration of alpelisib, which may increase the risk of toxicity. Avoid the use of BCRP inhibitors (e.g. eltrombopag, lapatinib, pantoprazole) in patients treated with Piqray. If no other medicinal products can be used, patients using Piqray in combination with BCRP must be closely observed for increased adverse drug reactions.

QTc prolongation

Piqray treatment is associated with QTc prolongation. An analysis of clinical ECG data shows that there was no significant effect on dQTc prolongation (i.e. >20 ms) with or without fulvestrant. Additional ECG monitoring is indicated if Piqray is used concomitantly with other medicinal products known to prolong the QTc interval and/or if hypokalaemia is present.

Pregnancy/Breast-feeding

Pregnancy

Piqray is not indicated in women of childbearing potential or pregnant women. The active substance alpelisib may harm the fetus due to the pharmacological mechanism of action. Teratogenic effects were observed in preclinical studies (see "Preclinical data"). The combination partner fulvestrant is contraindicated during pregnancy and breast-feeding.

Male patients with sexual partners who are pregnant or who could become pregnant should use condoms during sexual intercourse during treatment with Piqray and for at least 1 week thereafter.

Breast-feeding

Piqray is not indicated in breast-feeding women. It is not known whether alpelisib or its metabolites pass into human milk.

Fertility

There are no data on the effect of alpelisib on fertility. Based on repeat-dose toxicity studies in animals Piqray may impair fertility in males of reproductive potential and women of childbearing potential (see “Preclinical data”).

Effects on ability to drive and use machines

No relevant studies have been conducted. Caution is advised when driving and using machines as taking the product may cause nausea, vomiting and headaches.

Adverse effects

Summary of the safety profile

The safety evaluation of Piqray is based on data from a total of 572 patients (571 post-menopausal women and 1 man) from the phase III clinical study who were randomised in a 1:1 ratio to receive treatment with Piqray plus fulvestrant or treatment with placebo plus fulvestrant; 284 patients received Piqray at the recommended starting dose of 300 mg in combination with fulvestrant using the proposed treatment regimen.

The median duration of exposure to Piqray plus fulvestrant was 8.2 months, with 59.2% of patients exposed for >6 months.

Piqray dose reduction due to adverse events (AEs), regardless of causality, occurred in 57.7% of patients receiving Piqray plus fulvestrant and in 4.5% of patients receiving placebo plus fulvestrant. Permanent discontinuation of Piqray and/or fulvestrant due to adverse events was reported in 25% of patients compared to 4.5% with placebo and/or fulvestrant. The most common AEs leading to discontinuation of treatment with Piqray and/or fulvestrant were hyperglycaemia (6.3%), rash (3.2%), diarrhoea (2.8%) and fatigue (2.1%).

7 deaths (2.5%), regardless of causality, were reported during treatment with Piqray plus fulvestrant vs 12 deaths (4.2%) during treatment with placebo plus fulvestrant. In patients treated with Piqray plus fulvestrant disease progression (5 patients, 1.8%) was the most frequent cause of death; the other causes of death were cardiorespiratory arrest and second primary malignancy. Neither of these causes of death were considered related to treatment with Piqray.

The most common adverse drug reactions (ADRs) in Piqray plus fulvestrant-treated patients (reported at a frequency of $\geq 20\%$ and more frequently with Piqray plus fulvestrant than with placebo plus fulvestrant) were hyperglycaemia, diarrhoea, rash, nausea, fatigue and asthenia, decreased appetite, stomatitis, vomiting and weight loss.

The most common grade 3/4 ADRs (reported at a frequency of $\geq 2\%$ in the Piqray plus fulvestrant arm and more frequently than with placebo plus fulvestrant) were hyperglycaemia, rash, and maculopapular

rash, fatigue, diarrhoea, increased lipase, hypertension, hypokalaemia, anaemia, decreased weight, increased gamma-glutamyltransferase, lymphopenia, nausea, stomatitis, increased alanine aminotransferase and mucosal inflammation.

Summary of adverse drug reactions from clinical studies

ADRs from the phase III clinical study are listed by MedDRA system organ class. Within each system organ class the adverse drug reactions are listed by frequency, with the most frequent adverse drug frequent reactions first. Within each frequency grouping ADRs are listed in order of decreasing seriousness. In addition, the corresponding frequency category for each ADR is based on the following convention (CIOMS III): very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$).

Blood and lymphatic system disorders

Very common: Anaemia (10%; grade 3-4: 4%)

Common: Lymphopenia, thrombocytopenia

Eye disorders

Common: Blurred vision, dry eye

Gastrointestinal disorders

Very common: Diarrhoea (58%; grade 3-4: 7%), nausea (45%; grade 3-4: 3%), stomatitis (also includes aphthous ulcer and mouth ulceration) (30%; grade 3-4: 3%), vomiting (27%; grade 3-4: 1%), abdominal pain (17%; grade 3-4: 1%), dyspepsia (11%; grade 3-4: 0%)

Common: Toothache, gingivitis, cheilitis, gingival pain, increased lipase*

Uncommon: Pancreatitis

Hepatobiliary disorders

Common: Increased gamma-glutamyltransferase*, increased alanine aminotransferase*

General disorders and administration site conditions

Very common: Fatigue (42%; grade 3-4: 5%), mucosal inflammation (19%; grade 3-4: 2%), peripheral oedema (15%; grade 3-4: 0%), fever (14%; grade 3-4: 1%), mucosal dryness (12%; grade 3-4: $< 1\%$)

Common: Oedema (also includes facial oedema)

Immune system disorders

Common: Hypersensitivity (also includes allergic dermatitis, anaphylactic reactions and anaphylactic shock)

Infections and infestations

Very common: Urinary tract infection (also includes a single case of urosepsis) (10%; grade 3-4: 1%)

Metabolism and nutrition disorders

Very common: Hyperglycaemia (65%; grade 3-4: 37%), decreased appetite (36%; grade 3-4: 1%), decreased weight (27%; grade 3-4: 4%)

Common: Hypokalaemia, hypocalcaemia, dehydration, increased glycosylated haemoglobin

Uncommon: Ketoacidosis (also includes diabetic ketoacidosis)

Musculoskeletal and connective tissue disorders

Common: Muscle spasms, myalgia, osteonecrosis of the jaw

Nervous system disorders

Very common: Headache (18%; grade 3-4: 1%), dysgeusia (also includes ageusia, hypogeusia) (18%; grade 3-4: <1%)

Psychiatric disorders

Common: Insomnia

Renal and urinary disorders

Very common: Increased blood creatinine (10%; grade 3-4: 2%)

Common: Acute kidney injury

Respiratory, thoracic and mediastinal disorders

Common: Pneumonitis (also includes interstitial lung disease)

Skin and subcutaneous tissue disorders

Very common: Rash (52%; grade 3-4: 20%), alopecia (20%; grade 3-4: 0%), pruritus (18%; grade 3-4: 1%), dry skin (18%; grade 3-4: <1%)

Common: Erythema (includes generalised erythema), dermatitis (also includes acneiform dermatitis), palmar-plantar erythrodysesthesia syndrome, erythema multiforme

Uncommon: Stevens-Johnson syndrome

Vascular disorders

Common: Hypertension, lymphoedema

Post-marketing adverse effects

Skin and subcutaneous tissue disorders

Unknown: Drug reaction with eosinophilia and systemic symptoms (DRESS)

Description of selected adverse effects

Hyperglycaemia

In the phase III clinical study hyperglycaemia (FPG >160 mg/dl) was reported in 184 (64.8%) patients. Hyperglycaemia resolved to grade ≤1 (FPG <160 mg/dl) in 166 (88.8%) of the 187 patients. Interruptions of treatment and dose adjustments due to hyperglycaemia were reported in 26.8% and 28.9% of patients, respectively, in the Piqray plus fulvestrant arm. Hyperglycaemia leading to discontinuation of Piqray and/or fulvestrant was reported in 19 (6.7%) patients.

Rash

In the phase III clinical study rash (also includes cases of maculopapular rash, macular rash, generalised rash, papular rash, pruritic rash, dermatitis and acneiform dermatitis) were reported in 153 (53.9%) patients. Rash may be accompanied by pruritus and dry skin in some cases. Rash was predominantly mild or moderate (grade 1 or 2) and responded to therapy. Grade 2 and 3 rashes (maximum) were reported in 13.7% and 20.1% of patients, respectively. No grade 4 rashes were reported. Among the patients with grade 2 or 3 rash the median time to first onset of grade 2 or 3 rash was 12 days (range: 2 to 220 days). Interruptions of treatment and dose adjustments due to rash were reported in 21.8% and 9.2% of patients, respectively, in the Piqray plus fulvestrant arm.

Topical corticosteroid treatment should be initiated at the first signs of rash and oral corticosteroid treatment should be considered for moderate to severe rashes. Additionally, antihistamines are recommended to manage symptoms of rash. In the phase III study use of at least one topical corticosteroid was reported in 73.9% (113/153) of patients who developed a rash and use of at least one oral antihistamine in 67.3% (103/153). Systemic corticosteroids were administered in 23% (66/284) of patients to treat rashes. Of the patients who received systemic corticosteroids 55% (36/66) received oral corticosteroids to treat rash. At least one event of rash resolved in the majority of the patients (92%, 141/153). Treatment with Piqray and/or fulvestrant was discontinued due to rash in 12 patients (4.2%).

A subgroup of 86 patients received antirash treatment, including antihistamines, prior to the onset of rash. In these patients rash was reported less frequently than in the overall study population for all

grades of rash (26.7% vs 53.9%), grade 3 rash (11.6% vs 20.1%) and rash leading to permanent discontinuation of Piqray (3.5% vs 4.2%). Accordingly, antihistamines may be initiated prophylactically at the time of initiation of treatment with Piqray. Based on the severity of the rash interruption of treatment with Piqray, dose reduction or discontinuation of treatment may be required as described in Table 3 Dose modification and management for rash (see “Dosage/Administration”).

Gastrointestinal toxicity (nausea, diarrhoea, vomiting)

In the phase III study diarrhoea, nausea and vomiting (see “Adverse effects”) were reported in 57.7%, 44.7% and 27.1% of patients, respectively, and led to discontinuation of Piqray and/or fulvestrant in 8 (2.8%), 5 (1.8%) and 3 (1.1%) patients, respectively.

Grade 2 and 3 diarrhoea (maximum) were reported in 18.3% and 6.7% of patients, respectively. There were no cases of grade 4 diarrhoea reported in the phase III clinical study. Among the patients with grade ≥ 2 diarrhoea the median time to first onset of grade ≥ 2 diarrhoea was 46 days (range: 1 to 442 days).

Severe diarrhoea and clinical consequences such as dehydration and acute kidney injury have been reported during treatment with Piqray and resolved with appropriate treatment measures (see “Adverse effects”). Patients should be managed according to local standard of care, including electrolyte monitoring, administration of antiemetics and antidiarrhoeal medicinal products and/or fluid replacement and electrolyte supplements, as clinically indicated. In the phase III clinical study antiemetics (e.g. ondansetron) and antidiarrhoeal medicinal products (e.g. loperamide) were used in 27/149 (18.1%) and 104/164 (63.4%) of patients to manage symptoms.

Osteonecrosis of the jaw (ONJ)

In the phase III clinical study ONJ was reported in 4.2% patients (12/284) in the Piqray plus fulvestrant arm compared to 1.4% patients (4/287) in the placebo plus fulvestrant arm. All patients who experienced ONJ had also received prior or concomitant bisphosphonates (e.g. zoledronic acid). Therefore, in patients receiving Piqray and bisphosphonates an increased risk of development of ONJ cannot be excluded.

Laboratory abnormalities

The proportion of patients treated with alpelisib plus fulvestrant in the phase III clinical study who experienced blood laboratory abnormalities (for which the frequency with Piqray plus fulvestrant was $>5\%$ higher than the frequency with placebo plus fulvestrant) was as follows: 79% for increased glucose, 67% for increased creatinine, 52% for increased gamma-glutamyltransferase, 52% for decreased lymphocyte count, 44% for increased alanine aminotransferase, 42% for decreased haemoglobin, 42% for increased lipase, 27% for decreased corrected calcium, 26% for decreased

glucose, 21% for increased activated partial thromboplastin time, 14% for decreased potassium, 14% for decreased platelet count, 14% for decreased albumin and 11% for decreased magnesium.

Reporting suspected adverse effects after authorisation of the medicinal product is very important. It allows continued monitoring of the risk-benefit ratio of the medicinal product. Healthcare professionals are asked to report any suspected new or serious adverse effects via the online portal EIViS (Electronic Vigilance System). You can find further information at www.swissmedic.ch.

Overdose

There is only limited experience of overdose with Piqray in clinical studies. In the clinical studies Piqray was administered once daily at doses of up to 450 mg.

Signs and symptoms

In cases where accidental overdose of Piqray was reported in the clinical studies the adverse events associated with the overdose were consistent with the known safety profile of Piqray and comprised hyperglycaemia, nausea, asthenia and rash.

Treatment

General symptomatic and supportive measures should be initiated in all cases of overdose where necessary. There is no known antidote for Piqray.

Properties/Actions

ATC code: L01XX65

Mechanism of action

Alpelisib is a class I subunit-specific inhibitor of the α isoform of phosphatidylinositol 3-kinase (PI3K α).

Class I PI3K lipid kinases play a central role in the PI3K/AKT/mTOR signalling pathway.

Gain-of-function mutations in the gene encoding the catalytic α -subunit of PI3K (PIK3CA) lead to activation of PI3K α ; this is manifested by increased lipid kinase activity, growth factor-independent activation of AKT signalling, cellular transformation and the generation of tumours in a variety of preclinical models.

In vitro, alpelisib treatment inhibited the phosphorylation of PI3K downstream targets in the AKT cascade as well as its various downstream effectors in breast cancer cells and showed selectivity towards cell lines harbouring a PIK3CA mutation.

In vivo, alpelisib showed good tolerability as well as dose- and time-dependent inhibition of the PI3K/AKT pathway and dose-dependent tumour growth inhibition in relevant tumour xenograft models, including models of breast cancer.

PI3K inhibition by alpelisib treatment has been shown to induce an increase in oestrogen receptor (ER) transcription in breast cancer cells and therefore sensitises these cells to ER inhibition by fulvestrant treatment. Combination of alpelisib and fulvestrant demonstrated greater antitumour activity than either treatment method alone in xenograft models derived from ER+, PIK3CA-mutated breast cancer cell lines (MCF-7 and KPL1).

Pharmacodynamics

Cardiac electrophysiology

Piqray treatment is associated with QTc prolongation. Serial ECGs were performed following a single dose and at steady state to evaluate the effect of alpelisib on the QTcF interval in patients with advanced cancer. An analysis of clinical ECG data shows that there was no significant effect on mean QTcF prolongation (i.e. >20 ms) at the recommended 300 mg dose with or without fulvestrant.

In the phase III study 2 patients treated with Piqray plus fulvestrant exhibited new QTcF values of >500 ms as single, isolated events related to a potential or documented cardiac disorder; they were not associated with arrhythmias or cardiological sequelae. In this study increases in mean QTcF values remained within 10 ms and the associated confidence interval remained under 20 ms. However, patients with cardiac disorders and ECG anomalies were excluded from participation in the study.

Clinical efficacy

Piqray was evaluated in a pivotal phase III, randomised, double-blind, placebo-controlled study in combination with fulvestrant in men and postmenopausal women with HR+, HER2- locally advanced or metastatic breast cancer whose disease had progressed or recurred on or after treatment with an aromatase inhibitor (SOLAR-1).

PIK3CA mutation status was determined with a study-specific assay using tumour tissue. Patients were randomised to receive either 300 mg Piqray plus fulvestrant or placebo plus fulvestrant in a 1:1 ratio. Randomisation was stratified by presence of lung and/or liver metastases and previous treatment with (a) CDK4/6 inhibitor(s).

Study results

In the phase III study 169 patients were randomised to treatment with Piqray in combination with fulvestrant and 172 patients were randomised to treatment with placebo in combination with fulvestrant. Within this cohort 170 (49.9%) patients had liver/lung metastases. Only 20 (5.9%) patients had received prior CDK4/6 inhibitor treatment.

97.7% of patients had received prior hormonal therapy and 47.8% of patients already had a metastatic disease and 51.9% had last received adjuvant therapy. Overall, 85.6% of the patients were considered

to be endocrine resistant; primary endocrine resistance was observed in 13.2% of patients and secondary endocrine resistance in 72.4% of patients.

Demographic and baseline disease characteristics, ECOG performance status, tumour burden and prior antineoplastic therapy were well balanced between the treatment arms.

During the randomised treatment phase 300 mg Piqray or placebo was administered orally once daily on a continuous basis. 500 mg fulvestrant was administered intramuscularly in cycle 1 at days 1 and 15 and then at day 1 of a 28-day cycle during the treatment phase (administration ± 3 days).

Patients were not allowed to cross over from placebo to Piqray treatment during the study or after disease progression.

The primary endpoint of the study was progression-free survival (PFS) using Response Evaluation Criteria in Solid Tumors (RECIST version 1.1) based on the investigator assessment of patients with PIK3CA mutation advanced breast cancer. The key secondary endpoint was overall survival (OS).

Study participants had an average age of 63 years (range 25 to 92). 44.9% of patients were 65 years of age or over and <85 years of age. Study participants were white (66.3%), Asian (21.7%), black or African American (1.2%).

The median duration of follow-up was 20 months.

The efficacy results demonstrated a statistically significant improvement in PFS in patients receiving Piqray plus fulvestrant compared to patients receiving placebo plus fulvestrant (hazard ratio [HR] = 0.65 with 95% CI: 0.50, 0.85, one-sided stratified log-rank test $p=0.00065$), with an estimated 35% risk reduction of disease progression or death. Efficacy results from the study are summarised in Table 5.

Primary PFS results were supported by consistent results from a blinded independent review committee (BIRC) assessment, which included a randomly selected subset of 50% of randomised patients (HR: 0.48 with 95% CI: 0.32, 0.71). See Table 5 for further information.

PFS subgroup analyses by randomisation stratification factors demonstrated a homogeneous and generally consistent treatment effect per investigator assessment irrespective of CDK4/6 prior treatment, which only 20 patients received, and presence or absence of lung/liver metastases.

PFS subgroup analyses also demonstrated an overall homogeneous treatment effect in favour of the alpelisib arm across major demographic and other prognostic subgroups.

At the time of the final PFS analysis, overall survival data were not mature, with 92 of 178 deaths for the final analysis reported, corresponding to a 51.7% information fraction.

Treatment with the combination of Piqray plus fulvestrant was associated with improvements in ORR compared to placebo plus fulvestrant. The ORR was 26.6% (95% CI: 20.1, 34.0) in the Piqray plus fulvestrant arm and 12.8% (95% CI: 8.2, 18.7) in the placebo plus fulvestrant arm. See Table 6 for further information.

For patients with measurable disease at baseline the ORR was 35.7% (95% CI: 27.4, 44.7) in the Piqray plus fulvestrant arm and 16.2% (95% CI: 10.4, 23.5) in the placebo plus fulvestrant arm.

Table 5: C2301 – Summary of efficacy results based on RECIST criteria (cohort with PIK3CA mutation)

	Piqray + fulvestrant (n=169)	Placebo + fulvestrant (n=172)	Hazard ratio (HR)	p-value ^a
Median progression-free survival (PFS^a) (months, 95% CI)				
<i>Investigator radiological assessment</i>				
Cohort with PIK3CA mutation (N=341)	11.0 (7.5-14.5)	5.7 (3.7-7.4)	0.65 (0.50-0.85)	0.00065
<i>Blinded independent review committee (BIRC) assessment*</i>				
Cohort with PIK3CA mutation (N=173)	11.1 months (7.3-16.8)	3.7 (2.1-5.6)	0.48 (0.32-0.71)	N/A

CI = confidence interval; N = number of patients; N/A = not applicable

^a p-value is obtained from the one-sided stratified log-rank test.

*Based on 50% audit-based approach

Table 6: C2301 – Efficacy results (ORR) based on investigator assessment (cohort with PIK3CA mutation)

Analysis	Alpelisib plus fulvestrant (%, 95% CI)	Placebo plus fulvestrant (%, 95% CI)	p-value ^c
Full analysis set	N=169	N=172	
Objective response rate ^a (ORR)	26.6 (20.1, 34.0)	12.8 (8.2, 18.7)	0.0006
Patients with measurable disease	N=126	N=136	
Objective response rate ^a (ORR)	35.7 (27.4, 44.7)	16.2 (10.4, 23.5)	0.0002

^a ORR = proportion of patients with confirmed complete response (CR) or partial response (PR)

Pharmacokinetics

The pharmacokinetics of alpelisib were investigated in patients administered oral doses of 30 mg to 450 mg daily. Healthy subjects received single oral doses ranging from 300 mg to 400 mg. The PK were largely comparable in both oncology patients and healthy subjects.

Absorption

Following oral administration of alpelisib median time to reach peak plasma concentration (T_{max}) was between 2.0 and 4.0 hours independent of dose, time and regimen. Steady-state plasma levels of alpelisib after daily administration can be expected to be reached on the third day following onset of therapy in most patients.

Food effect

Alpelisib absorption is affected by food. In healthy volunteers after a single 300 mg oral dose of alpelisib, compared to the fasted state, a high-fat, high-calorie (HFHC) meal (985 calories with 58.1 g of fat) increased AUC_{inf} by 73% and C_{max} by 84%. A low-fat, low-calorie (LFLC) meal (334 calories with 8.7 g of fat) increased AUC_{inf} by 77% and C_{max} by 145%. No significant difference was found in AUC_{inf} between LFLC and HFHC, with a geometric mean ratio of 0.978 (CI: 0.876, 1.09), showing that neither fat content nor overall calorific intake has a considerable impact on absorption.

Reduction of pH value

The co-administration of the H2 receptor antagonist ranitidine in combination with a single 300 mg oral dose of alpelisib slightly reduced the bioavailability of alpelisib and decreased overall exposure of alpelisib. After ingestion of a LFLC meal AUC_{inf} was decreased on average by 21% and C_{max} by 36% with ranitidine. If food was not ingested, the effect was more pronounced with a 30% decrease in AUC_{inf} and a 51% decrease in C_{max} with ranitidine compared to the fasted state without co-administration of ranitidine. Piqray can be co-administered with acid-reducing agents if Piqray is taken immediately after food. Population pharmacokinetic analysis showed no significant effect of co-administration of acid-reducing agents such as proton pump inhibitors, H2 receptor antagonists and antacids on the PK of Piqray.

Distribution

Alpelisib moderately binds to protein with a free fraction of 10.8% regardless of concentration. Alpelisib was equally distributed between red blood cells and plasma with a mean *in vivo* blood-to-plasma ratio of 1.03. The volume of distribution of alpelisib at steady state (V_{ss}/F) is estimated at 114 l (interindividual coefficient of variability 46%).

Metabolism

In *in vitro* studies formation of the hydrolysis metabolite BZG791 by chemical and enzymatic amide hydrolysis proved to be the major metabolic pathway, with minor involvement of CYP3A4. Alpelisib hydrolysis occurs systemically by both chemical decomposition and enzymatic hydrolysis via ubiquitously expressed, high-capacity enzymes (esterases, amidases, choline esterase) not limited to the liver. CYP3A4-mediated metabolites (~12%) and glucuronides amounted to ~15% of the dose.

Metabolic interactions

Based on the results of metabolic *in vitro* induction and inhibition studies alpelisib may induce the metabolic clearance of co-administered medicinal products metabolised by CYP2B6, CYP2C9 and CYP3A4 and may inhibit the metabolic clearance of co-administered medicinal products metabolised by CYP3A4 (time-dependent inhibition) if sufficiently high concentrations are achieved *in vivo*.

In a drug interaction study co-administration of alpelisib with everolimus (a CYP3A4 and P-gp substrate) confirmed that there are no clinically significant pharmacokinetic interactions (increase in AUC by 11.2%) between alpelisib and CYP3A4 substrates.

Transporter-based interaction

Data from *in vitro* studies showed that alpelisib inhibits P-gp. Alpelisib showed only weak *in vitro* inhibition towards the ubiquitously expressed efflux transporters (BCRP, MRP2, BSEP), solute transport proteins (carrier or membrane proteins) at the liver inlet (OATP1B1, OATP1B3, OCT1) and SLC transporters in the kidney (OAT1, OAT3, OCT2, MATE1, MATE2K). As unbound systemic steady-state concentrations (or concentrations at the liver inlet) at both the therapeutic dose and maximum tolerated dose are significantly lower than the experimentally determined unbound inhibition constants or IC₅₀, the inhibition is not expected to have clinical significance. Due to the high alpelisib concentrations in the intestinal lumen an effect on intestinal P-gp cannot be completely ruled out.

Fulvestrant

Data from a clinical study in breast cancer patients showed no effect of fulvestrant on alpelisib exposure (and vice versa) following co-administration of the medicinal products.

Elimination

Alpelisib exhibits low clearance, at 9.2 l/h (CV% 21%), based on a population pharmacokinetic analysis after food intake. The study population-derived half-life, independent of dose and time, was 8 to 9 hours at steady state with 300 mg once daily.

In a human mass-balance study 81.0% of the administered dose was excreted in the faeces (36% unchanged alpelisib, 32% BZG791). Excretion in the urine is minor (13.5%), primarily as BZG791 (~7%) and unchanged alpelisib (2%). Following a single oral dose of [¹⁴C] alpelisib 94.5% of the total administered radioactive dose was detected within 8 days.

Linearity/non-linearity

The pharmacokinetics proved to be linear with respect to dose and time after administration with food between 30 mg and 450 mg. After multiple doses alpelisib exposure (AUC) at steady state is only slightly higher than that of a single dose, with an average accumulation of 1.3 to 1.5 with daily dosing.

Pharmacokinetics in special populations

The population pharmacokinetic analysis (pooled phase I and phase II) showed that there are no clinically relevant effects of age (21-87 years), body weight (37-181 kg), ethnicity

(Japanese/Caucasian) or gender (90% female) on the systemic exposure of alpelisib that would require a Piqray dose adjustment.

Hepatic impairment

No dose adjustment is necessary in patients with mild, moderate or severe hepatic impairment (Child-Pugh A, B and C).

Based on a pharmacokinetic study in patients with hepatic impairment, moderate or severe hepatic impairment had a negligible effect on the exposure of alpelisib (see “Dosage/Administration”). The mean exposure to alpelisib was increased 1.26-fold in patients with severe hepatic impairment (GMR: 1.00 for C_{max} ; 1.26 for AUC_{last}/AUC_{inf}).

Renal impairment

No dose adjustment is necessary in patients with mild or moderate renal impairment. Patients with severe renal impairment have not been studied and caution is required in these patients. Based on a population pharmacokinetic analysis of pooled phase I and phase III data which included 270 patients with normal renal function (eGFR ≥ 90 ml/min/1.73 m²)/(CLcr ≥ 90 ml/min), 180 patients with mild renal impairment (eGFR 60 to < 90 ml/min/1.73 m²)/(CLcr 60 to < 90 ml/min), 65 patients with moderate renal impairment (eGFR 30 to < 60 ml/min/1.73 m²) and 1 patient with severe renal impairment (eGFR < 30 ml/min/1.73 m²), mild to moderate renal impairment had no effect on the exposure of alpelisib (see “Dosage/Administration”).

Elderly patients

Of 284 patients who received Piqray in the phase III study (in the Piqray plus fulvestrant arm), 117 patients were ≥ 65 years of age and 34 patients were ≥ 75 years of age. No overall differences in the safety or effectiveness of Piqray were detected between these patients and younger patients (see “Dosage/Administration”).

Children and adolescents

The pharmacokinetics of Piqray in children and adolescents have not been studied.

Safety pharmacology and single/repeat-dose toxicity

The majority of the observed effects of alpelisib were related to pharmacological activity, such as the influence on glucose homeostasis resulting in hyperglycaemia and the risk of increased blood pressure.

The main target organs for toxicity in rats and dogs were the bone marrow and lymphoid tissue, skin, mucosal tissue, pancreas and some reproductive organs in both genders. Adverse effects occurred in both species at clinically relevant plasma concentrations. The changes were fully or partially reversible following discontinuation of treatment.

In rats alpelisib showed no effect on the function of the nervous system or lungs at clinically relevant plasma concentrations.

Cardiovascular safety pharmacology: In an *in vitro* hERG test an IC₅₀ of 9.4 µM (4.2 µg/ml) was found. No relevant electrophysiological effect was seen in several studies in dogs up to single doses of 180 mg/kg. An *in vivo* telemetry study in dogs showed an elevated blood pressure at an exposure lower than the exposure in humans at the highest recommended dose of 300 mg/day.

Genotoxicity and carcinogenicity

No carcinogenicity studies have been conducted.

Alpelisib was not mutagenic in a bacterial reverse mutation test nor aneugenic or clastogenic in human cell micronucleus and chromosome aberration tests *in vitro*. Also, an *in vivo* micronucleus test in peripheral blood reticulocytes after 4 weeks of repeated dosing at up to 20 mg/kg/day in rats was negative with regard to genotoxicity. The plasma exposure of the animals was approximately 1.7-fold the exposure in humans at the highest recommended dose of 300 mg/day based on AUC.

Reproductive toxicity

In embryo-fetal development studies in rats and rabbits pregnant animals received oral doses of alpelisib up to 30 mg/kg/day during the period of organogenesis.

In rats oral administration of alpelisib at 30 mg/kg/day was associated with maternal toxicity and loss of all embryos. The plasma exposure of the animals at this dose was approximately 3.2-fold (based on AUC) the exposure in humans at the highest recommended dose of 300 mg. The administration of 10 mg/kg/day (approximately 0.9 times clinical exposure) led to reduced fetal body weight and to skeletal malformations, decreased ossification and increased incidences of enlarged brain ventricle in fetuses.

In rabbits at dosages of ≥25 mg/kg/day maternal body weight loss was observed. At dosages of ≥15 mg/kg/day embryo-fetal deaths and malformations, primarily in the tail and head region, occurred more frequently. The dose of 15 mg/kg/day in rabbits is equivalent to approximately 5.5 times (based on AUC) the exposure at the highest recommended human dose.

In rats and rabbits maternal exposure (AUC) at the NOAEL for fetal abnormalities (3 mg/kg/day) was below the clinical exposure at the highest recommended dose of 300 mg.

Fertility: A fertility study in rats has not been performed. However, in repeated-dose toxicity studies of up to 13 weeks' duration adverse effects were observed in reproductive organs of male and female animals such as vaginal atrophy and oestrus cycle variations in rats (at plasma exposure levels (AUC) below the clinical exposure at the highest recommended dose of 300 mg/day) or prostate atrophy in dogs (at plasma exposure levels of about 2.8 times the exposure in humans at the highest recommended dose of 300 mg/day based on AUC).

Phototoxicity

An *in vitro* phototoxicity test on the mouse Balb/c 3T3 fibroblast cell line did not identify a relevant phototoxicity potential for alpelisib.

Juvenile animal studies

Juvenile animal studies are not available.

Other information

Incompatibilities

Not applicable.

Shelf life

Do not use after the expiry date (= EXP) printed on the pack.

Special precautions for storage

Do not store above 30°C.

Store the container in the outer carton to protect the contents from moisture.

Keep out of the reach of children.

Swissmedic number

67359

Pack sizes

Piqray 150: Packs of 28 or 56 film-coated tablets

Piqray 200: Packs of 14 or 28 film-coated tablets

Piqray 200 + 50: Packs of 14 + 14 or 28 + 28 film-coated tablets

Marketing authorisation holder

Novartis Pharma Schweiz AG, Risch, Switzerland

Information last revised

March 2020