SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Piqray®150 mg film coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Piqray 150 mg film coated tablets

Each film coated tablet contains 150 mg of alpelisib.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Light red, ovaloid, curved film-coated tablet with bevelled edges, imprinted with “YL7” on one side and “NVR” on the other side. Approximate size: 16.2 mm (length); 6.5 mm (width).

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Treatment with Piqray should be initiated by a physician experienced in the use of anticancer therapies.

Patients with HR-positive, HER2-negative advanced breast cancer should be selected based on the presence of a PIK3CA mutation in tumour or plasma specimens, using a validated test. If a mutation is not detected in a plasma specimen, tumour tissue should be tested if available.

Posology

The recommended dose is 300 mg alpelisib (2x 150 mg film-coated tablets) taken once daily on a continuous basis. The maximum recommended daily dose of Piqray is 300 mg.

If a dose is missed, it can be taken immediately following food and within 9 hours after the time it is usually administered. After more than 9 hours, the dose should be skipped for that day. On the next day, the dose should be taken at the usual time. If the patient vomits after taking the dose, the patient should not take an additional dose on that day and should resume the usual dosing schedule the next day at the usual time.

Piqray should be co-administered with fulvestrant. 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 of fulvestrant.

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

Dose modifications
Management of severe or intolerable adverse drug reactions (ADRs) may require temporary dose interruption, reduction, and/or discontinuation of Piqray. If dose reduction is required, the dose reduction guidelines for ADRs are listed in Table 1. A maximum of 2 dose reductions are recommended, after which the patient should be permanently discontinued from treatment with Piqray. Dose reduction should be based on the worst preceding toxicity.

Table 1 Recommended dose reduction guidelines for ADRs [1]

Piqray dose level	**Dose and schedule**	**Number and strength of tablets**
Starting dose	300 mg/day continuously	2x 150 mg tablets
First dose reduction	250 mg/day continuously	1x 200 mg tablet and 1x 50 mg tablet
Second dose reduction	200 mg/day continuously	1x 200 mg tablet
[1] Only one dose reduction is permitted for pancreatitis.		

Tables 2-5 summarise the recommendations for dose interruption, reduction or discontinuation of Piqray in the management of specific ADRs. The clinical judgement of the treating physician, including confirmation of laboratory values if deemed necessary, should guide the management plan of each patient based on the individual benefit/risk assessment.

Hyperglycaemia
Consultation with a healthcare professional experienced in the treatment of hyperglycaemia should always be considered and is recommended for patients who are pre-diabetic or those with fasting glucose (FG) >250 mg/dl or 13.9 mmol/l, body mass index (BMI) ≥30 or age ≥75 years.

Consultation with a diabetologist or a healthcare professional experienced in the treatment of hyperglycaemia should always take place for patients with diabetes.

Table 2 Dose modification and management for hyperglycaemia

Fasting glucose (FG) values[1]	**Recommendation**
Dose modification and management should only be based on fasting glucose (plasma/blood) values.	
>ULN-160 mg/dl or >ULN-8.9 mmol/l	No Piqray dose adjustment required. Initiate or intensify oral antidiabetic treatment[2].
>160-250 mg/dl or >8.9-13.9 mmol/l	No Piqray dose adjustment required. Initiate or intensify oral antidiabetic treatment[2]. If FG does not decrease to ≤160 mg/dl or 8.9 mmol/l within 21 days with appropriate oral antidiabetic treatment[2,3], reduce Piqray dose by 1 dose level and follow FG-value-specific recommendations.
>250-500 mg/dl or >13.9-27.8 mmol/l	Interrupt Piqray. Initiate or intensify oral antidiabetic treatment[2] and consider additional antidiabetic medicinal products such as insulin[3] for 1-2 days until hyperglycaemia resolves, as clinically indicated. Administer intravenous hydration and consider appropriate treatment (e.g. intervention for electrolyte / ketoacidosis / hyperosmolar disturbances). If FG decreases to ≤160 mg/dl or 8.9 mmol/l within 3 to 5 days under appropriate antidiabetic treatment, resume Piqray at next lower dose level. If FG does not decrease to ≤160 mg/dl or 8.9 mmol/l within 3 to 5 days under appropriate antidiabetic treatment, consultation with a healthcare professional with expertise in the treatment of hyperglycaemia is recommended. If FG does not decrease to ≤160 mg/dl or 8.9 mmol/l within 21 days following appropriate antidiabetic treatment[2,3], permanently discontinue Piqray treatment.

>500 mg/dl or >27.8 mmol/l	Interrupt Piqray. Initiate or intensify appropriate antidiabetic treatment[2,3] (administer intravenous hydration and consider appropriate treatment [e.g. intervention for electrolyte / ketoacidosis / hyperosmolar disturbances]), re-check within 24 hours and as clinically indicated. If FG decreases to ≤500 mg/dl or ≤27.8 mmol/l, then follow FG-value-specific recommendations for <500 mg/dl. If FG is confirmed at >500 mg/dl or >27.8 mmol/l after 24 hours, permanently discontinue Piqray treatment.

[1] Fasting glucose levels reflect hyperglycaemia grading according to CTCAE Version 4.03 CTCAE = Common Terminology Criteria for Adverse Events.

[2] Applicable antidiabetic medicinal products, such as metformin, SGLT2 inhibitors or insulin sensitisers (such as thiazolidinediones or dipeptidyl peptidase-4 inhibitors), should be initiated and the respective prescribing information should be reviewed for dosing and dose titration recommendations, including local diabetic treatment guidelines. Metformin was recommended in the phase III clinical study with the following guidance: 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 further increase to 1000 mg twice daily if needed (see section 4.4).

[3] As recommended in the phase III clinical study, insulin may be used for 1-2 days until hyperglycaemia resolves. However, this may not be necessary in the majority of cases of alpelisib-induced hyperglycaemia, given the short half-life of alpelisib and the expectation that glucose levels will normalise following interruption of Piqray.

Baseline diabetic and pre-diabetic status, baseline BMI ≥30 and baseline age ≥75 years have been found to be risk factors for hyperglycaemia in patients treated with alpelisib. These risk factors were present in 74.9% of patients with any grade of hyperglycaemia and in 84.7% of patients with grade 3 or 4 hyperglycaemia (see section 4.4).

Rash

Oral antihistamine administration may be considered prophylactically, at the time of initiation of treatment with Piqray. Additionally, antihistamines are recommended to manage symptoms of rash.

Topical corticosteroid treatment should be initiated at the first signs of rash and systemic corticosteroids should be considered for moderate to severe rashes. Based on the severity of rash, Piqray may require dose interruption, reduction or discontinuation as described in Table 3 (see section 4.8).

Table 3 Dose modification and management for rash

Grade[1]	**Recommendation**
All grades	Consultation with a dermatologist should always be considered.
Grade 1 (<10% body surface area [BSA] with active skin toxicity)	No Piqray dose adjustment required. Initiate topical corticosteroid treatment. Consider adding oral antihistamine treatment to manage symptoms. If active rash is not improved within 28 days of appropriate treatment, add a low dose systemic corticosteroid.
Grade 2 (10-30% BSA with active skin toxicity)	No Piqray dose adjustment required. Initiate or intensify topical corticosteroid and oral antihistamine treatment. Consider low-dose systemic corticosteroid treatment. If rash improves to grade ≤1 within 10 days, systemic corticosteroid may be discontinued.
Grade 3 (e.g. severe rash not responsive to medical management) (>30% BSA with active skin toxicity)	Interrupt Piqray until rash improves to grade ≤1. Initiate or intensify topical/systemic corticosteroid and antihistamine treatment. Once rash improves to grade ≤1, resume Piqray at next lower dose level.
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	

Diarrhoea or colitis

Table 4 Dose modification and management for diarrhoea or colitis

Grade[1]	**Recommendation**
Grade 1	No Piqray dose adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated.
Grade 2[2]	Interrupt Piqray dose. Initiate or intensify appropriate medical therapy and monitor as clinically indicated. If diarrhoea or colitis improves to grade ≤1, then resume Piqray at same dose level. For recurrent diarrhoea or colitis grade ≥2, interrupt Piqray dose until improvement to grade ≤1, then resume Piqray at the next lower dose level.
Grade 3[2,3]	Interrupt Piqray dose. Initiate or intensify appropriate medical therapy and monitor as clinically indicated. If diarrhoea or colitis improves to grade ≤1, then resume Piqray at the next lower dose level.
Grade 4[2,3]	Permanently discontinue Piqray.

[1] Grading according to CTCAE Version 5.0.
[2] For grade ≥2 consider additional treatment, such as steroids.
[3] Patients should additionally 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.

Other toxicities

Table 5 Dose modification and management for other toxicities (excluding hyperglycaemia, rash and diarrhoea or colitis)

Grade[1]	**Recommendation**
Grade 1 or 2	No Piqray dose adjustment required. Initiate appropriate medical therapy and monitor as clinically indicated[2,3].
Grade 3	Interrupt Piqray dose until improvement to grade ≤1, then resume 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 Piqray dose until improvement to grade ≤1 and resume at next lower dose level. Only one dose reduction is permitted. If toxicity recurs, permanently discontinue Piqray treatment.
[3] For grade 2 total bilirubin elevation, interrupt Piqray dose until recovery to grade ≤1 and resume at the same dose if resolved in ≤14 days or resume at the next lower dose level if resolved in >14 days.

Special populations
Elderly
No dose regimen adjustment is required in patients aged 65 years or above (see section 5.2). There are limited data in patients aged ≥75 years, and especially for those ≥85 years.

Renal impairment
Based on population pharmacokinetic analysis, no dose adjustment is necessary in patients with mild or moderate renal impairment (see section 5.2). Caution should be used in patients with severe renal impairment as there is no experience with Piqray in this population.

Hepatic impairment
Based on a hepatic impairment study in non-cancer subjects with impaired hepatic function, no dose adjustment is necessary in patients with mild, moderate or severe hepatic impairment (Child-Pugh class A, B or C, respectively) (see section 5.2).

Paediatric population
The safety and efficacy of Piqray in children aged 0-18 years have not been established. No data are available.

Method of administration

Piqray is for oral use. The tablets should be swallowed whole. They should not be chewed, crushed or split prior to swallowing. Tablets that are broken, cracked or otherwise not intact should not be ingested.

The tablets should be taken immediately after food, at approximately the same time each day (see section 5.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Fulvestrant

Due to limited data in patients with prior fulvestrant use (n=39, study CBYL719X2101), efficacy is not considered established in this population (see section 5.1).

Hypersensitivity (including anaphylactic reaction)

Serious hypersensitivity reactions (including anaphylactic reaction, anaphylactic shock and angioedema), manifested by symptoms including, but not limited to, dyspnoea, flushing, rash, fever or tachycardia, were reported in patients treated with Piqray (see section 4.8). 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

Severe cutaneous reactions have been reported with alpelisib. In the phase III clinical study, Stevens-Johnson syndrome (SJS) and erythema multiforme (EM) were reported in 1 (0.4%)

and 3 (1.1%) patients, respectively. Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported in the post-marketing setting (see section 4.8).

Treatment should not be initiated in patients with a history of severe cutaneous reactions.

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, Piqray should be interrupted until the aetiology of the reaction has been determined. A consultation with a dermatologist is recommended.

If a severe cutaneous reaction is confirmed, Piqray should be permanently discontinued. It should not be re-introduced in patients who have experienced previous severe cutaneous reactions. If a severe cutaneous reaction is not confirmed, Piqray may require treatment interruption, dose reduction or treatment discontinuation as described in Table 3 (see section 4.2).

Hyperglycaemia

Severe hyperglycaemia, in some cases associated with hyperglycaemic hyperosmolar nonketotic syndrome (HHNKS) or ketoacidosis, has been observed in patients treated with Piqray. Some cases of ketoacidosis with fatal outcome have been reported in the post-marketing setting.

In the phase III clinical study, hyperglycaemia occurred more frequently in patients who were diabetic (0 out of 12 patients [0%] with grade 1-2, and 10 out of 12 patients [83.3%] with grade 3-4), pre-diabetic (43 out of 159 patients [27.0%] with grade 1-2, and 77 out of 159 patients [48.4%] with grade 3-4), had BMI $\geq$30 at screening (14 out of 74 patients [18.9%] with grade 1-2, and 38 out of 74 patients [51.4%] with grade 3-4) or $\geq$75 years of age (6 out of 34 patients [17.6%] with grade 1-2, and 19 out of 34 patients [55.9%] with grade 3-4).

As hyperglycaemia may occur with a rapid onset after starting treatment, it is recommended to self-monitor frequently in the first 4 weeks and especially within the first 2 weeks of treatment, as clinically indicated. A specific schedule for fasting glucose monitoring is recommended in Table 6.

In the phase III clinical study, patients with a history of diabetes mellitus intensified use of antidiabetic medicinal products while on treatment with Piqray.

All patients should be instructed on lifestyle changes that may reduce hyperglycaemia (e.g. dietary restrictions and physical activity).

Table 6 Schedule of fasting glucose monitoring

<table>
<tr><th></th><th>Recommended schedule for the monitoring of fasting glucose and HbA1c levels in all patients treated with Piqray</th><th>Recommended schedule of monitoring of fasting glucose and HbA1c levels in patients with diabetes, pre-diabetes, BMI ≥30 or age ≥75 years treated with Piqray</th></tr>
<tr><td>At screening, before initiating treatment with Piqray</td><td colspan="2">Test for fasting plasma glucose (FPG), HbA1c, and optimise the patient’s level of blood glucose (see Table 2).</td></tr>
<tr><td rowspan="3">After initiating treatment with Piqray</td><td colspan="2">Monitor fasting glucose at weeks 1, 2, 4, 6 and 8 after treatment start and monthly thereafter.</td></tr>
<tr><td>Monitor/self-monitor fasting glucose regularly, more frequently in the first 4 weeks and especially within the first 2 weeks of treatment, according to the instructions of a healthcare professional*.</td><td>Monitor/self-monitor fasting glucose daily for the first 2 weeks of treatment. Then continue to monitor fasting glucose as frequently as needed to manage hyperglycaemia according to the instructions of a healthcare professional*.</td></tr>
<tr><td colspan="2">HbA1c should be monitored after 4 weeks of treatment and every 3 months thereafter.</td></tr>
<tr><td rowspan="2">If hyperglycaemia develops after initiating treatment with Piqray</td><td colspan="2">Monitor fasting glucose regularly, as per local standard of care and at least until fasting glucose decreases to normal levels.</td></tr>
<tr><td colspan="2">During treatment with antidiabetic medication, continue monitoring fasting glucose at least once a week for 8 weeks, followed by once every 2 weeks, and monitor fasting glucose according to the instructions of a healthcare professional with expertise in the treatment of hyperglycaemia.</td></tr>
<tr><td colspan="3">* All glucose monitoring should be performed at the physician’s discretion as clinically indicated.</td></tr>
</table>

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 weight loss).

In the 191 patients with hyperglycaemia, 86.9% (166/191) were managed with antidiabetic medication, and 75.9% (145/191) reported use of metformin as single agent or in combination with other antidiabetic medication (e.g. insulin, dipeptidyl peptidase-4 (DPP-4) inhibitors, SGLT2 inhibitors and sulfonylureas).

Oral antidiabetic medication was used in 154 patients. Out of these 154 patients, 17 (11.0%) discontinued study treatment due to hyperglycaemia. Concomitant insulin medication was used in 56 patients; of these 13 (23.2%) discontinued study treatment due to hyperglycaemia.

Out of 164 patients with grade ≥2 hyperglycaemia, 157 had at least 1 grade improvement, median time to improvement from the first event was 8 days (95% CI: 8 to 10 days).

Of the patients with elevated FPG who continued fulvestrant treatment after discontinuing Piqray (n=61), 93.4% (n=57) had FPG levels that returned to baseline.

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 medical history of Type 2 diabetes were included. Patients with a history of diabetes mellitus may require intensified diabetic treatment and should be closely monitored.

Based on the severity of the hyperglycaemia, Piqray may require dose interruption, reduction or discontinuation as described in Table 2 (see section 4.2).

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 who have new or worsening respiratory symptoms or are suspected to have developed pneumonitis, Piqray treatment should be interrupted immediately and the patient should be evaluated for pneumonitis. A diagnosis of non-infectious pneumonitis should be considered in patients presenting with non-specific respiratory signs and symptoms such as hypoxia, cough, dyspnoea, or interstitial infiltrates on radiological examination and in whom infectious, neoplastic and other causes have been excluded by means of appropriate investigations. Piqray should be permanently discontinued in all patients with confirmed pneumonitis.

Diarrhoea or colitis

Patients should be monitored for diarrhoea and other symptoms of colitis, such as abdominal pain and mucus or blood in stools.

Severe diarrhoea and clinical consequences, such as dehydration and acute kidney injury, have been reported during treatment with Piqray and resolved with appropriate intervention. 59.9% of patients (n=170) experienced diarrhoea during treatment with Piqray. Grade 3 diarrhoea occurred in 7.4% (n=21) of patients with no reported cases of grade 4. Among patients with grade 2 or 3 diarrhoea (n=79), the median time to onset was 54 days (range: 1 to 1 731 days).

Dose reductions of Piqray were required in 6.3% of patients and 2.8% of patients discontinued Piqray due to diarrhoea. In the 170 patients who experienced diarrhoea, antidiarrhoeal medications (e.g. loperamide) were required to manage symptoms in 65.3% (111/170).

Based on the severity of the diarrhoea or colitis, Piqray may require dose interruption, reduction or discontinuation as described in Table 4 (see section 4.2).

Patients should be advised to start antidiarrhoeal treatment, increase oral fluids and notify their physician if diarrhoea or other symptoms of colitis occur while taking Piqray. In case of colitis, additional treatment, such as steroids, may be considered as clinically indicated.

Osteonecrosis of the jaw

Caution should be exercised when Piqray and bisphosphonates or RANK-ligand inhibitors (e.g. denosumab) are used either simultaneously or sequentially. Piqray treatment should not be initiated in patients with ongoing osteonecrosis of the jaw from previous or concurrent treatment with bisphosphonates/denosumab. Patients should be advised to promptly report any new or worsening oral symptoms (such as dental mobility, pain or swelling, non-healing of mouth sores, or discharge) during treatment with Piqray.

In patients who develop osteonecrosis of the jaw, standard medical management should be initiated.

Symptomatic visceral disease

The efficacy and safety of this medicinal product have not been studied in patients with symptomatic visceral disease.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Medicinal products that may increase alpelisib plasma concentrations

Breast cancer resistance protein (BCRP) inhibitors
Alpelisib is a substrate for BCRP *in vitro*. BCRP is involved in the hepatobiliary export and intestinal secretion of alpelisib, therefore inhibition of BCRP in the liver and in the intestine during elimination may lead to an increase in systemic exposure of alpelisib. Therefore, caution and monitoring for toxicity are advised during concomitant treatment with inhibitors of BCRP (e.g. eltrombopag, lapatinib, pantoprazole).

Medicinal products that may decrease alpelisib plasma concentrations

Acid-reducing agents
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. In the presence of a low-fat low-calorie (LFLC) meal, AUC_{inf} was decreased on average by 21% and C_{max} by 36% with ranitidine. In the absence of food, 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. Population pharmacokinetic analysis showed no significant effect of co-administration of acid-reducing agents, including proton pump inhibitors, H2 receptor antagonists and antacids, on the pharmacokinetics of alpelisib. Therefore, alpelisib can be co-administered with acid-reducing agents, provided alpelisib is taken immediately after food (see section 4.2).

CYP3A4 inducers
Once-daily administration of 600 mg rifampin (a strong CYP3A4 inducer) for 7 days followed by co-administration with a single 300 mg oral dose of alpelisib on day 8, decreased alpelisib C_{max} by 38% and AUC by 57% in healthy adults (N=25). Co-administration of rifampin 600 mg once daily for 15 days with alpelisib 300 mg once daily starting from day 8 to day 15 decreased the steady-state alpelisib C_{max} by 59% and AUC by 74%.

Co-administration with a strong CYP3A4 inducer decreases alpelisib AUC, which may reduce alpelisib efficacy. Co-administration of alpelisib with strong CYP3A4 inducers (e.g. apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort) should be avoided and selection of an alternative concomitant medicinal product, with no or minimal potential to induce CYP3A4, should be considered.

Medicinal products whose plasma concentrations may be altered by alpelisib

CYP3A4, CYP2C8, CYP2C9, CYP2C19 and CYP2B6 substrates
No dose adjustment is required when co-administering alpelisib with CYP3A4 substrates (e.g. everolimus, midazolam), CYP2C8 substrates (e.g. repaglinide), CYP2C9 substrates (e.g. warfarin), CYP2C19 substrates (e.g. omeprazole). For CYP2B6 substrate, no relevant changes in the exposure were observed when co-administered with alpelisib however the results should be considered with caution due to limited data (see section 5.2).

In a drug-drug interaction study, co-administration of alpelisib with everolimus, a sensitive CYP3A4 substrate, confirmed that there are no clinically significant pharmacokinetic interactions (decrease in AUC by 11.2%) between alpelisib and CYP3A4 substrates. No change in everolimus exposure was observed at alpelisib doses ranging from 250 to 300 mg.

In healthy subjects, co-administration of a CYP2C9 substrate (S-warfarin) with alpelisib increased S-warfarin exposure on average by 34% and 19% for AUCinf and Cmax respectively, compared to administration with S-warfarin alone, which indicates that alpelisib is a mild inhibitor of CYP2C9.

Substances that are substrates of transporters
In vitro evaluations indicated that alpelisib (and/or its metabolite BZG791) has a potential to inhibit the activities of OAT3 drug transporters and intestinal BCRP and P-gp. Alpelisib should be used with caution in combination with sensitive substrates of these transporters which exhibit a narrow therapeutic index because alpelisib may increase the systemic exposure of these substrates.

Hormonal contraceptives

No clinical studies were conducted assessing the drug-drug interaction potential between alpelisib and hormonal contraceptives.

4.6 Fertility, pregnancy and lactation

Piqray is indicated in men and postmenopausal women. It is not to be used in women who are, or may be, pregnant or breast-feeding (see section 4.1).

Women of childbearing potential/Contraception in males and females

Females of reproductive potential should be advised that animal studies and the mechanism of action have shown that alpelisib can be harmful to the developing foetus. Embryo-foetal development studies in rats and rabbits have demonstrated that oral administration of alpelisib during organogenesis induced embryotoxicity, foetotoxicity and teratogenicity (see section 5.3).

In case females of reproductive potential take Piqray, they should use effective contraception (e.g. double-barrier method) during therapy and for at least 1 week after stopping treatment with Piqray.

Male patients with sexual partners who are pregnant, possibly pregnant or who could become pregnant should use condoms during sexual intercourse while taking Piqray and for at least 1 week after stopping treatment.

Please refer to section 4.6 of the prescribing information for fulvestrant.

Pregnancy

Piqray is not indicated and is not to be used in women who are, or may be, pregnant (see section 4.1).

There are no data from the use of alpelisib in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Piqray is not recommended during pregnancy and in women of childbearing potential not using contraception.

The pregnancy status of females of reproductive potential should be verified prior to starting treatment with Piqray.

Breast-feeding

It is not known if alpelisib is excreted in human or animal milk.

Because of the potential for serious adverse reactions in the breast-fed infant, it is recommended that women should not breast-feed during treatment and for at least 1 week after the last dose of Piqray.

Fertility

There are no clinical data available on the effects of alpelisib on fertility. Based on repeated dose toxicity and fertility studies in animals, alpelisib may impair fertility in males and females of reproductive potential (see section 5.3).

4.7 Effects on ability to drive and use machines

Piqray has minor influence on the ability to drive and use machines. Patients should be advised to be cautious when driving or using machines in case they experience fatigue or blurred vision during treatment (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

Study CBYL719C2301 (SOLAR-1)
The safety profile is based on data from 284 patients in the Piqray plus fulvestrant arm of the double-blind, placebo-controlled phase III study.

The most common ADRs (reported at a frequency >20% in the combined mutant and non-mutant study population) were plasma glucose increased (79.2%), creatinine increased (68.0%), diarrhoea (59.9%), lymphocyte count decreased (55.6%), gamma-glutamyltransferase increased (54.2%), rash (52.1%), nausea (46.8%), anaemia (45.4%), alanine aminotransferase increased (45.1%), fatigue (44.0%), lipase increased (43.3%), decreased appetite (37.0%), stomatitis (30.6%), vomiting (29.6%), weight decreased (28.2%), hypocalcaemia (27.8%), plasma glucose decreased (27.5%), activated partial thromboplastin time (aPTT) prolonged (23.9%) and alopecia (20.4%).

The most common grade 3 or 4 ADRs (reported at a frequency ≥2%) were plasma glucose increased (39.4%), rash (19.4%), gamma-glutamyltransferase increased (12.3%), lymphocyte count decreased (9.9%), diarrhoea (7.4%), lipase increased (7.0%), hypokalaemia (6.7%), weight decreased (6.0%), fatigue (5.6%), anaemia (5.3%), hypertension (5.3%), alanine aminotransferase increased (4.6%), creatinine increased (3.2%), nausea (2.8%), osteonecrosis of jaw (2.8%), stomatitis (2.5%), hypocalcaemia (2.1%), acute kidney injury (2.1%) and mucosal inflammation (2.1%).

The most common ADRs leading to treatment discontinuation were hyperglycaemia (6.3%), rash (4.2%), diarrhoea (2.8%) and fatigue (2.5%).

CBYL719X2402 (BYLieve)
Additional safety evaluations were performed in the Phase II, multicenter, open-label, three-cohort, non-comparative study of alpelisib plus endocrine therapy (either fulvestrant or letrozole) in patients (pre- and post-menopausal women, and men) with HR-positive, HER2-negative advanced breast cancer harbouring PIK3CA mutation(s) in the tumour, and whose disease has progressed on or after prior treatments.

In the cohort of patients who had progressed on or after a CDK4/6 inhibitor plus an aromatase inhibitor before treatment with alpelisib plus fulvestrant (Cohort A; n=127 patients), ADRs that were reported in ≥20% of patients were diarrhoea (59.8%), hyperglycaemia (58.3%), nausea (45.7%), rash (39.4%), fatigue (29.1%), decreased appetite (28.3%), stomatitis (26.8%) and vomiting (23.6%).

Grade 3 or grade 4 ADRs that were reported in ≥5% of patients were hyperglycaemia (28.3%), rash (18.9%), and diarrhoea (5.5%).

The most common serious adverse drug reactions (ADRs), reported in ≥2% of patients were hyperglycaemia (5.5%) and rash (3.1%). Serious adverse events reported in ≥2% of patients were dyspnoea (2.4%) and pleural effusion (2.4%). Serious adverse events related to the gastrointestinal tract included colitis and erosive oesophagitis (each 0.8%).

Tabulated list of adverse reactions

ADRs from the phase III clinical study and post-marketing experience (Table 7) are listed by MedDRA system organ class. Within each system organ class, the ADRs are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, ADRs are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Table 7 ADRs observed in phase III clinical study and during post-marketing experience

Adverse drug reaction	**Any grade (%)**		**Grade 3 or 4 (%)**
Infections and infestations			
Urinary tract infection[1]	Very common	29 (10.2)	2 (0.7)*
Blood and lymphatic system disorders			
Anaemia	Very common	129 (45.4)	15 (5.3)*
Lymphocyte count decreased	Very common	158 (55.6)	28 (9.9)
Platelet count decreased	Very common	42 (14.8)	3 (1.1)
Immune system disorders			
Hypersensitivity[2]	Common	12 (4.2)	2 (0.7)*
Metabolism and nutrition disorders			
Glucose plasma increased	Very common	225 (79.2)	112 (39.4)
Glucose plasma decreased	Very common	78 (27.5)	1 (0.4)
Decreased appetite	Very common	105 (37.0)	3 (1.1)*
Hypokalaemia	Very common	43 (15.1)	19 (6.7)
Hypocalcaemia	Very common	79 (27.8)	6 (2.1)
Magnesium decreased	Very common	36 (12.7)	1 (0.4)*
Dehydration	Common	10 (3.5)	1 (0.4)*
Ketoacidosis[3]	Common	3 (1.1)	3 (1.1)
Hyperglycaemic hyperosmolar nonketotic syndrome (HHNKS)[#]	Not known	Not known	Not known
Psychiatric disorders			
Insomnia	Common	22 (7.7)	
Nervous system disorders			
Headache	Very common	55 (19.4)	2 (0.7)*
Dysgeusia[4]	Very common	44 (15.5)	1 (0.4)*
Eye disorders			
Vision blurred	Common	15 (5.3)	1 (0.4)*
Dry eye	Common	10 (3.5)	
Uveitis	Not known	Not known	Not known
Vascular disorders			
Hypertension	Very common	30 (10.6)	15 (5.3)
Lymphoedema	Common	17 (6.0)	
Respiratory, thoracic and mediastinal disorders			
Pneumonitis[5]	Common	5 (1.8)	1 (0.4)*

Gastrointestinal disorders			
Diarrhoea	Very common	170 (59.9)	21 (7.4)*
Nausea	Very common	133 (46.8)	8 (2.8)*
Stomatitis[6]	Very common	87 (30.6)	7 (2.5)*
Vomiting	Very common	84 (29.6)	2 (0.7)*
Abdominal pain	Very common	53 (18.7)	4 (1.4)*
Dyspepsia	Very common	33 (11.6)	
Toothache	Common	13 (4.6)	1 (0.4)*
Gingivitis	Common	11 (3.9)	1 (0.4)*
Gingival pain	Common	11 (3.9)	
Cheilitis	Common	8 (2.8)	
Pancreatitis	Uncommon	1 (0.4)	1 (0.4)
Colitis[#]	Not known	Not known	Not known
Skin and subcutaneous tissue disorders			
Rash[7]	Very common	148 (52.1)	55 (19.4)*
Alopecia	Very common	58 (20.4)	
Pruritus	Very common	54 (19.0)	2 (0.7)*
Dry skin[8]	Very common	53 (18.7)	1 (0.4)*
Erythema[9]	Common	19 (6.7)	2 (0.7)*
Dermatitis[10]	Common	10 (3.5)	2 (0.7)*
Palmar-plantar erythrodysaesthesia syndrome	Common	5 (1.8)	
Erythema multiforme	Common	3 (1.1)	2 (0.7)*
Stevens-Johnson syndrome	Uncommon	1 (0.4)	1 (0.4)*
Drug reaction with eosinophilia and systemic symptoms (DRESS)[#]	Not known	Not known	Not known
Angioedema[#]	Not known	Not known	Not known
Musculoskeletal and connective tissue disorders			
Muscle spasms	Common	23 (8.1)	
Myalgia	Common	20 (7.0)	1 (0.4)*
Osteonecrosis of jaw	Common	16 (5.6)	8 (2.8)*
Renal and urinary disorders			
Acute kidney injury	Common	17 (6.0)	6 (2.1)
General disorders and administration site conditions			
Fatigue[11]	Very common	125 (44.0)	16 (5.6)*
Mucosal inflammation	Very common	56 (19.7)	6 (2.1)*
Oedema peripheral	Very common	48 (16.9)	
Pyrexia	Very common	48 (16.9)	2 (0.7)
Mucosal dryness[12]	Very common	37 (13.0)	1 (0.4)
Oedema[13]	Common	20 (7.0)	

Investigations			
Weight decreased	Very common	80 (28.2)	17 (6.0)*
Blood creatinine increased	Very common	193 (68.0)	9 (3.2)
Gamma-glutamyltransferase increased	Very common	154 (54.2)	35 (12.3)
Alanine aminotransferase increased	Very common	128 (45.1)	13 (4.6)
Lipase increased	Very common	123 (43.3)	20 (7.0)
Activated partial thromboplastin time (aPTT) prolonged	Very common	68 (23.9)	2 (0.7)*
Albumin decreased	Very common	44 (15.5)	1 (0.4)*
Glycosylated haemoglobin increased	Common	9 (3.2)	

* No grade 4 ADRs were observed

\# Adverse reactions reported during post-marketing experience. These are derived from spontaneous reports for which it is not always possible to reliably establish frequency or a causal relationship to exposure to the medicinal product.

[1] Urinary tract infection: also includes a single case of urosepsis

[2] Hypersensitivity: also includes allergic dermatitis

[3] Ketoacidosis: also includes diabetic ketoacidosis (see section 4.4)

[4] Dysgeusia: also includes ageusia, hypogeusia

[5] Pneumonitis: also includes interstitial lung disease

[6] Stomatitis: also includes aphthous ulcer and mouth ulceration

[7] Rash: also includes rash maculopapular, rash macular, rash generalised, rash papular, rash pruritic

[8] Dry skin: also includes skin fissures, xerosis, xeroderma

[9] Erythema: also includes erythema generalised

[10] Dermatitis: also includes dermatitis acneiform

[11] Fatigue: also includes asthenia

[12] Mucosal dryness: also includes dry mouth, vulvovaginal dryness

[13] Oedema: also includes face swelling, face oedema, eyelid oedema

Description of selected ADRs

Hyperglycaemia

Hyperglycaemia was reported in 191 (67.3%) patients; grade 2 (FPG >160-250 mg/dl), 3 (FPG >250-500 mg/dl) and 4 (FPG >500 mg/dl) events were reported in 15.8%, 34.5% and 4.6% of patients, respectively.

Based on baseline FPG and HbA1c values, 56% of patients were considered pre-diabetic (FPG >100-125 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%). 75.5% of patients who were pre-diabetic at baseline experienced hyperglycaemia (any grade) when treated with alpelisib. Among all patients with hyperglycaemia of grade ≥2 (FPG >160 mg/dl), the median time to first occurrence was 15 days (range: 5 days to 1 458 days) (based on laboratory findings). The median duration of grade ≥2 hyperglycaemia was 10 days (95% CI: 8 to 13 days). In patients with grade ≥2 hyperglycaemia, median time to improvement (at least one grade from the first event) was 8 days (95% CI: 8 to 10 days). In 93.4% of patients who continued on fulvestrant after discontinuing Piqray, FPG levels returned to baseline (normal).

Hyperglycaemia was managed with antidiabetic medicinal products, see section 4.4.

Rash
Rash events (including rash maculopapular, macular, generalised, papular and pruritic, dermatitis and dermatitis acneiform) were reported in 154 (54.2%) patients. Rash was predominantly mild or moderate (grade 1 or 2) and responsive to therapy, and in some cases rash was accompanied by pruritus and dry skin. Grade 2 and 3 events were reported in 13.7% and 20.1% of patients, respectively, with a median time to first onset of 12 days (range: 2 days to 220 days).

Among patients who received prophylactic antirash treatment including antihistamines, rash was reported less frequently than in the overall population; 25.8% vs 54.2% for all grades, 11.2% vs 20.1% for grade 3, and 3.4% vs 4.2% for rash leading to the permanent discontinuation of Piqray. Accordingly, antihistamines may be initiated prophylactically, at the time of initiation of treatment with Piqray.

Gastrointestinal toxicity (nausea, diarrhoea, vomiting)
Diarrhoea, nausea and vomiting were reported in 59.9%, 46.8% and 29.6% of the patients, respectively (see Table 7).

Grade 2 and 3 diarrhoea events were reported in 20.4% and 7.4% of patients, respectively, with a median time to onset of grade ≥2 diarrhoea of 54 days (range: 1 day to 1 731 days).

Severe diarrhoea and clinical consequences, such as dehydration and acute kidney injury, have been reported during treatment with Piqray and resolved with appropriate intervention (see Table 4). Antiemetics (e.g. ondansetron) and antidiarrhoeal medicinal products (e.g. loperamide) were used in 29/153 (19.0%) and 111/170 (65.3%) patients, respectively, to manage symptoms.

Osteonecrosis of the jaw (ONJ)
ONJ was reported in 6.0% patients (17/284) in the Piqray plus fulvestrant arm. All patients experiencing ONJ were exposed to prior or concomitant bisphosphonates (e.g. zoledronic acid) or RANK-ligand inhibitors (e.g. denosumab). Therefore, in patients receiving Piqray and bisphosphonates or RANK-ligand inhibitors, an increased risk of development of ONJ cannot be excluded.

Special populations

Elderly
In patients ≥65 years of age treated with alpelisib plus fulvestrant, there was a higher incidence of grade 3-4 hyperglycaemia (45.3%) compared to patients <65 years of age (34.7%), while in patients <75 years of age, grade 3-4 hyperglycaemia was 36.8% compared to 55.9% in patients ≥75 years of age.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

The adverse reactions associated with overdose have been consistent with the safety profile of Piqray and included hyperglycaemia, nausea, asthenia and rash.

Management

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, Protein kinase inhibitors, Phosphatidylinositol-3-kinase (PI3K) inhibitors, ATC code: L01EM03

Mechanism of action

Alpelisib is an α-specific class I phosphatidylinositol3kinase (PI3Kα) inhibitor.
Gain-of-function mutations in the gene encoding the catalytic α-subunit of PI3K (PIK3CA) lead to activation of PI3Kα and AKT-signalling, cellular transformation and the generation of tumours in *in vitro* and *in vivo* models.

In breast cancer cell lines, alpelisib inhibited the phosphorylation of PI3K downstream targets including AKT, and showed activity in cell lines harbouring a PIK3CA mutation.

In vivo, alpelisib inhibited the PI3K/AKT signalling pathway and reduced tumour growth in 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. The combination of alpelisib and fulvestrant demonstrated increased anti-tumour activity compared to either treatment alone in xenograft models derived from ER-positive, PIK3CA mutated breast cancer cell lines.

The PI3K/AKT signalling pathway is responsible for glucose homeostasis, and hyperglycaemia is an expected on-target adverse reaction of PI3K inhibition.

Clinical efficacy and safety

Study CBYL719C2301 (SOLAR-1)
Piqray was evaluated in a pivotal phase III, randomised, double-blind, placebo-controlled study of alpelisib in combination with fulvestrant in postmenopausal women, and men, with HR+, HER2- advanced (locoregionally recurrent or metastatic) breast cancer whose disease

had progressed or recurred on or after an aromatase-inhibitor-based treatment (with or without CDK4/6 inhibitor combination).

A total of 572 patients were enrolled into two cohorts, one cohort with PIK3CA mutation and one cohort without PIK3CA mutation breast cancer. Patients were randomised to receive either alpelisib 300 mg plus fulvestrant or placebo plus fulvestrant in a 1:1 ratio. Randomisation was stratified by presence of lung and/or liver metastasis and previous treatment with CDK4/6 inhibitor(s).

In the cohort with PIK3CA mutation, 169 patients with one or more PIK3CA mutations (C420R, E542K, E545A, E545D [1635G>T only], E545G, E545K, Q546E, Q546R, H1047L, H1047R or H1047Y) were randomised to receive alpelisib in combination with fulvestrant and 172 patients were randomised to receive placebo in combination with fulvestrant. In this cohort 170 (49.9%) patients had liver/lung metastases and 20 (5.9%) patients had received prior CDK4/6 inhibitor treatment.

Patients had a median age of 63 years (range: 25 to 92 years). 44.9% patients were 65 years of age or older and ≤85 years. The patients included were White (66.3%), Asian (21.7%) and Black or African American (1.2%). The study population included one male subject enrolled in the PIK3CA mutant cohort and treated with alpelisib and fulvestrant. 66.0% and 33.4% of subjects had an ECOG performance status of 0 and 1, respectively.

97.7% of patients had received prior endocrine therapy. In 67.7% of subjects, the last therapy prior to study enrollment was endocrine therapy. Letrozole and anastrozole were the most commonly used endocrine therapies. The setting of last endocrine therapy prior to study enrollment was therapeutic in 47.8% of subjects and adjuvant therapy in 51.9% of subjects. Overall, 85.6% of the patients were considered to have endocrine-resistant disease; primary endocrine resistance (*de novo* resistance) was observed in 13.2% and secondary endocrine resistance (relapse/progression following an initial response) in 72.4% of patients.

In both cohorts (with or without PIK3CA mutation), demographics and baseline disease characteristics, ECOG performance status, tumour burden and prior antineoplastic therapy were well balanced between the study arms.

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

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

The primary endpoint for the study was progression-free survival (PFS) using Response Evaluation Criteria in Solid Tumors (RECIST v1.1), based on the investigator assessment in patients harbouring a PIK3CA mutation. The key secondary endpoint was overall survival (OS) for patients with a PIK3CA mutation status.

Other secondary endpoints included PFS for patients without PIK3CA mutation, OS for patients without PIK3CA mutation.

Primary efficacy analysis

At the final PFS analysis, the median duration of follow-up (between randomisation and data cut-off date of 12-June 2018) was 20 months. The results demonstrated a statistically significant improvement in PFS by investigator assessment in the PIK3CA mutant cohort for patients receiving alpelisib plus fulvestrant, compared to patients receiving placebo plus fulvestrant with an estimated 35% risk reduction of disease progression or death in favour of treatment with alpelisib plus fulvestrant.

Primary PFS results were supported by consistent results from a blinded independent review committee (BIRC) assessment in this cohort, from a randomly selected subset of 50% of randomised patients.

Table 8 Study C2301 - Summary of efficacy results (cohort with PIK3CA mutation)

	Piqray + fulvestrant (n=169)	**Placebo + fulvestrant (n=172)**
Data using primary analysis data cut-off date of 12 June 2018		
Median progression free survival (PFS) (months, 95% CI)		
Investigator radiological assessment[#]		
PIK3CA mutant cohort (N=341)	11.0 (7.5 to 14.5)	5.7 (3.7 to7.4)
Hazard ratio (95% CI)	0.65 (0.50 to 0.85)	
p-value[a]	0.00065	
Blinded independent review committee assessment*[#]		
PIK3CA mutant cohort (N=173)	11.1 (7.3 to16.8)	3.7 (2.1 to5.6)
Hazard ratio (95% CI)	0.48 (0.32 to 0.71)	
p-value	N/A	

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

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

[#] Per RECIST 1.1

* Based on 50% sample-based audit approach

In the cohort with PIK3CA mutation, PFS subgroup analyses per investigator assessment by randomisation stratification factors showed a generally consistent treatment effect in favour of the alpelisib arm, irrespective of presence or absence of lung/liver metastases.

In the subgroup of 170 patients with presence of lung/liver metastases, the PFS HR (95% CI) was 0.56 (0.40, 0.79); median PFS was 3.7 months (95% CI: 2.9, 6.1) in the placebo plus fulvestrant arm and 9.0 months (95% CI: 5.6, 14.5) in the alpelisib plus fulvestrant arm.

Among 20 patients with prior CDK4/6 inhibitor use the hazard ratio (HR) for PFS was 0.48 (95% CI: 0.17, 1.36); median PFS was 1.8 months (95% CI: 1.7, 3.6) in the placebo plus fulvestrant arm and 5.5 months (95% CI: 1.6, 16.8) in the alpelisib plus fulvestrant arm.

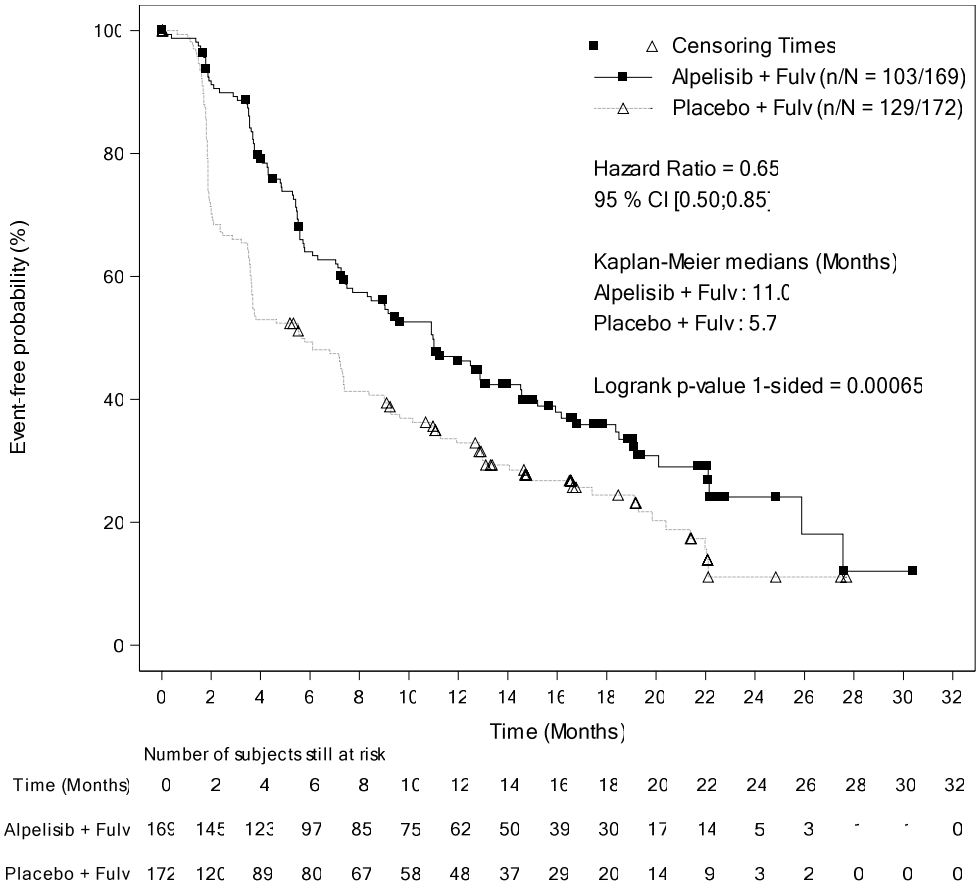
Overall response rates are summarized in Table 9.

Table 9 Overall response rate and clinical benefit rate in the PIK3CA mutant cohort per investigator assessment (Data cut-off date: 18-Jun-2018)

Analysis	**Piqray plus fulvestrant (%, 95% CI)**	**Placebo plus fulvestrant (%, 95% CI)**	**p-value[c]**
Full analysis set	N=169	N=172	
Objective Response Rate[a]	26.6 (20.1 to 34.0)	12.8 (8.2 to 18.7)	0.0006
Clinical Benefit Rate[b]	61.5 (53.8to 68.9)	45.3 (37.8 to 53.1)	0.002
Patients with measurable disease[d]	N=126	N=136	
Objective Response Rate[a]	35.7 (27.4 to 44.7)	16.2 (10.4 to 23.5)	0.0002
Clinical Benefit Rate[b]	57.1 (48.0 to 65.9)	44.1 (35.6 to 52.9)	0.02

[a] *ORR= proportion of patients with confirmed Complete Response or Partial Response*
[b] *CBR: proportion of patients with confirmed Complete Response or Partial Response, or (Stable Disease or Non-Complete Response/Non-Progression Disease >=24 weeks)*
[c] *p-values are nominal and are obtained from the Cochran-Mantel Haenszel test.*
[d] *measurable disease: the presence of at least one measurable nodal or non-nodal lesion at Baseline.*

Figure 1 Kaplan-Meier plot of progression free survival in the PIK3CA mutant cohort per investigator assessment (Data cut-off date: 18-Jun-2018)



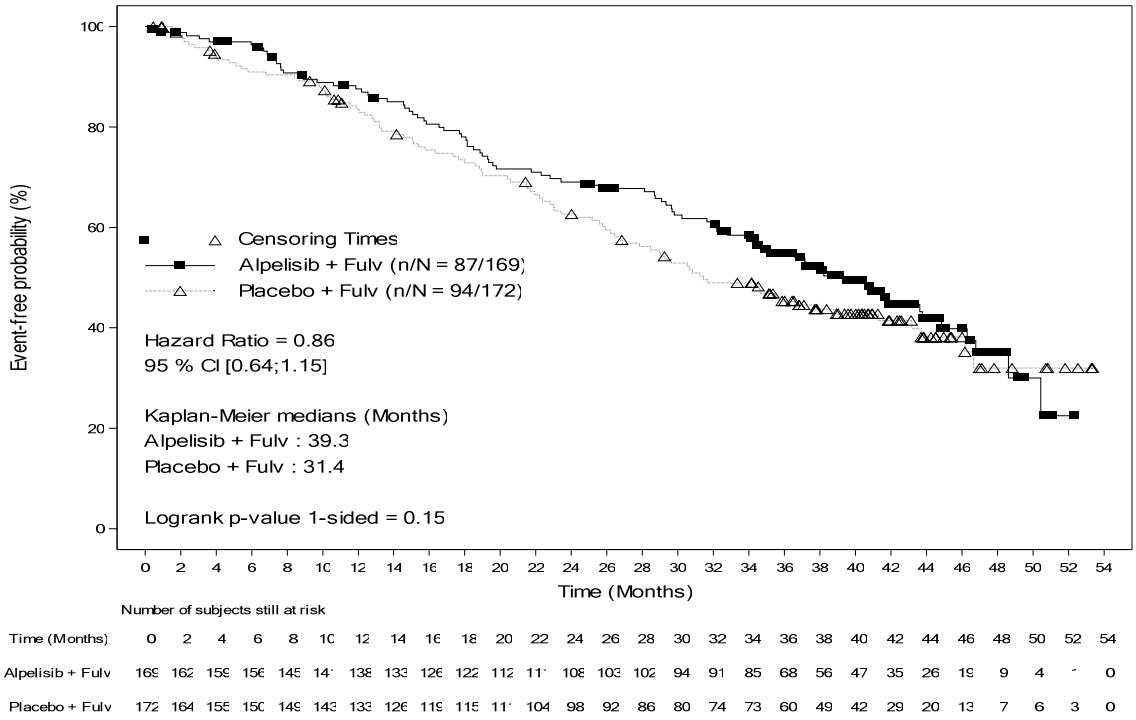
Time (Months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32
Alpelisib + Fulv	169	145	123	97	85	75	62	50	39	30	17	14	5	3	-	-	0
Placebo + Fulv	172	120	89	80	67	58	48	37	29	20	14	9	3	2	0	0	0

Final overall survival analysis

The final OS analysis was conducted using a data cut-off date of 23-Apr-2020.

With a median duration from randomisation to data cut-off of approximately 42 months, a total of 87 (51.5%) deaths were reported in the alpelisib plus fulvestrant arm and 94 (54.7%) in the placebo plus fulvestrant arm, the HR was 0.86 (95% CI: 0.64, 1.15; p = 0.15, one-sided) and the pre-specified O'Brien-Fleming efficacy boundary of $p \leq 0.0161$ was not crossed. Median OS was 31.4 months (95% CI: 26.8, 41.3) in the placebo plus fulvestrant arm and 39.3 months (95% CI: 34.1, 44.9) in the alpelisib plus fulvestrant arm.

Figure 2 Kaplan-Meier plot of overall survival in cohort with PIK3CA mutation (cut-off date of 23-Apr-2020)



Number of subjects still at risk

Time (Months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52	54
Alpelisib + Fulv	169	162	159	156	145	14·	138	133	126	122	112	11·	108	103	102	94	91	85	68	56	47	35	26	19	9	4	·	0
Placebo + Fulv	172	164	155	150	149	143	133	126	119	115	11·	104	98	92	86	80	74	73	60	49	42	29	20	13	7	6	3	0

OS subgroup analyses by randomisation stratification factors demonstrated a generally consistent treatment effect.

Cohort without PIK3CA mutation

No PFS benefit was observed in patients whose tumours did not have a PIK3CA tissue mutation.

CBYL719X2402 (BYLieve)

Alpelisib was evaluated in a Phase II, multicenter, open-label, three-cohort, non-comparative study in combination with endocrine therapy (either fulvestrant or letrozole) in adult patients (pre- and post-menopausal women and men), 18 years or older, with HR-positive, HER2-negative locally advanced or metastatic breast cancer harbouring PIK3CA mutation(s), and whose disease has progressed on or after prior treatments.

Table 10 CBYL719X2402 Patients assignment based on most recent prior therapy and treatment regimen

	Cohort A	Cohort B	Cohort C

Patient inclusion, based on their most recent prior therapy	CDK4/6i plus any AI	CDK4/6i plus fulvestrant	Patients who failed prior AI based therapy and received systemic chemotherapy or endocrine therapy
Treatment received in Study X2402	Alpelisib 300 mg plus fulvestrant (500 mg)	Alpelisib 300 mg plus letrozole (2.5 mg)	Alpelisib 300 mg plus fulvestrant (500 mg)

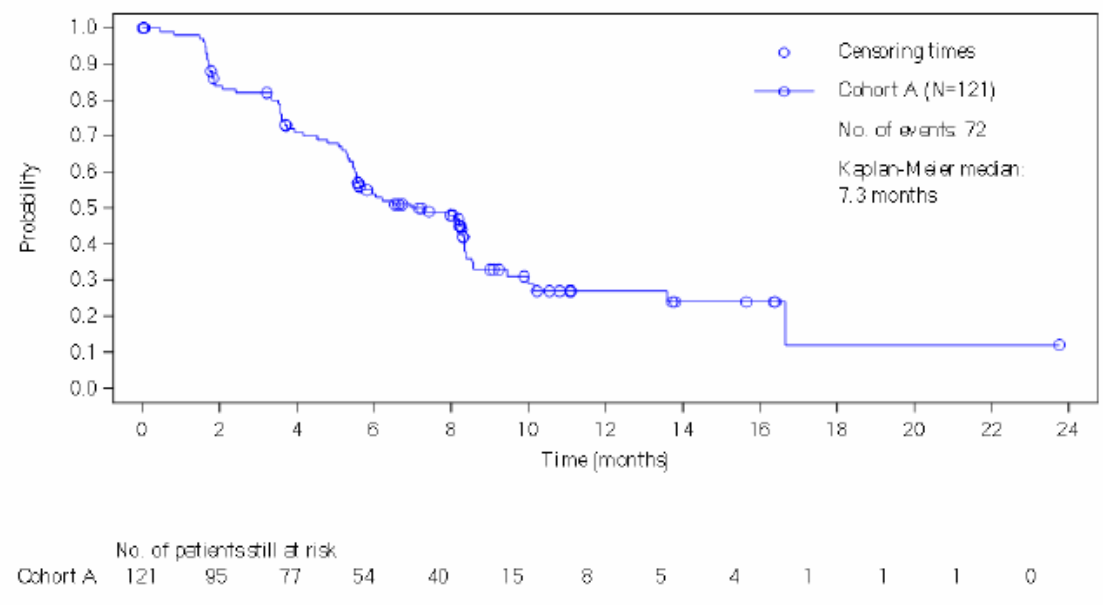
Patients were treated until disease progression, intolerable toxicity, or until 18 months after last subject first treatment. Treatment crossover between cohorts was not permitted in this study

The primary objective of the study was to assess the proportion of patients who were alive without disease progression at 6 months based on local Investigator assessment per RECIST 1.1. Analysis of the primary endpoint was to be performed separately for each cohort.

Using a data cut-off date of 17 December 2019, data for Cohort A only are available. The primary analysis was performed for the modified Full analysis set (mFAS), defined as all subjects in Cohort A with a PIK3CA mutation confirmed by a Novartis-designated laboratory who received at least one dose of study treatment (n=121). With a median duration of follow-up of 11.7 months (calculated from the start of treatment to the date of data cut-off), 61/121 patients (50.4%, 95% CI: 41.2, 59.6) were alive without disease progression at 6 months.

Median progression-free survival (PFS), one of the secondary endpoints was 7.3 months (95% CI: 5.6, 8.3) in Cohort A, based on investigator assessment.

Figure 3 Kaplan-Meier plot of time of PFS per local Investigator assessment (Cohort A) – mFAS (cut-off date of 17-Dec-2019)



Prior use of fulvestrant in study CBYL719X2102

Patients with prior fulvestrant use were not included in the pivotal study. In the phase I study CBYL719X2101, 39 subjects reported prior fulvestrant use. The best overall responses to treatment with alpelisib plus fulvestrant for the 21 subjects with PIK3CA mutations and

measurable disease at baseline were partial response in 7 subjects, stable disease in 11 subjects, and progressive disease in 2 subjects. Hence, the evidence of efficacy of this treatment in patients previously treated with fulvestrant is not established due to the limited data at this time (see section 4.4).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Piqray in all subsets of the paediatric population in breast cancer (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetics of alpelisib were investigated in patients under an oral dosing regimen ranging from 30 to 450 mg daily. Healthy subjects received single oral doses ranging from 300 to 400 mg. The pharmcokinetics were comparable in both oncology patients and healthy subjects.

Absorption

Following oral administration of alpelisib, median time to reach peak plasma concentration (T_{max}) ranged between 2.0 to 4.0 hours, independent of dose, time or regimen. Based on absorption modelling bioavailability was estimated to be very high (>99%) under fed conditions but lower under fasted conditions (~68.7% at a 300 mg dose). Steady-state plasma levels of alpelisib after daily dosing can be expected to be reached on day 3 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%, and a 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 for 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. The increase in gastrointestinal solubility by bile, secreted in response to food intake, is the potential cause of the food effect. Hence, Piqray should be taken immediately after food at approximately the same time each day.

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. As alpelisib is a substrate of human efflux transporters, penetration of the blood-brain barrier is not expected to occur in humans. The volume of distribution of alpelisib at steady state (Vss/F) is estimated at 114 litres (intersubject CV% 49%).

Biotransformation

In vitro studies demonstrated that formation of the hydrolysis metabolite BZG791 by chemical and enzymatic amide hydrolysis was a major metabolic pathway, followed by CYP3A4-mediated hydroxylation. 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 and glucuronides amounted to ~15% of the dose; BZG791 accounted for ~40-45% of the dose. The rest of the dose, which was found as unchanged alpelisib in urine and faeces, was either excreted as alpelisib or not absorbed.

Elimination

Alpelisib exhibits low clearance with 9.2 l/h (CV% 21%) based on population pharmacokinetic analysis under fed conditions. The 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, after oral administration, alpelisib and its metabolites were primarily found in the faeces (81.0%) as alpelisib, or metabolised as BZG791. Excretion in the urine is minor (13.5%), with unchanged alpelisib (2%). Following a single oral dose of [14C]-alpelisib, 94.5% of the total administered radioactive dose was recovered within 8 days.

Linearity/non-linearity

The pharmacokinetics were found to be linear with respect to dose and time under fed conditions between 30 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 a daily dosing regimen.

Metabolic interaction

CYP3A4, CYP2C8, CYP2C9, CYP2C19 and CYP2B6 substrates

In a drug-drug interaction study, co-administration of repeated doses of alpelisib 300 mg with a single dose of sensitive substrates of CYP3A4 (midazolam), CYP2C8 (repaglinide), CYP2C9 (warfarin), CYP2C19 (omeprazole) and CYP2B6 (bupropion), administered as a cocktail, showed that there is no clinically signficant pharmacokinetic interaction. The data from CYP2B6 substrate (bupropion) should be interpreted with caution due to the small sample size.

In healthy subjects, co-administration of a CYP2C9 substrate (S-warfarin) -with repeated doses of 300 mg alpelisib at steady state, increased S-warfarin exposure on average by 34% and 19% for AUC_{inf} and C_{max} respectively, compared to administration of S-warfarin alone. This indicates that alpelisib is a mild inhibitor of CYP2C9.

In a drug-drug interaction study with the sensitive CYP3A4 and P-gp substrate everolimus, in patients with advanced solid tumours, AUC decreased by 11.2%. No clinically meaningful change is expected as a result of drug interaction with CYP3A4 substrates.

CYP3A4 inducers

In a drug-drug interaction study co-administration of alpelisib and rifampin, a strong CYP3A4 inducer, confirmed that there is a clinically significant pharmacokinetic interaction between alpelisib and strong CYP3A4 inducers (see section 4.5).

Transporter-based interaction

Based on *in vitro* data, inhibition of the renal organic anion transporter OAT3 by alpelisib (and/or its metabolite BZG791) cannot be discarded in patients at the therapeutic dose.

Alpelisib showed only weak *in vitro* inhibition towards the ubiquitously expressed efflux transporters (P-gp, BCRP, MRP2, BSEP), solute carrier transporters at the liver inlet (OATP1B1, OATP1B3, OCT1) and solute carrier transporters in the kidney (OAT1, 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 IC_{50}, the inhibition will not translate into clinical significance. Due to high alpelisib concentrations in the intestinal lumen, an effect on intestinal P-gp and BCRP cannot be fully excluded.

Special populations

Effect of age, weight and gender
The population pharmacokinetic analysis showed that there are no clinically relevant effects of age, body weight, or gender on the systemic exposure of alpelisib that would require Piqray dose adjustment.

Paediatric patients (below 18 years)
The pharmacokinetics of Piqray in children aged 0-18 years have not been established. No data are available.

Elderly (age 65 years or above)
Of 284 patients who received Piqray in the phase III study (in the alpelisib plus fulvestrant arm), 117 patients were ≥65 years of age and 34 patients were between 75 and 87 years of age. No overall differences in exposure of Piqray were observed between these patients and younger patients (see section 4.2).

Race/Ethnicity
Population pharmacokinetic analyses and pharmacokinetic analyses from a phase I study in Japanese cancer patients showed that there are no clinically relevant effects of ethnicity on the systemic exposure of Piqray.

Non-compartmental pharmacokinetic parameters after single and multiple daily doses of Piqray for Japanese patients were very similar to those reported in the Caucasian population.

Renal impairment
Based on a population pharmacokinetic analysis that included 117 patients with normal renal function (eGFR ≥90 ml/min/1.73 m^2) / (CLcr ≥90 ml/min), 108 patients with mild renal impairment (eGFR 60 to <90 ml/min/1.73 m^2)/ (CLcr 60 to <90 ml/min), and 45 patients with moderate renal impairment (eGFR 30 to <60 ml/min/1.73 m^2), mild and moderate renal impairment had no effect on the exposure of alpelisib (see section 4.2).

Hepatic impairment
Based on a pharmacokinetic study in patients with hepatic impairment, moderate and severe hepatic impairment had negligible effect on the exposure of alpelisib (see section 4.2). The mean exposure for alpelisib was increased 1.26-fold in patients with severe (GMR: 1.00 for C_{max}; 1.26 for AUC_{last}/AUC_{inf}) hepatic impairment.

Based on a population pharmacokinetic analysis that included 230 patients with normal hepatic function, 41 patients with mild hepatic impairment and no patients with moderate hepatic impairment, further supporting the findings from the dedicated hepatic impairment study, mild and moderate hepatic impairment had no effect on the exposure of alpelisib (see section 4.2).

5.3 Preclinical safety data

Safety pharmacology and repeated dose toxicity

The majority of the observed alpelisib effects were related to the pharmacological activity of alpelisib as a p110α-specific inhibitor of the PI3K pathway, such as the influence on the glucose homeostasis resulting in hyperglycaemia and the risk of increased blood pressure. The bone marrow and lymphoid tissue, pancreas and some reproductive organs of both genders were the main target organs for adverse events. Effects on bone marrow and lymphoid tissue were generally reversible on cessation of treatment. Effects on the pancreas and reproductive organs did not fully reverse but showed a tendency towards reversion. In exploratory rat studies evidence of inflammatory changes of the skin was found.

Cardiovascular safety pharmacology
In vitro inhibition of hERG channels (IC_{50} of 9.4 µM) was shown at concentrations ~13-fold higher than the exposure in humans, at the recommended dose of 300 mg/day. No relevant electrophysiological effect was seen in dogs.

Genotoxicity / Carcinogenicity
Results of standard genotoxicity *in vitro* studies with alpelisib were negative. Alpelisib was not genotoxic in a repeated-dose rat toxicity study where micronucleus analysis was integrated, up to exposure levels approximately twice the estimated exposure (AUC) in humans at the recommended dose of 300 mg.
Alpelisib was not carcinogenic in a 2-year carcinogenicity study conducted in rats when administered by daily oral gavage at doses up to 4 mg/kg (approximately 0.2 times the clinical exposure in patients at the highest recommended dose of 300 mg/day based on AUC).

Reproductive toxicity

Embryo-foetal development studies in rats and rabbits have demonstrated that oral administration of alpelisib during organogenesis induced embryotoxicity, foetotoxicity and teratogenicity. In rats and rabbits, following prenatal exposure to alpelisib, increased incidences of pre- and post-implantation losses, reduced foetal weights and increased incidences of foetal abnormalities (enlarged brain ventricle, decreased bone ossification and skeletal malformations) were observed starting at exposures below those in humans at the highest recommended dose of 300 mg, indicating potential clinical relevance.

In repeated dose toxicity studies, adverse events were observed in reproductive organs, such as vaginal or uterine atrophy and oestrus cycle variations in rats, decreases in prostate and testes weight in rats and dogs and prostate atrophy in dogs at clinically relevant doses based on AUC.

In fertility studies conducted in male and female rats, similar effects on fertility were observed. In females, increased pre- and post-implantation losses, which led to reduced

numbers of implantation sites and live embryos, were observed at exposure levels (AUC) approximately twice the recommended human dose of 300 mg. In males, fertility and reproductive performance, including sperm count and motility parameters, were unaffected at exposure levels approximately twice the estimated exposure (AUC) in humans at the recommended dose of 300 mg. However, at exposure levels (AUC) at or below the recommended human dose of 300 mg, accessory gland weights (seminal vesicles, prostate) were reduced and correlated microscopically with atrophy and/or reduced secretion in prostate and seminal vesicles, respectively.

Phototoxicity

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Cellulose microcrystalline
Mannitol
Sodium starch glycolate
Hypromellose
Magnesium stearate

Film coating

Hypromellose
Iron oxide, black (E172)
Iron oxide, red (E172)
Titanium dioxide (E171)
Macrogol
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

This medical product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PCTFE/alu (polyvinylchloride/polychlorotrifluoroethylene/aluminium) blister sealed into a blister card containing 14 film-coated tablets.

Packs containing 14 or 28 film-coated tablets.

Multipacks containing 84 (3x 28) film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Novartis Pharmaceuticals UK Limited

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White City Place

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London

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United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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