**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

## 1. NAME OF THE MEDICINAL PRODUCT

Vijoice 50 mg film-coated tablets
Vijoice 125 mg film-coated tablets
Vijoice 200 mg film-coated tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Vijoice 50 mg film-coated tablets

Each film-coated tablet contains 50 mg alpelisib.

Vijoice 125 mg film-coated tablets

Each film-coated tablet contains 125 mg alpelisib.

Vijoice 200 mg film-coated tablets

Each film-coated tablet contains 200 mg alpelisib.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Vijoice 50 mg film-coated tablets

Light yellow, round, curved film-coated tablet with bevelled edges, debossed with “C7” on one side and “NVR” on the other side. Approximate diameter: 7 mm.

Vijoice 125 mg film-coated tablets

Dark yellow, ovaloid, curved film-coated tablet with bevelled edges, debossed with “Y7” on one side and “NVR” on the other side. Approximate size: 13 mm x 6 mm.

Vijoice 200 mg film-coated tablets

Pale yellow, ovaloid, curved film-coated tablet with bevelled edges, debossed with “CL7” on one side and “NVR” on the other side. Approximate size: 16 mm x 7 mm.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Vijoice is indicated for the treatment of adult and paediatric patients aged 2 years and older with severe or life-threatening manifestations of PIK3CA-related overgrowth spectrum (PROS) who require systemic therapy.

## 4.2 Posology and method of administration

Treatment with Vijoice should be initiated by a physician with experience in the management of PROS.

Posology

*Adults*
The recommended dose in adult patients is 250 mg, taken once daily. Treatment should be discontinued if disease progression, worsening of PROS-related symptoms, or unacceptable toxicity occurs, as assessed by the treating physician.

*Paediatric population (2 to < 18 years of age)*
The recommended initial dose in paediatric patients is 50 mg, taken once daily. Treatment should be discontinued if disease progression, worsening of PROS-related symptoms, or unacceptable toxicity occurs, as assessed by the treating physician.

In paediatric patients ≥ 6 years old, a dose increase to 125 mg once daily should be considered for response optimisation (clinical/radiological) after 24 weeks of treatment at 50 mg once daily. When a paediatric patient turns 18 years old, a gradual dose increase up to 250 mg should be considered. Recommended dose increases by age group are listed in Table 1.

**Table 1 Recommended dose levels for paediatric population (2 to < 18 years of age)**

| Patient age (years) | Initial dose | Dose increase |
|---|---|---|
| 2 to < 6 | 50 mg once daily | Not applicable |
| 6 to < 18 | 50 mg once daily | 125 mg once daily |

*Missed dose*
If a dose is missed, it can be taken immediately after food within 9 hours after the time it is usually taken. After more than 9 hours, the dose should be skipped for that day. The next day, the dose should be taken at the usual time.

*Vomiting*
If the patient vomits after taking the dose, the patient should not take an additional dose on that day and should resume the dosing schedule the next day at the usual time.

*Dose modifications*
Management of severe or intolerable adverse drug reactions (ADRs) may require temporary dose interruption, reduction and/or discontinuation of Vijoice.

The recommended Vijoice dose reductions for ADRs in the adult and paediatric populations are listed in Table 2.

**Table 2 Vijoice dose reduction recommendations for ADRs in adult and paediatric patients**

| Action | Vijoice dose prior to dose reduction | Reduced Vijoice dose |
|---|---|---|
| **Adult patients** | | |
| First dose reduction | 250 mg once daily | 125 mg once daily |
| Second dose reduction | 125 mg once daily | 50 mg once daily |
| **Paediatric patients** | | |
| Dose reduction | 125 mg once daily | 50 mg once daily |
| | 50 mg once daily | Not applicable |

Vijoice should be discontinued in adults or paediatric patients who cannot tolerate 50 mg daily.

Tables 3 to 6 summarise the recommendations for dose interruption, reduction or discontinuation of Vijoice 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 3 Dose modification and management for hyperglycaemia**

| **FG values[1]** | **Recommendation for adult and paediatric patients** |
|---|---|
| **Dose modification and management should only be based on FG (plasma/blood) values.** | |
| Grade 1<br>> ULN*-160 mg/dl or<br>> ULN-8.9 mmol/l | No Vijoice dose adjustment required.<br>Initiate or intensify oral antidiabetic treatment[2]. |
| Grade 2<br>> 160-250 mg/dl or<br>> 8.9-13.9 mmol/l | No Vijoice dose adjustment required.<br>Initiate or intensify oral antidiabetic treatment[2].<br>**Adult patients:**<br>• 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 Vijoice dose by 1 dose level, and follow FG-value-specific recommendations.<br>**Paediatric patients:**<br>• If FG does not decrease to ≤ 160 mg/dl or 8.9 mmol/l within 21 days under appropriate oral antidiabetic treatment[2,3], interrupt Vijoice until improvement to grade ≤ 1, then resume Vijoice at 50 mg, and follow FG-value-specific recommendations. |

| | |
|---|---|
| Grade 3<br>> 250-500 mg/dl or<br>> 13.9-27.8 mmol/l | Interrupt Vijoice.<br>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.<br>Administer intravenous hydration and consider appropriate treatment (e.g. intervention for electrolyte / ketoacidosis / hyperosmolar disturbances).<br>**Adult patients:**<br>• If FG decreases to ≤ 160 mg/dl or 8.9 mmol/l within 3 to 5 days under appropriate antidiabetic treatment, resume Vijoice at the next lower dose level.<br>• 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.<br>• 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 Vijoice treatment.<br>**Paediatric patients:**<br>• If FG decreases to ≤ 160 mg/dl or 8.9 mmol/l within 3 to 5 days under appropriate antidiabetic treatment, resume Vijoice at 50 mg.<br>• 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 to determine if treatment with Vijoice should be resumed or permanently discontinued.<br>• 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 Vijoice.<br>• If hyperglycaemia recurs at grade ≥ 3, consider permanent discontinuation of Vijoice. |
| Grade 4<br>> 500 mg/dl or<br>> 27.8 mmol/l | Interrupt Vijoice.<br>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 FG within 24 hours and as clinically indicated.<br>• If FG decreases to ≤ 500 mg/dl or ≤ 27.8 mmol/l, follow FG-value-specific recommendations for grade 3.<br>• If FG is confirmed at > 500 mg/dl or > 27.8 mmol/l, permanently discontinue Vijoice treatment. |

*ULN: upper limit of normal

[1] Fasting glucose (FG) 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 in patients ≥ 10 years or SGLT2 inhibitors or insulin sensitisers (such as thiazolidinediones or dipeptidyl peptidase-4 inhibitors) in adult patients, should be initiated and the recommendations for dosing and dose titration included in the respective prescribing information should be reviewed together with local diabetic treatment guidelines.

[3] As recommended in the compassionate use programme, 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 the interruption of Vijoice.

*Rash*

Oral antihistamine administration may be considered prophylactically, at the time of initiation of treatment with Vijoice. 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, Vijoice may require dose interruption, reduction or discontinuation as described in Table 4. If the diagnosis is determined to be a severe cutaneous adverse reaction (SCAR), Vijoice should be permanently discontinued (see section 4.4).

**Table 4 Dose modification and management for rash**

| **Grade[1]** | **Recommendation for adult and paediatric patients[2]** |
|---|---|
| All grades | Consultation with a dermatologist should always be considered. |
| Grade 1<br>(< 10% BSA* with active skin toxicity) | No Vijoice dose adjustment required.<br>Initiate topical corticosteroid treatment.<br>Consider adding oral antihistamine treatment to manage symptoms.<br>If active rash is not improved within 28 days of appropriate treatment, add a low-dose systemic corticosteroid. |
| Grade 2<br>(10-30% BSA with active skin toxicity) | No Vijoice dose adjustment required.<br>Initiate or intensify topical corticosteroid and oral antihistamine treatment.<br>Consider low-dose systemic corticosteroid treatment.<br>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)<br>(> 30% BSA with active skin toxicity) | Interrupt Vijoice and initiate or intensify topical/systemic corticosteroid and oral antihistamine treatment.<br>**Adult patients:**<br>• Once rash improves to grade ≤ 1, resume Vijoice at next lower dose level.<br>**Paediatric patients:**<br>• Once rash improves to grade ≤ 1, either resume Vijoice at 50 mg while continuing oral antihistamine treatment or permanently discontinue Vijoice.<br>• Permanently discontinue Vijoice if:<br>o Antihistamines were ongoing at the time of rash onset and their dose cannot be increased<br>o Rash recurs at grade ≥ 3 |
| Grade 4 (e.g. severe bullous, blistering or exfoliating skin conditions)<br>(any % BSA associated with extensive superinfection, with intravenous antibiotics indicated; life-threatening consequences) | Permanently discontinue Vijoice. |
| *BSA: body surface area<br>[1] Grading according to CTCAE Version 5.0.<br>[2] Antihistamines administered prior to rash onset may decrease incidence and severity of rash. | |

*Diarrhoea or colitis*
In paediatric patients, consultation with a physician with experience in the treatment of gastrointestinal conditions should be considered.

**Table 5 Dose modification and management for diarrhoea or colitis**

| **Grade**[1] | **Recommendation for adult and paediatric patients** |
|---|---|
| Grade 1 | No Vijoice dose adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated. |
| Grade 2 | Interrupt Vijoice dose until improvement to grade ≤ 1, then resume Vijoice at the same dose level.<br>Initiate or intensify appropriate medical therapy and monitor as clinically indicated.<br>**Adult patients**[2]**:**<br>• For recurrent grade ≥ 2, interrupt Vijoice dose until improvement to grade ≤ 1, then resume Vijoice at the next lower dose level.<br>**Paediatric patients**[2]**:**<br>• For recurrent grade ≥ 2, interrupt Vijoice dose until improvement to grade ≤ 1, then resume Vijoice at 50 mg. |
| Grade 3 | Interrupt Vijoice dose until improvement to grade ≤ 1.<br>Initiate or intensify appropriate medical therapy and monitor as clinically indicated.<br>**Adult patients**[2,3]**:**<br>• Once improved to grade ≤ 1, then resume Vijoice at the next lower dose level.<br>**Paediatric patients**[2,3]**:**<br>• Once improved to grade ≤ 1, either resume Vijoice at 50 mg or permanently discontinue Vijoice.<br>• For recurrent grade ≥ 3, consider permanent discontinuation of Vijoice. |
| Grade 4 | Permanently discontinue Vijoice[3]. |

[1] Grading according to the CTCAE Version 5.0.
[2] For grade 2 and 3 colitis, consider additional treatment, such as steroids.
[3] For grade 3 and 4 diarrhoea, 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.

*Other toxicities*

**Table 6 Dose modification and management for other toxicities (excluding hyperglycaemia, rash, diarrhoea or colitis)**

| **Grade**[1] | **Recommendation for adult and paediatric patients** |
|---|---|
| Grade 1 or 2 | No Vijoice dose adjustment required. Initiate appropriate medical therapy and monitor as clinically indicated[2,3,4,5]. |
| Grade 3 | Interrupt Vijoice dose until improvement to grade ≤ 1.<br>**Adult patients[2,3]:**<br>• Once improved to grade ≤ 1, resume Vijoice at the next lower dose level.<br>**Paediatric patients[4,5]:**<br>• Once improved to grade ≤ 1, either resume Vijoice at 50 mg or permanently discontinue Vijoice.<br>• If ADR recurs at grade ≥ 3, consider permanent discontinuation of Vijoice.<br>• Consider consultation with a qualified physician with specific expertise in the field of the concerned ADR. |
| Grade 4 | Permanently discontinue Vijoice. |

[1] Grading according to CTCAE Version 5.0
[2] For grade 2 total bilirubin elevation in adult patients, interrupt Vijoice dose until improvement to grade ≤ 1. If improvement occurs in ≤ 14 days, resume at the same dose level. If improvement occurs in > 14 days, resume Vijoice at the next lower dose level.
[3] For grade 2 and 3 pancreatitis in adult patients, interrupt Vijoice dose until improvement to grade ≤ 1 and resume at next lower dose level. Only one dose reduction is permitted. If toxicity recurs, permanently discontinue Vijoice treatment.
[4] For grade 2 total bilirubin elevation in paediatric patients, interrupt Vijoice dose until improvement to grade ≤ 1. If improvement occurs in ≤ 14 days, resume at the same dose level. If improvement occurs in > 14 days resume Vijoice at 50 mg (in patients receiving 125 mg or 50 mg doses).
[5] For grade 2 and 3 pancreatitis in paediatric patients, interrupt Vijoice dose until improvement to grade ≤ 1 and resume Vijoice at 50 mg. If toxicity recurs, permanently discontinue Vijoice treatment.

*Special populations*

*Elderly*
No dose adjustment is required in patients aged 65 years or above (see section 5.2). Caution should be used in this population as no clinical data are available.

*Hepatic impairment*
Based on a hepatic impairment study in adult participants with normal or 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).

*Renal impairment*
Based on a population pharmacokinetic (PK) analysis in adult patients with cancer and adult and paediatric patients with PROS, no dose adjustment is necessary in patients with mild (eGFR 60 to < 90 ml/min/1.73 $m^2$) / (CLcr 60 to < 90 ml/min) or moderate (eGFR 30 to < 60 ml/min/1.73 $m^2$) renal impairment (see section 5.2). Caution should be used in patients with severe (eGFR ≤ 30 ml/min/1.73 $m^2$) renal impairment as there is no experience with alpelisib in this population.

*Paediatric population*
The safety and efficacy of Vijoice in children aged < 2 years have not been established (see section 5.1). No data are available.

Method of administration

Vijoice is for oral use. It should be taken immediately after food, at approximately the same time each day (see section 5.2).

The tablets should be swallowed whole (they should not be chewed or split prior to swallowing) or administered as an oral suspension in patients who are not able to swallow tablets (see section 6.6).

Vijoice tablets that are broken, cracked or otherwise damaged at the time of opening the blister pack should not be used.

For patients who are not able to swallow, Vijoice can be administered via a feeding tube. The film-coated tablets should be prepared as a suspension and administered via a 5-12 Fr diameter silicone or polyurethane nasogastric tube or via a 12-24 Fr diameter silicone gastric tube (see section 6.6).

*Alternative pharmaceutical form*
Vijoice is also available as 50 mg granules in sachet. Vijoice granules should only be used to achieve the 50 mg dose; multiple sachets or a partial sachet of granules should not be used.
Please refer to the Summary of Product Characteristics for Vijoice 50 mg granules in sachet.

## 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

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, have occurred in patients treated with Vijoice (see section 4.8). Vijoice should be permanently discontinued and should not be re-introduced in patients with serious hypersensitivity reactions. Appropriate treatment should be promptly initiated.

Severe cutaneous adverse reactions (SCARs)

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), erythema multiforme (EM), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS), have occurred in adult patients treated with alpelisib in the oncology setting and may occur in patients treated with Vijoice.

Treatment should not be initiated in patients with a history of SCARs.

Patients should be advised of the signs and symptoms of SCARs (e.g. a prodrome of fever, flu-like symptoms, mucosal lesions or progressive skin rash). If signs or symptoms of SCARs occur, Vijoice should be interrupted until the aetiology of the reaction has been determined. A consultation with a dermatologist is recommended.

If a SCAR is confirmed, Vijoice should be permanently discontinued. Vijoice should not be re-introduced in patients who have experienced previous SCARs. If a SCAR is not confirmed, Vijoice may require dose modifications, topical or systemic corticosteroids, or oral antihistamine treatment as described in Table 4 (see section 4.2).

Hyperglycaemia

Severe hyperglycaemia, in some cases associated with hyperglycaemic hyperosmolar nonketotic syndrome (HHNKS), has occurred in patients treated with Vijoice (see section 4.8). Fatal cases of ketoacidosis have occurred in patients treated with alpelisib in the oncology setting.

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 in the oncology setting.

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 FG monitoring is recommended in Table 7.

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

**Table 7 Schedule of FG monitoring**

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

The safety of Vijoice in patients with Type 1 and uncontrolled Type 2 diabetes has not been established. Patients with a history of diabetes mellitus may require intensified diabetic treatment and should be closely monitored.

Based on the severity of hyperglycaemia, Vijoice may require dose interruption, reduction or discontinuation as described in Table 3 (see section 4.2).

Pneumonitis

Pneumonitis, including serious cases of pneumonitis/acute interstitial lung disease, has occurred in adult patients treated with alpelisib in the oncology setting and may occur in patients treated with Vijoice. 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, Vijoice 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. Vijoice should be permanently discontinued in all patients with confirmed pneumonitis.

Diarrhoea or colitis

Severe diarrhoea and its clinical consequences, such as dehydration and acute kidney injury, and colitis have occurred in adult patients during treatment with alpelisib in the oncology setting and may occur in patients treated with Vijoice.

Patients should be monitored for diarrhoea and other symptoms of colitis, such as abdominal pain and mucus or blood in stools. Based on the severity of the diarrhoea or colitis, Vijoice may require dose interruption, reduction or discontinuation as described in Table 5 (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 Vijoice. Patients with colitis may require additional treatment, such as enteric-acting and/or systemic steroids.

Women of childbearing potential/Contraception in males and females

Women of childbearing potential should use effective contraception during treatment with alpelisib and for at least 1 week after stopping treatment with alpelisib. As it is currently unknown whether alpelisib may reduce the effectiveness of systemically acting hormonal contraceptives, women using hormonal contraceptives should also use a barrier method (see section 4.6).

Male patients with sexual partners who are pregnant, possibly pregnant or who could become pregnant should use condoms during sexual intercourse while taking alpelisib and for at least 1 week after stopping treatment with alpelisib (see section 4.6).

Paediatric population

The long-term effects of Vijoice on growth and development in paediatric patients 2 to < 18 years of age with PROS are not known.

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. ciclosporin).

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 recommended in the oncology setting 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 PK 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 rifampicin (a strong CYP3A4 inducer) for 7 days followed by co-administration with a single oral dose of alpelisib 300 mg on day 8, decreased alpelisib $C_{max}$ by 38% and AUC by 57% in healthy adults (N=25). Co-administration of rifampicin 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, rifampicin, St. John's wort [*Hypericum perforatum*]) 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) or CYP2C19 substrates (e.g. omeprazole). For CYP2B6 substrates (e.g. bupropion), 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 PK 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 $AUC_{inf}$ and $C_{max}$ 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.

Paediatric population

Interaction studies have only been performed in adult healthy volunteers and cancer patients (see section 5.2).

## 4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Women of childbearing potential should use effective contraception during treatment and for at least 1 week after stopping treatment. As it is currently unknown whether alpelisib may reduce the effectiveness of systemically acting hormonal contraceptives, women using hormonal contraceptives should also use a barrier method.

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

Pregnancy

There are no data from the use of alpelisib in pregnant women. However, the mechanism of action of alpelisib suggests a risk of congenital malformation. Studies in animals have shown reproductive toxicity (see section 5.3).

Vijoice should not be used during pregnancy unless the clinical condition of the woman requires treatment with alpelisib.

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

Breast-feeding

It is not known if alpelisib is excreted in human 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 Vijoice.

Fertility

There are no clinical data 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

Vijoice has minor influence on the ability to drive and use machines. Fatigue and blurred vision have occurred in adult patients treated with alpelisib in the oncology setting and may occur in patients treated with Vijoice. Patients should be advised to be cautious when driving or using machines in case they experience fatigue or blurred vision during treatment.

## 4.8 Undesirable effects

Summary of the safety profile

In adult patients enrolled in the retrospective chart review studies, the most common ADRs (all grades) were hyperglycaemia (27.8%), diarrhoea (27.8%), headache (22.2%), stomatitis (16.7%), alopecia (16.7%), dermatitis (16.7%), dry skin (16.7%) and nausea (11.1%). Grade 3-4 ADRs were decreased blood phosphate (11.1%), dehydration (5.6%), increased blood creatinine (5.6%) and increased glucose (5.6%). Serious ADRs (all grades) were dehydration (5.6%) and hyperglycaemia (5.6%). The ADR alopecia (all grades) led to dose reduction (5.6%). ADRs leading to dose interruptions (all grades) were vomiting (5.6%), nausea (5.6%), mucosal dryness (5.6%) and headache (5.6%).

In paediatric patients enrolled in the retrospective chart review studies, the most common ADRs (all grades) were stomatitis (23.1%) and diarrhoea (12.8%). No grade 3-4 ADRs were reported. Serious ADRs (all grades) were vomiting (2.6%) and dehydration (2.6%). ADRs leading to dose interruptions (all grades) were vomiting (2.6%) and dehydration (2.6%).

The most common ADRs in paediatric patients enrolled in the phase II interventional clinical study (all grades) were abdominal pain (33.7%), headache (30.3%), diarrhoea (28.1%) and vomiting (24.7%). Grade 3-4 ADRs were increased lipase (3.4%), decreased appetite (1.1%) and diarrhoea (1.1%). Serious ADRs (all grades) were diarrhoea (1.1%), headache (1.1%) and rash (1.1%). Dose interruptions due to an ADR occurred in 9.0% of patients; the most common ADRs which required dose interruption were vomiting (2.2%), rash (2.2%) and diarrhoea (2.2%). ADRs leading to permanent discontinuation (all grades) were alopecia (2.2%) and decreased appetite (1.1%).

Tabulated list of adverse reactions

The list of adverse reactions is based on data from retrospective chart review studies in 18 adult and 39 paediatric patients, who were treated with alpelisib in a compassionate use programme with an initial starting dose of 250 mg in adult patients and 50 mg in paediatric patients. The median duration of exposure was 42 months (range: 3.4 to 74.8 months). The list of adverse reactions is also based on data from a phase II interventional clinical study in 89 paediatric patients (including 82 patients 6 to < 18 years of age and 7 patients 2 to < 6 years of age), who were treated with alpelisib with an initial starting dose of 50 mg, for a median duration of exposure of approximately 30 months. 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 ADR 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 (frequency cannot be estimated from the available data).

**Table 8 ADRs observed in patients who received Vijoice**

| **Adverse drug reactions** | **EPIK-P1 and EPIK-P3* retrospective period pooled data** | | **EPIK-P2[1]** | **Highest frequency category across adult and paediatric patients** |
|---|---|---|---|---|
| | **Adult patients N = 18** | **Paediatric patients N = 39** | **Paediatric patients N = 89** | |
| | **All grades n (%)** | **All grades n (%)** | **All grades n (%)** | |
| **Immune system disorders** | | | | |
| Hypersensitivity[#] | - | - | - | Common |
| **Metabolism and nutrition disorders** | | | | |
| Hyperglycaemia[2] | 5 (27.8) | 3 (7.7) | 6 (6.7) | Very common |
| Decreased appetite | 1 (5.6) | 0 | 10 (11.2) | Very common |
| Dehydration | 1 (5.6) | 1 (2.6) | - | Common |
| **Nervous system disorders** | | | | |
| Headache | 4 (22.2) | 0 | 27 (30.3) | Very common |

| | | | | |
|---|---|---|---|---|
| **Gastrointestinal disorders** | | | | |
| Diarrhoea | 5 (27.8) | 5 (12.8) | 25 (28.1) | Very common |
| Vomiting | 1 (5.6) | 1 (2.6) | 22 (24.7) | Very common |
| Stomatitis | 3 (16.7) | 9 (23.1) | 17 (19.1) | Very common |
| Nausea | 2 (11.1) | 1 (2.6) | 15 (16.9) | Very common |
| Abdominal pain | 1 (5.6) | 0 | 30 (33.7) | Very common |
| **Skin and subcutaneous tissue disorders** | | | | |
| Rash[3] | - | - | 10 (11.2) | Very common |
| Dermatitis[4] | 3 (16.7) | 1 (2.6) | 12 (13.5) | Very common |
| Dry skin | 3 (16.7) | 2 (5.1) | 3 (3.4) | Very common |
| Alopecia | 3 (16.7) | 0 | 11 (12.4) | Very common |
| Acne[5] | 1 (5.6) | 0 | 4 (4.5) | Common |
| Pruritus | 0 | 1 (2.6) | 2 (2.2) | Common |
| **General disorders and administration site conditions** | | | | |
| Mucosal dryness[6] | 1 (5.6) | 1 (2.6) | 2 (2.2) | Common |
| **Investigations[7]** | | | | |
| Blood phosphate decreased | 11 (61.1) | 27 (69.2) | 2 (2.2) | Very common |
| Blood calcium decreased[8,9] | 12 (66.7) | 25 (64.1) | 17 (19.1) | Very common |
| Blood creatinine increased | 2 (11.1) | 19 (48.7) | 22 (24.7) | Very common |
| Glycosylated haemoglobin increased[9] | 12 (66.7) | 11 (28.2) | 5 (5.6) | Very common |
| Glucose increased | 4 (22.3) | 8 (20.5) | 27 (30.3) | Very common |
| Lipase increased[10] | - | - | 22 (24.7) | Very common |

Grading according to CTCAE Version 4.03.

[1] EPIK-P2 data refers to the alpelisib-treatment period which includes paediatric patients who received at least one dose of alpelisib, including patients who switched from placebo to alpelisib after the 16-week placebo-controlled period.

[2] Hyperglycaemia: including hyperglycaemia, glycosylated haemoglobin increased and blood glucose increased.

[3] Rash: including rash, rash erythematous, rash macular, rash maculo-papular and rash papular. Rash was reported in 13.8% of adult patients treated at the non-recommended alpelisib dose of 125 mg in EPIK-P2.

[4] Dermatitis: including dermatitis, drug eruption and eczema.

[5] Acne: including acne and dermatitis acneiform.

[6] Mucosal dryness: including dry mouth and vulvovaginal dryness.

[7] Frequencies of laboratory terms reflect the proportion of patients who experienced worst-post-baseline laboratory measurements.

[8] Calcium corrected values were used for this parameter.

[9] No CTCAE grading available.

[10] Lipase increased was reported in 23.8% of adult patients treated at the non-recommended alpelisib dose of 125 mg in EPIK-P2.

* Forty patients in EPIK-P3 continued to be treated with alpelisib in a prospective period. Additional safety data from the 3-year analysis of the EPIK-P3 prospective period, with an additional median duration of exposure of 39.1 months (range: 17-42 months) did not show additional ADRs or clinically relevant laboratory abnormalities.

\# Adverse drug reactions reported outside of the EPIK-P1/EPIK-P2/EPIK-P3 safety population considered. The frequency category is estimated from the EPIK-P2 study as per the SmPC Guideline 2009 section 4.8, *Adverse reactions from spontaneous reporting.*

Description of selected adverse drug reactions

*Gastrointestinal adverse reactions*

In patients enrolled in the retrospective chart review studies who experienced at least one event of diarrhoea (10/57), the median time to onset of any grade diarrhoea was 61.3 weeks (range: 3.3 to 123.1 weeks) and 12.4 weeks (range: 2.4 to 133.4 weeks) in adult and paediatric patients, respectively. Grade 2 diarrhoea (maximum grade) was reported in 2.6% of paediatric patients. Antidiarrhoeal medicinal products were used in 11.1% of adult patients to manage symptoms (see section 4.2).

In paediatric patients enrolled in the phase II interventional clinical study who experienced at least one event of diarrhoea (25/89), the median time to onset of any grade diarrhoea was 14.1 weeks (range: 0.1 to 71.1 weeks). Grade 2 and grade 3 diarrhoea were reported in 3.4% and 1.1% patients, respectively. The maximum grade was grade 3. Antidiarrhoeal medicinal products were used in 13.5% of paediatric patients to manage symptoms (see section 4.2).

*Alopecia*
In adult patients enrolled in the retrospective chart review studies who experienced at least one event of alopecia (3/18), the median time to onset of any grade alopecia was 31.6 weeks (range: 13.0 to 34.0 weeks). In adult patients enrolled in the phase II interventional clinical study treated at the non-recommended alpelisib dose of 125 mg, alopecia was reported in 36.3% patients.

In paediatric patients enrolled in the phase II interventional clinical study who experienced at least one event of alopecia (11/89), the median time to onset of any grade alopecia was 40.4 weeks (range: 3.6 to 110.6 weeks).

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 national reporting system listed in Appendix V.

### 4.9 Overdose

Symptoms

The adverse reactions associated with overdose in the oncology setting have been consistent with the safety profile of alpelisib 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 Vijoice.

## 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 phosphatidylinositol-3-kinase (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.

Somatic activating mutations in PIK3CA, leading to a mosaic genotype, have been found to induce a spectrum of overgrowths and malformations comprising a wide group of clinically recognisable disorders known as PROS.

Clinical efficacy and safety

*EPIK-P1*
Vijoice was evaluated in a retrospective chart review study in 57 patients aged 2 years and older with PROS who received Vijoice as part of a compassionate use programme. Eligible patients had clinical manifestations of PROS that were assessed by the treating physician as severe or life-threatening and necessitating treatment and had documented evidence of mutation in the PIK3CA gene.

EPIK-P1 included 18 adult patients in whom the recommended Vijoice dose was 250 mg. The study also included 39 paediatric patients (2 to < 18 years of age), of whom 35 received the recommended Vijoice starting dose of 50 mg. Twenty-five percent (25.6%) of paediatric patients required at least one Vijoice dose increase during the study.

At enrolment, patients had a median age of 14 years (range: 2 to 50 years). 19.3% of patients were 2 to < 6 years of age, 21.1% were 6 to < 12 years of age, 28.1% were 12 to < 18 years of age, and 31.6% were ≥ 18 years of age; 57.9% were female. Of the patients enrolled, 93.0% had congenital overgrowth and 7.0% had early childhood-onset of overgrowth. Patients had heterogeneous manifestations of PROS including congenital, lipomatous overgrowth, vascular malformations, epidermal nevi and scoliosis/skeletal/spinal anomalies syndrome (CLOVES; 73.7%), megalencephaly-capillary malformation polymicrogyria (MCAP; 14.0%), Klippel-Trenaunay syndrome (KTS; 8.8%), facial infiltrating lipomatosis (FIL; 5.3%), megalencephaly-capillary malformation (MCM; 1.8%), and other (3.5%). Seven percent (7.0%) of patients had concurrent manifestations of CLOVES and MCAP.

The median duration of exposure to Vijoice was 18.1 months (range: 3.4 to 49.9 months) in all patients, 19.2 months (range: 8 to 49.9 months) in adult patients, and 18 months (range: 3.4 to 41.8 months) in paediatric patients. Seventy-nine percent (78.9%) of all patients, 83.3% of adult patients and 76.9% of paediatric patients received Vijoice for more than 12 months.

The main efficacy endpoint for the study was the proportion of patients with radiological response at week 24 as determined by independent central radiology review (ICRR), defined by achieving ≥ 20% reduction from baseline in the sum of measurable target lesion volume (1 to 3 lesions), provided that none of the individual target lesions had ≥ 20% increase from baseline and in the absence of progression of non-target lesions and without new lesions.

Additional efficacy endpoints included duration of response (DOR), defined as the time from the first documented response to the date of the first documented disease progression or death due to any cause.

Efficacy results for adult, paediatric and all patients are presented in Table 9. The primary analysis was performed on a subset of the efficacy population (N=37), comprising 32 patients without a missing response at week 24 (complete case analysis).

**Table 9 Summary of efficacy results in EPIK-P1**

| Efficacy parameters | Adult patients | Paediatric patients | All patients |
|---|---|---|---|
| **Primary analysis[1, 2]** | | | |
| Responders at week 24, % (n/N)<br>95% CI | 55.6 (5/9)<br>21.2, 86.3 | 30.4 (7/23)<br>13.2, 52.9 | 37.5 (12/32)<br>21.1, 56.3 |
| **Duration of response (DOR)** | | | |
| Median in months (range) | NR (2.8+, 29.7+) | NR (0.03+, 42.9+) | NR (0.03+, 42.9+) |
| % ≥ 6 months | 40 | 71 | 58 |
| % ≥ 12 months | 20 | 71 | 50 |

NR: Not reached
+: censored observation
[1] At baseline, 81% of patients had 1 target lesion, 16% had 2 target lesions, and 3% had 3 target lesions.
[2] As determined by ICRR.

Two paediatric patients required surgery due to clinical disease progression (not radiologically confirmed) after week 24. No patients developed a new lesion while receiving Vijoice during the study. At the end of the study, 91.2% of all patients (88.9% of adult patients and 92.3% of paediatric patients) were still receiving Vijoice.

*EPIK-P3*
EPIK-P3 is a phase II multicentre, open-label, interventional study (preceded by a retrospective non-interventional period) in adult and paediatric patients with severe or life-threatening complications of PROS who were treated with Vijoice as part of a compassionate use programme, participated in EPIK-P1, and continued to receive treatment with alpelisib after the end of EPIK-P1. This was mainly a safety study which included some efficacy outcomes as secondary endpoints. The median duration of exposure to Vijoice was 6.7 years (range: 0.4 to 9.5).

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Vijoice in one or more subsets of the paediatric population in the treatment of PROS as per paediatric investigation plan (PIP) P/0412/2022, for the granted indication (see section 4.2 for information on paediatric use).

Conditional approval

This medicinal product has been authorised under a so-called 'conditional approval' scheme. This means that further evidence on this medicinal product is awaited.
The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

## 5.2 Pharmacokinetic properties

The pharmacokinetics of alpelisib film-coated tablets have been studied in patients 2 years of age and older with PROS under an oral dosing regimen ranging from 50 mg to 250 mg daily under fed conditions.

Absorption

Following oral administration of alpelisib with food, the median time to reach peak plasma concentration ($T_{max}$) was 3.0 hours. Food affects alpelisib absorption at high doses and Vijoice should be taken immediately after food at approximately the same time each day (see sections 4.2 and 6.6).

*Relative bioavailability*
A crushed film-coated tablet administered as an oral suspension in water has not been demonstrated to be bioequivalent to an intact film-coated tablet. However, in a comparative study of relative bioavailability at a dose of 300 mg recommended in the oncology setting, the crushed suspension showed similar exposure to the intact tablets ($C_{max}$ ratio 1.00; AUC ratio 0.96), indicating no clinically meaningful differences in exposure.

Alpelisib 50 mg film-coated tablets are bioequivalent to alpelisib 50 mg granules in the fed state following a LFLC meal, indicating there is no clinically relevant difference in the rate and extent of absorption of alpelisib from these two pharmaceutical forms when administered with food.

*Food effect*
Alpelisib absorption is affected by food at high doses. In healthy adult volunteers after a single 300 mg oral dose of alpelisib recommended in the oncology setting, compared to the fasted state, a high-fat high-calorie (HFHC) meal increased $AUC_{inf}$ by 73% and $C_{max}$ by 84%, and a LFLC meal increased $AUC_{inf}$ by 77% and $C_{max}$ by 145%. The increase in gastrointestinal solubility by bile, secreted in response to food intake independent of the fat or calorie content of the meal, is the potential cause of the food effect.

No clinically relevant food effect on alpelisib pharmacokinetics was observed after a single 50 mg oral dose of alpelisib as granules taken with a LFLC meal as compared to fasted administration (please refer to the Summary of Product Characteristics for Vijoice 50 mg granules in sachet).

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. Alpelisib steady-state distribution volume following oral dosing (Vss/F) was estimated by population PK modelling to be approximately 136 litres in a reference patient with PROS (female, normal renal function, 61 kg).

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

The half-life of alpelisib was estimated by population PK modelling to be 7.7 hours for a reference patient with PROS (female, normal renal function, 61 kg).

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 [$^{14}$C]-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 significant PK interaction. The data for the 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 rifampicin, a strong CYP3A4 inducer, confirmed that there is a clinically significant PK 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 ruled out 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 the 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 and gender*
Population PK analyses based on data from adult cancer patients and adult and paediatric patients with PROS indicated that the effects of age and gender on the systemic exposure of alpelisib are not predicted to require dose adjustment.

*Effect of body weight*
Population PK analyses based on data from adult patients with cancer and adult and paediatric patients with PROS indicate that alpelisib apparent clearance and volume of distribution increase with body weight. As a result, lower body weight is associated with higher systemic exposure, whereas higher body weight is associated with lower exposure for the same dose. Based on the available data, the magnitude of this effect is not considered clinically relevant and does not warrant dose adjustment in adult patients with PROS.

*Paediatric population (below 18 years)*
Observed steady-state PK data in paediatric patients with PROS indicate a clear effect of body weight on alpelisib exposure. In paediatric patients 6 to < 18 years old treated with alpelisib 50 mg once daily, mean steady-state $AUC_{24h}$ decreased from approximately 7 250 ng·h/ml in patients < 30 kg to 2 540 ng·h/ml in patients ≥ 60 kg (≈65% decrease), while mean $C_{max,ss}$ decreased from about 747 ng/ml to 300 ng/ml (≈60% decrease).

The pharmacokinetics of alpelisib in paediatric patients below the age of 2 years have not been established.

*Elderly*
Based on a population PK analysis in patients with cancer and patients with PROS that included 174 patients with cancer aged 65 years or older, with a maximum age of 87 years, no clinically relevant effect of age on the systemic exposure of alpelisib is predicted. No PK data are available for elderly patients with PROS.

*Race/Ethnicity*
The population PK analysis of data from adult patients with cancer and adult and paediatric patients with PROS that included 542 White patients, 107 Asian patients, 12 Black or African American patients, 21 patients of other race and 15 patients of unknown race indicates no clinically relevant effect of race on the systemic exposure of alpelisib.

The population PK analysis of data from adult patients with cancer and adult and pediatric patients with PROS that included 105 patients of Hispanic or Latino ethnicity, 523 patients not of Hispanic or Latino ethnicity and 69 patients of unknown ethnicity indicates no clinically relevant effect of ethnicity on the systemic exposure of alpelisib.

*Hepatic impairment*
A PK study in adult participants with normal or impaired hepatic function indicated that moderate and severe hepatic impairment have no clinically meaningful effect on the exposure of alpelisib (see section 4.2). In participants with severe hepatic impairment, peak alpelisib exposure was comparable to that in healthy participants ($C_{max}$ GMR [geometric mean ratio]=1.00) and total alpelisib exposure was approximately 26% higher ($AUC_{last}$ GMR=1.26, $AUC_{inf}$ GMR=1.25).

*Renal impairment*
The population PK analysis of data from adult patients with cancer and adult and paediatric patients with PROS that included 433 patients with normal renal function (eGFR ≥ 90 ml/min/1.73 $m^2$) / (CLcr ≥ 90 ml/min), 198 patients with mild renal impairment (eGFR 60 to < 90 ml/min/1.73 $m^2$) / (CLcr 60 to < 90 ml/min), and 66 patients with moderate renal impairment (eGFR 30 to < 60 ml/min/1.73 $m^2$), indicates that mild and moderate renal impairment have no effect on the exposure to alpelisib that would require dose adjustment. No PK data are available for patients with severe renal impairment (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. In 4- or 13-week repeated dose toxicity studies initiated in 8- to 10-week-old rats, degenerative effects were seen in the incisors and growth plates of bones. At the no observed adverse effect level (NOAEL) in 4-week repeated dose toxicity studies, exposure levels were 1.3 and 2.5 times the estimated exposure (AUC) in adult and paediatric patients at the recommended dose of 250 and 50 mg/day, respectively. In 13-week repeated dose toxicity studies, exposure levels were 0.2 and 0.3 times the estimated exposure (AUC) in adult and paediatric patients at the recommended dose of 250 and 50 mg/day, respectively. Effects on bone marrow, growth plates of bones, incisors 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. In repeated dose toxicity studies, adverse events were observed at clinically relevant doses based on AUC.

Cardiovascular safety pharmacology

*In vitro* inhibition of hERG channels ($IC_{50}$ of 9.4 µM, corresponding to approximately 4.2 µg/ml free drug) was shown at concentrations ~21-fold and ~31-fold higher than the estimated maximum (peak) plasma concentration of unbound alpelisib in humans at the recommended maximum alpelisib adult and paediatric doses of 250 mg/day (adult) or 50 mg/day (ages 2 to 5 years), respectively. No relevant electrophysiological effect was seen in dogs.

Carcinogenicity and genotoxicity

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 0.3 times the clinical exposure in patients at the highest recommended dose of 250 mg/day based on AUC).

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 2.6 and 5.0 times the estimated exposure (AUC) in humans at the recommended alpelisib dose of 250 or 50 mg/day, respectively.

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 at exposures below the average exposure expected for adult patients treated with 250 mg/day alpelisib, 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 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 two times the recommended adult dose of 250 mg/day. In males, fertility and reproductive performance, including sperm count and motility parameters, were unaffected at exposure levels equivalent to the estimated exposure (AUC) in humans at the recommended adult dose of 250 mg/day. However, at exposure levels (AUC) at or below the adult human dose of 250 mg/day, 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.

Juvenile animal studies

In a 9-week rat juvenile toxicity study initiated in 7-day-old animals, the NOAEL of 6 mg/kg/day resulted in lower exposure levels (AUC) than in paediatric patients at the recommended dose of 50 mg/day. At the dose of 20 mg/kg/day (2.2 to 4.2 times the estimated exposure [AUC] in paediatric patients at the recommended dose of 50 mg/day), adverse and non-reversible kidney effects were observed and included minimal to moderate increased vascular/perivascular extracellular matrix deposition in small vessels and minimal to moderate tubular degeneration/regeneration in the renal papilla and medulla. Correlating minimally higher urea nitrogen concentrations were observed at the end of the recovery period. These effects are not anticipated to be clinically relevant for patients aged 2 years and older based on interspecies comparison of postnatal renal development.

In addition, lower body weights, reduced body weight gains, delayed sexual maturation in the males and reduced femur lengths were observed at 20 mg/kg/day. No histopathological findings in the bone (including the growth plate) were reported.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Tablet core

Cellulose microcrystalline (E460)
Mannitol (E421)
Sodium starch glycolate
Hypromellose (E464)
Magnesium stearate (E470b)

Film coating

Hypromellose (E464)
Iron oxide, yellow (E172)
Iron oxide, red (E172), applicable only to 50 mg and 200 mg strengths
Titanium dioxide (E171)
Macrogol (E1521)
Talc (E553b)

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years.

### 6.4 Special precautions for storage

This medicinal 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.

Vijoice 50 mg film-coated tablets

Packs containing 28 film-coated tablets.

Vijoice 125 mg film-coated tablets

Packs containing 28 film-coated tablets.

Vijoice 50 mg and 200 mg film-coated tablets

Packs containing 56 film-coated tablets (28 of 50 mg and 28 of 200 mg).

Not all pack sizes may be marketed.

## 6.6 Special precautions for disposal and other handling

Instructions for preparation and administration of Vijoice as an oral suspension

For patients who are not able to swallow tablets, Vijoice may be prepared as an oral suspension and taken with food (see section 4.2):

- Place the Vijoice tablet(s) in a cup containing 50 to 150 ml water and let stand for approximately 5 minutes before crushing. Make the suspension with water only.
- Crush the tablet(s) with a spoon and stir until an oral suspension is obtained.
- Administer the oral suspension immediately after preparation.
- After administration of the oral suspension, add approximately 20 to 50 ml water to the same cup. Stir with the same spoon to re-suspend any remaining particles and administer the entire contents of the cup. If particles remain, repeat this step.
- Discard the oral suspension if it is not administered within 60 minutes after preparation.

Instructions for preparation and administration of Vijoice via feeding tube

For patients who are not able to swallow, Vijoice can be administered via a feeding tube. Vijoice film-coated tablets should be prepared as a suspension and administered via a 5-12 Fr diameter silicone or polyurethane nasogastric tube (maximum tube length evaluated: 160 cm) or via a 12-24 Fr diameter silicone gastric tube (maximum tube length evaluated: 3.5 cm) (see section 4.2).

Vijoice tablets should be prepared as a suspension as follows:

- Place the Vijoice tablet(s) in a cup containing approximately 40 ml water and let stand for approximately 5 minutes before crushing. Make the suspension with water only.
- Crush the tablet(s) with a spoon and stir until a suspension is obtained.
- Immediately after preparation, withdraw the suspension from the cup into a syringe and administer it via the feeding tube.
- After administration of the suspension via the feeding tube, add approximately 40 ml water to the same cup. Stir the liquid with the same spoon to re-suspend any remaining particles. Withdraw the contents of the cup into the same syringe and administer it via the feeding tube. If particles remain, repeat this step.
- Discard the suspension if it is not administered within 60 minutes after preparation.

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

## 7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/26/2042/001-003

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

## 1. NAME OF THE MEDICINAL PRODUCT

Vijoice 50 mg granules in sachet

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet contains 50 mg alpelisib.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Granules in sachet (granules).

White to almost white free-flowing mixture of powder and granules.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Vijoice is indicated for the treatment of adult and paediatric patients aged 2 years and older with severe or life-threatening manifestations of PIK3CA-related overgrowth spectrum (PROS) who require systemic therapy.

### 4.2 Posology and method of administration

Treatment with Vijoice should be initiated by a physician with experience in the management of PROS.

Posology

*Adults*
The recommended dose in adult patients is 250 mg, taken once daily. Treatment should be discontinued if disease progression, worsening of PROS-related symptoms, or unacceptable toxicity occurs, as assessed by the treating physician.

*Paediatric population (2 to < 18 years of age)*
The recommended initial dose in paediatric patients is 50 mg, taken once daily. Treatment should be discontinued if disease progression, worsening of PROS-related symptoms, or unacceptable toxicity occurs, as assessed by the treating physician.

In paediatric patients ≥ 6 years old, a dose increase to 125 mg once daily should be considered for response optimisation (clinical/radiological) after 24 weeks of treatment at 50 mg once daily. When a paediatric patient turns 18 years old, a gradual dose increase up to 250 mg should be considered. Recommended dose increases by age group are listed in Table 1.

**Table 1 Recommended dose levels for paediatric population (2 to < 18 years of age)**

| Patient age (years) | Initial dose | Dose increase |
|---|---|---|
| 2 to < 6 | 50 mg once daily | Not applicable |
| 6 to < 18 | 50 mg once daily | 125 mg once daily |

The 50 mg granules in sachet pharmaceutical form should only be used to achieve a 50 mg dose. In adult patients, the 50 mg granules in sachet pharmaceutical form is only to be used in case of dose reduction (see Table 2). Multiple sachets of 50 mg granules should not be combined to achieve a dose of 125 mg, 200 mg or 250 mg.

*Missed dose*
If a dose is missed, it can be taken immediately after food within 9 hours after the time it is usually taken. After more than 9 hours, the dose should be skipped for that day. The next day, the dose should be taken at the usual time.

*Vomiting*
If the patient vomits after taking the dose, the patient should not take an additional dose on that day and should resume the dosing schedule the next day at the usual time.

*Dose modifications*
Management of severe or intolerable adverse drug reactions (ADRs) may require temporary dose interruption, reduction and/or discontinuation of Vijoice.

The recommended Vijoice dose reductions for ADRs in the adult and paediatric populations are listed in Table 2.

**Table 2 Vijoice dose reduction recommendations for ADRs in adult and paediatric patients**

| Action | Vijoice dose prior to dose reduction | Reduced Vijoice dose |
|---|---|---|
| **Adult patients** | | |
| First dose reduction | 250 mg once daily | 125 mg once daily |
| Second dose reduction | 125 mg once daily | 50 mg once daily |
| **Paediatric patients** | | |
| Dose reduction | 125 mg once daily | 50 mg once daily |
| | 50 mg once daily | Not applicable |

Vijoice should be discontinued in adults or paediatric patients who cannot tolerate 50 mg daily.

Tables 3 to 6 summarise the recommendations for dose interruption, reduction or discontinuation of Vijoice 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 3 Dose modification and management for hyperglycaemia**

| FG values[1] | Recommendation for adult and paediatric patients |
|---|---|
| **Dose modification and management should only be based on FG (plasma/blood) values.** | |
| Grade 1<br>> ULN*-160 mg/dl or<br>> ULN-8.9 mmol/l | No Vijoice dose adjustment required.<br>Initiate or intensify oral antidiabetic treatment[2]. |
| Grade 2<br>> 160-250 mg/dl or<br>> 8.9-13.9 mmol/l | No Vijoice dose adjustment required.<br>Initiate or intensify oral antidiabetic treatment[2].<br>**Adult patients:**<br>• 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 Vijoice dose by 1 dose level, and follow FG-value-specific recommendations.<br>**Paediatric patients:**<br>• If FG does not decrease to ≤ 160 mg/dl or 8.9 mmol/l within 21 days under appropriate oral antidiabetic treatment[2,3], interrupt Vijoice until improvement to grade ≤ 1, then resume Vijoice at 50 mg, and follow FG-value-specific recommendations. |
| Grade 3<br>> 250-500 mg/dl or<br>> 13.9-27.8 mmol/l | Interrupt Vijoice.<br>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.<br>Administer intravenous hydration and consider appropriate treatment (e.g. intervention for electrolyte / ketoacidosis / hyperosmolar disturbances).<br>**Adult patients:**<br>• If FG decreases to ≤ 160 mg/dl or 8.9 mmol/l within 3 to 5 days under appropriate antidiabetic treatment, resume Vijoice at the next lower dose level.<br>• 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.<br>• 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 Vijoice treatment.<br>**Paediatric patients:**<br>• If FG decreases to ≤ 160 mg/dl or 8.9 mmol/l within 3 to 5 days under appropriate antidiabetic treatment, resume Vijoice at 50 mg.<br>• 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 to determine if treatment with Vijoice should be resumed or permanently discontinued.<br>• 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 Vijoice.<br>• If hyperglycaemia recurs at grade ≥ 3, consider permanent discontinuation of Vijoice. |

| | |
|---|---|
| Grade 4<br>> 500 mg/dl or<br>> 27.8 mmol/l | Interrupt Vijoice.<br>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 FG within 24 hours and as clinically indicated.<br>• If FG decreases to ≤ 500 mg/dl or ≤ 27.8 mmol/l, follow FG-value-specific recommendations for grade 3.<br>• If FG is confirmed at > 500 mg/dl or > 27.8 mmol/l, permanently discontinue Vijoice treatment. |

*ULN: upper limit of normal

[1] Fasting glucose (FG) 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 in patients ≥ 10 years or SGLT2 inhibitors or insulin sensitisers (such as thiazolidinediones or dipeptidyl peptidase-4 inhibitors) in adult patients, should be initiated and the recommendations for dosing and dose titration included in the respective prescribing information should be reviewed together with local diabetic treatment guidelines.

[3] As recommended in the compassionate use programme, 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 the interruption of Vijoice.

*Rash*

Oral antihistamine administration may be considered prophylactically, at the time of initiation of treatment with Vijoice. 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, Vijoice may require dose interruption, reduction or discontinuation as described in Table 4. If the diagnosis is determined to be a severe cutaneous adverse reaction (SCAR), Vijoice should be permanently discontinued (see section 4.4).

**Table 4 Dose modification and management for rash**

| **Grade[1]** | **Recommendation for adult and paediatric patients[2]** |
|---|---|
| All grades | Consultation with a dermatologist should always be considered. |
| Grade 1<br>(< 10% BSA* with active skin toxicity) | No Vijoice dose adjustment required.<br>Initiate topical corticosteroid treatment.<br>Consider adding oral antihistamine treatment to manage symptoms.<br>If active rash is not improved within 28 days of appropriate treatment, add a low-dose systemic corticosteroid. |
| Grade 2<br>(10-30% BSA with active skin toxicity) | No Vijoice dose adjustment required.<br>Initiate or intensify topical corticosteroid and oral antihistamine treatment.<br>Consider low-dose systemic corticosteroid treatment.<br>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)<br>(> 30% BSA with active skin toxicity) | Interrupt Vijoice and initiate or intensify topical/systemic corticosteroid and oral antihistamine treatment.<br>**Adult patients:**<br>• Once rash improves to grade ≤ 1, resume Vijoice at next lower dose level.<br>**Paediatric patients:**<br>• Once rash improves to grade ≤ 1, either resume Vijoice at 50 mg while continuing oral antihistamine treatment or permanently discontinue Vijoice.<br>• Permanently discontinue Vijoice if:<br>o Antihistamines were ongoing at the time of rash onset and their dose cannot be increased<br>o Rash recurs at grade ≥ 3 |
| Grade 4 (e.g. severe bullous, blistering or exfoliating skin conditions)<br>(any % BSA associated with extensive superinfection, with intravenous antibiotics indicated; life-threatening consequences) | Permanently discontinue Vijoice. |
| *BSA: body surface area<br>[1] Grading according to CTCAE Version 5.0.<br>[2] Antihistamines administered prior to rash onset may decrease incidence and severity of rash. | |

*Diarrhoea or colitis*
In paediatric patients, consultation with a physician with experience in the treatment of gastrointestinal conditions should be considered.

**Table 5 Dose modification and management for diarrhoea or colitis**

| **Grade**[1] | **Recommendation for adult and paediatric patients** |
|---|---|
| Grade 1 | No Vijoice dose adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated. |
| Grade 2 | Interrupt Vijoice dose until improvement to grade ≤ 1, then resume Vijoice at the same dose level.<br>Initiate or intensify appropriate medical therapy and monitor as clinically indicated.<br>**Adult patients**[2]**:**<br>• For recurrent grade ≥ 2, interrupt Vijoice dose until improvement to grade ≤ 1, then resume Vijoice at the next lower dose level.<br>**Paediatric patients**[2]**:**<br>• For recurrent grade ≥ 2, interrupt Vijoice dose until improvement to grade ≤ 1, then resume Vijoice at 50 mg. |
| Grade 3 | Interrupt Vijoice dose until improvement to grade ≤ 1.<br>Initiate or intensify appropriate medical therapy and monitor as clinically indicated.<br>**Adult patients**[2,3]**:**<br>• Once improved to grade ≤ 1, then resume Vijoice at the next lower dose level.<br>**Paediatric patients**[2,3]**:**<br>• Once improved to grade ≤ 1, either resume Vijoice at 50 mg or permanently discontinue Vijoice.<br>• For recurrent grade ≥ 3, consider permanent discontinuation of Vijoice. |
| Grade 4 | Permanently discontinue Vijoice[3]. |

[1] Grading according to the CTCAE Version 5.0.
[2] For grade 2 and 3 colitis, consider additional treatment, such as steroids.
[3] For grade 3 and 4 diarrhoea, 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.

*Other toxicities*

**Table 6 Dose modification and management for other toxicities (excluding hyperglycaemia, rash, diarrhoea or colitis)**

| **Grade**[1] | **Recommendation for adult and paediatric patients** |
|---|---|
| Grade 1 or 2 | No Vijoice dose adjustment required. Initiate appropriate medical therapy and monitor as clinically indicated[2,3,4,5]. |
| Grade 3 | Interrupt Vijoice dose until improvement to grade ≤ 1.<br>**Adult patients[2,3]:**<br>• Once improved to grade ≤ 1, resume Vijoice at the next lower dose level.<br>**Paediatric patients[4,5]:**<br>• Once improved to grade ≤ 1, either resume Vijoice at 50 mg or permanently discontinue Vijoice.<br>• If ADR recurs at grade ≥ 3, consider permanent discontinuation of Vijoice.<br>• Consider consultation with a qualified physician with specific expertise in the field of the concerned ADR. |
| Grade 4 | Permanently discontinue Vijoice. |

[1] Grading according to CTCAE Version 5.0
[2] For grade 2 total bilirubin elevation in adult patients, interrupt Vijoice dose until improvement to grade ≤ 1. If improvement occurs in ≤ 14 days, resume at the same dose level. If improvement occurs in > 14 days, resume Vijoice at the next lower dose level.
[3] For grade 2 and 3 pancreatitis in adult patients, interrupt Vijoice dose until improvement to grade ≤ 1 and resume at next lower dose level. Only one dose reduction is permitted. If toxicity recurs, permanently discontinue Vijoice treatment.
[4] For grade 2 total bilirubin elevation in paediatric patients, interrupt Vijoice dose until improvement to grade ≤ 1. If improvement occurs in ≤ 14 days, resume at the same dose level. If improvement occurs in > 14 days resume Vijoice at 50 mg (in patients receiving 125 mg or 50 mg doses).
[5] For grade 2 and 3 pancreatitis in paediatric patients, interrupt Vijoice dose until improvement to grade ≤ 1 and resume Vijoice at 50 mg. If toxicity recurs, permanently discontinue Vijoice treatment.

*Special populations*

*Elderly*
No dose adjustment is required in patients aged 65 years or above (see section 5.2). Caution should be used in this population as no clinical data are available.

*Hepatic impairment*
Based on a hepatic impairment study in adult participants with normal or 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).

*Renal impairment*
Based on a population pharmacokinetic (PK) analysis in adult patients with cancer and adult and paediatric patients with PROS, no dose adjustment is necessary in patients with mild (eGFR 60 to < 90 ml/min/1.73 $m^2$) / (CLcr 60 to < 90 ml/min) or moderate (eGFR 30 to < 60 ml/min/1.73 $m^2$) renal impairment (see section 5.2). Caution should be used in patients with severe (eGFR ≤ 30 ml/min/1.73 $m^2$) renal impairment as there is no experience with alpelisib in this population.

*Paediatric population*
The safety and efficacy of Vijoice in children aged < 2 years have not been established (see section 5.1). No data are available.

Method of administration

Vijoice is for oral use. It should be taken immediately after food, at approximately the same time each day (see section 5.2).

The granules can be either poured directly onto the tongue or mixed with water, milk, apple juice, yogurt or apple sauce (puréed apple) (see section 6.6).

Each sachet is for single use only. Partial quantities of granules from a sachet should not be used to prepare a dose.

No sachet should be used if the sachet seal is broken.

For patients who are not able to swallow, Vijoice can be administered via a feeding tube. The granules should be administered via a 8-12 Fr diameter silicone or polyurethane nasogastric tube or via a 12-24 Fr diameter silicone gastric tube (see section 6.6).

Vijoice granules in sachet and Vijoice film-coated tablets should not be combined to achieve the prescribed dose of 125 mg or 250 mg. Patients should be administered film-coated tablets to achieve these higher doses. Please refer to the Summary of Product Characteristics for Vijoice film-coated tablets.

## 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

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, have occurred in patients treated with Vijoice (see section 4.8). Vijoice should be permanently discontinued and should not be re-introduced in patients with serious hypersensitivity reactions. Appropriate treatment should be promptly initiated.

Severe cutaneous adverse reactions (SCARs)

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), erythema multiforme (EM), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS), have occurred in adult patients treated with alpelisib in the oncology setting and may occur in patients treated with Vijoice.

Treatment should not be initiated in patients with a history of SCARs.

Patients should be advised of the signs and symptoms of SCARs (e.g. a prodrome of fever, flu-like symptoms, mucosal lesions or progressive skin rash). If signs or symptoms of SCARs occur, Vijoice should be interrupted until the aetiology of the reaction has been determined. A consultation with a dermatologist is recommended.

If a SCAR is confirmed, Vijoice should be permanently discontinued. Vijoice should not be re-introduced in patients who have experienced previous SCARs. If a SCAR is not confirmed, Vijoice may require dose modifications, topical or systemic corticosteroids, or oral antihistamine treatment as described in Table 4 (see section 4.2).

Hyperglycaemia

Severe hyperglycaemia, in some cases associated with hyperglycaemic hyperosmolar nonketotic syndrome (HHNKS), has occurred in patients treated with Vijoice (see section 4.8). Fatal cases of ketoacidosis have occurred in patients treated with alpelisib in the oncology setting.

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 in the oncology setting.

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 FG monitoring is recommended in Table 7.

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

**Table 7 Schedule of FG monitoring**

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

The safety of Vijoice in patients with Type 1 and uncontrolled Type 2 diabetes has not been established. Patients with a history of diabetes mellitus may require intensified diabetic treatment and should be closely monitored.

Based on the severity of hyperglycaemia, Vijoice may require dose interruption, reduction or discontinuation as described in Table 3 (see section 4.2).

Pneumonitis

Pneumonitis, including serious cases of pneumonitis/acute interstitial lung disease, has occurred in adult patients treated with alpelisib in the oncology setting and may occur in patients treated with Vijoice. 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, Vijoice 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. Vijoice should be permanently discontinued in all patients with confirmed pneumonitis.

Diarrhoea or colitis

Severe diarrhoea and its clinical consequences, such as dehydration and acute kidney injury, and colitis have occurred in adult patients during treatment with alpelisib in the oncology setting and may occur in patients treated with Vijoice.

Patients should be monitored for diarrhoea and other symptoms of colitis, such as abdominal pain and mucus or blood in stools. Based on the severity of the diarrhoea or colitis, Vijoice may require dose interruption, reduction or discontinuation as described in Table 5 (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 Vijoice. Patients with colitis may require additional treatment, such as enteric-acting and/or systemic steroids.

Women of childbearing potential/Contraception in males and females

Women of childbearing potential should use effective contraception during treatment with alpelisib and for at least 1 week after stopping treatment with alpelisib. As it is currently unknown whether alpelisib may reduce the effectiveness of systemically acting hormonal contraceptives, women using hormonal contraceptives should also use a barrier method (see section 4.6).

Male patients with sexual partners who are pregnant, possibly pregnant or who could become pregnant should use condoms during sexual intercourse while taking alpelisib and for at least 1 week after stopping treatment with alpelisib (see section 4.6).

Paediatric population

The long-term effects of Vijoice on growth and development in paediatric patients 2 to < 18 years of age with PROS are not known.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per sachet, 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. ciclosporin).

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 recommended in the oncology setting 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 PK 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 rifampicin (a strong CYP3A4 inducer) for 7 days followed by co-administration with a single oral dose of alpelisib 300 mg on day 8, decreased alpelisib $C_{max}$ by 38% and AUC by 57% in healthy adults (N=25). Co-administration of rifampicin 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, rifampicin, St. John's wort [*Hypericum perforatum*]) 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) or CYP2C19 substrates (e.g. omeprazole). For CYP2B6 substrates (e.g. bupropion), 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 PK 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 $AUC_{inf}$ and $C_{max}$ 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.

Paediatric population

Interaction studies have only been performed in adult healthy volunteers and cancer patients (see section 5.2.).

## 4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Women of childbearing potential should use effective contraception during treatment and for at least 1 week after stopping treatment. As it is currently unknown whether alpelisib may reduce the effectiveness of systemically acting hormonal contraceptives, women using hormonal contraceptives should also use a barrier method.

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

Pregnancy

There are no data from the use of alpelisib in pregnant women. However, the mechanism of action of alpelisib suggests a risk of congenital malformation. Studies in animals have shown reproductive toxicity (see section 5.3).

Vijoice should not be used during pregnancy unless the clinical condition of the woman requires treatment with alpelisib.

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

Breast-feeding

It is not known if alpelisib is excreted in human 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 Vijoice.

Fertility

There are no clinical data 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

Vijoice has minor influence on the ability to drive and use machines. Fatigue and blurred vision have occurred in adult patients treated with alpelisib in the oncology setting and may occur in patients treated with Vijoice. Patients should be advised to be cautious when driving or using machines in case they experience fatigue or blurred vision during treatment.

## 4.8 Undesirable effects

Summary of the safety profile

In adult patients enrolled in the retrospective chart review studies, the most common ADRs (all grades) were hyperglycaemia (27.8%), diarrhoea (27.8%), headache (22.2%), stomatitis (16.7%), alopecia (16.7%), dermatitis (16.7%), dry skin (16.7%) and nausea (11.1%). Grade 3-4 ADRs were decreased blood phosphate (11.1%), dehydration (5.6%), increased blood creatinine (5.6%) and increased glucose (5.6%). Serious ADRs (all grades) were dehydration (5.6%) and hyperglycaemia (5.6%). The ADR alopecia (all grades) led to dose reduction (5.6%). ADRs leading to dose interruptions (all grades) were vomiting (5.6%), nausea (5.6%), mucosal dryness (5.6%) and headache (5.6%).

In paediatric patients enrolled in the retrospective chart review studies, the most common ADRs (all grades) were stomatitis (23.1%) and diarrhoea (12.8%). No grade 3-4 ADRs were reported. Serious ADRs (all grades) were vomiting (2.6%) and dehydration (2.6%). ADRs leading to dose interruptions (all grades) were vomiting (2.6%) and dehydration (2.6%).

The most common ADRs in paediatric patients enrolled in the phase II interventional clinical study (all grades) were abdominal pain (33.7%), headache (30.3%), diarrhoea (28.1%) and vomiting (24.7%). Grade 3-4 ADRs were increased lipase (3.4%), decreased appetite (1.1%) and diarrhoea (1.1%). Serious ADRs (all grades) were diarrhoea (1.1%), headache (1.1%) and rash (1.1%). Dose interruptions due to an ADR occurred in 9.0% of patients; the most common ADRs which required dose interruption were vomiting (2.2%), rash (2.2%) and diarrhoea (2.2%). ADRs leading to permanent discontinuation (all grades) were alopecia (2.2%) and decreased appetite (1.1%).

Tabulated list of adverse reactions

The list of adverse reactions is based on data from retrospective chart review studies in 18 adult and 39 paediatric patients, who were treated with alpelisib in a compassionate use programme with an initial starting dose of 250 mg in adult patients and 50 mg in paediatric patients. The median duration of exposure was 42 months (range: 3.4 to 74.8 months). The list of adverse reactions is also based on data from a phase II interventional clinical study in 89 paediatric patients (including 82 patients 6 to < 18 years of age and 7 patients 2 to < 6 years of age), who were treated with alpelisib with an initial starting dose of 50 mg, for a median duration of exposure of approximately 30 months. 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 ADR 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 (frequency cannot be estimated from the available data).

**Table 8 ADRs observed in patients who received Vijoice**

| **Adverse drug reactions** | **EPIK-P1 and EPIK-P3* retrospective period pooled data** | | **EPIK-P2[1]** | **Highest frequency category across adult and paediatric patients** |
|---|---|---|---|---|
| | **Adult patients N = 18** | **Paediatric patients N = 39** | **Paediatric patients N = 89** | |
| | **All grades n (%)** | **All grades n (%)** | **All grades n (%)** | |
| **Immune system disorders** | | | | |
| Hypersensitivity[#] | - | - | - | Common |
| **Metabolism and nutrition disorders** | | | | |
| Hyperglycaemia[2] | 5 (27.8) | 3 (7.7) | 6 (6.7) | Very common |
| Decreased appetite | 1 (5.6) | 0 | 10 (11.2) | Very common |
| Dehydration | 1 (5.6) | 1 (2.6) | - | Common |
| **Nervous system disorders** | | | | |
| Headache | 4 (22.2) | 0 | 27 (30.3) | Very common |

| | | | | |
|---|---|---|---|---|
| **Gastrointestinal disorders** | | | | |
| Diarrhoea | 5 (27.8) | 5 (12.8) | 25 (28.1) | Very common |
| Vomiting | 1 (5.6) | 1 (2.6) | 22 (24.7) | Very common |
| Stomatitis | 3 (16.7) | 9 (23.1) | 17 (19.1) | Very common |
| Nausea | 2 (11.1) | 1 (2.6) | 15 (16.9) | Very common |
| Abdominal pain | 1 (5.6) | 0 | 30 (33.7) | Very common |
| **Skin and subcutaneous tissue disorders** | | | | |
| Rash[3] | - | - | 10 (11.2) | Very common |
| Dermatitis[4] | 3 (16.7) | 1 (2.6) | 12 (13.5) | Very common |
| Dry skin | 3 (16.7) | 2 (5.1) | 3 (3.4) | Very common |
| Alopecia | 3 (16.7) | 0 | 11 (12.4) | Very common |
| Acne[5] | 1 (5.6) | 0 | 4 (4.5) | Common |
| Pruritus | 0 | 1 (2.6) | 2 (2.2) | Common |
| **General disorders and administration site conditions** | | | | |
| Mucosal dryness[6] | 1 (5.6) | 1 (2.6) | 2 (2.2) | Common |
| **Investigations[7]** | | | | |
| Blood phosphate decreased | 11 (61.1) | 27 (69.2) | 2 (2.2) | Very common |
| Blood calcium decreased[8,9] | 12 (66.7) | 25 (64.1) | 17 (19.1) | Very common |
| Blood creatinine increased | 2 (11.1) | 19 (48.7) | 22 (24.7) | Very common |
| Glycosylated haemoglobin increased[9] | 12 (66.7) | 11 (28.2) | 5 (5.6) | Very common |
| Glucose increased | 4 (22.3) | 8 (20.5) | 27 (30.3) | Very common |
| Lipase increased[10] | - | - | 22 (24.7) | Very common |

Grading according to CTCAE Version 4.03.

[1] EPIK-P2 data refers to the alpelisib-treatment period which includes paediatric patients who received at least one dose of alpelisib, including patients who switched from placebo to alpelisib after the 16-week placebo-controlled period.

[2] Hyperglycaemia: including hyperglycaemia, glycosylated haemoglobin increased and blood glucose increased.

[3] Rash: including rash, rash erythematous, rash macular, rash maculo-papular and rash papular. Rash was reported in 13.8% of adult patients treated at the non-recommended alpelisib dose of 125 mg in EPIK-P2.

[4] Dermatitis: including dermatitis, drug eruption and eczema.

[5] Acne: including acne and dermatitis acneiform.

[6] Mucosal dryness: including dry mouth and vulvovaginal dryness.

[7] Frequencies of laboratory terms reflect the proportion of patients who experienced worst-post-baseline laboratory measurements.

[8] Calcium corrected values were used for this parameter.

[9] No CTCAE grading available.

[10] Lipase increased was reported in 23.8% of adult patients treated at the non-recommended alpelisib dose of 125 mg in EPIK-P2.

* Forty patients in EPIK-P3 continued to be treated with alpelisib in a prospective period. Additional safety data from the 3-year analysis of the EPIK-P3 prospective period, with an additional median duration of exposure of 39.1 months (range: 17-42 months) did not show additional ADRs or clinically relevant laboratory abnormalities.

\# Adverse drug reactions reported outside of the EPIK-P1/EPIK-P2/EPIK-P3 safety population considered. The frequency category is estimated from the EPIK-P2 study as per the SmPC Guideline 2009 section 4.8, *Adverse reactions from spontaneous reporting.*

Description of selected adverse drug reactions

*Gastrointestinal adverse reactions*

In patients enrolled in the retrospective chart review studies who experienced at least one event of diarrhoea (10/57), the median time to onset of any grade diarrhoea was 61.3 weeks (range: 3.3 to 123.1 weeks) and 12.4 weeks (range: 2.4 to 133.4 weeks) in adult and paediatric patients, respectively. Grade 2 diarrhoea (maximum grade) was reported in 2.6% of paediatric patients. Antidiarrhoeal medicinal products were used in 11.1% of adult patients to manage symptoms (see section 4.2).

In paediatric patients enrolled in the phase II interventional clinical study who experienced at least one event of diarrhoea (25/89), the median time to onset of any grade diarrhoea was 14.1 weeks (range: 0.1 to 71.1 weeks). Grade 2 and grade 3 diarrhoea were reported in 3.4% and 1.1% patients, respectively. The maximum grade was grade 3. Antidiarrhoeal medicinal products were used in 13.5% of paediatric patients to manage symptoms (see section 4.2).

*Alopecia*
In adult patients enrolled in the retrospective chart review studies who experienced at least one event of alopecia (3/18), the median time to onset of any grade alopecia was 31.6 weeks (range: 13.0 to 34.0 weeks). In adult patients enrolled in the phase II interventional clinical study treated at the non-recommended alpelisib dose of 125 mg, alopecia was reported in 36.3% patients.

In paediatric patients enrolled in the phase II interventional clinical study who experienced at least one event of alopecia (11/89), the median time to onset of any grade alopecia was 40.4 weeks (range: 3.6 to 110.6 weeks).

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 national reporting system listed in Appendix V.

### 4.9 Overdose

Symptoms

The adverse reactions associated with overdose in the oncology setting have been consistent with the safety profile of alpelisib 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 Vijoice.

## 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 phosphatidylinositol-3-kinase (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.

Somatic activating mutations in PIK3CA, leading to a mosaic genotype, have been found to induce a spectrum of overgrowths and malformations comprising a wide group of clinically recognisable disorders known as PROS.

Clinical efficacy and safety

*EPIK-P1*
Vijoice was evaluated in a retrospective chart review study in 57 patients aged 2 years and older with PROS who received Vijoice as part of a compassionate use programme. Eligible patients had clinical manifestations of PROS that were assessed by the treating physician as severe or life-threatening and necessitating treatment and had documented evidence of mutation in the PIK3CA gene.

EPIK-P1 included 18 adult patients in whom the recommended Vijoice dose was 250 mg. The study also included 39 paediatric patients (2 to < 18 years of age), of whom 35 received the recommended Vijoice starting dose of 50 mg. Twenty-five percent (25.6%) of paediatric patients required at least one Vijoice dose increase during the study.

At enrolment, patients had a median age of 14 years (range: 2 to 50 years). 19.3% of patients were 2 to < 6 years of age, 21.1% were 6 to < 12 years of age, 28.1% were 12 to < 18 years of age, and 31.6% were ≥ 18 years of age; 57.9% were female. Of the patients enrolled, 93.0% had congenital overgrowth and 7.0% had early childhood-onset of overgrowth. Patients had heterogeneous manifestations of PROS including congenital, lipomatous overgrowth, vascular malformations, epidermal nevi and scoliosis/skeletal/spinal anomalies syndrome (CLOVES; 73.7%), megalencephaly-capillary malformation polymicrogyria (MCAP; 14.0%), Klippel-Trenaunay syndrome (KTS; 8.8%), facial infiltrating lipomatosis (FIL; 5.3%), megalencephaly-capillary malformation (MCM; 1.8%), and other (3.5%). Seven percent (7.0%) of patients had concurrent manifestations of CLOVES and MCAP.

The median duration of exposure to Vijoice was 18.1 months (range: 3.4 to 49.9 months) in all patients, 19.2 months (range: 8 to 49.9 months) in adult patients, and 18 months (range: 3.4 to 41.8 months) in paediatric patients. Seventy-nine percent (78.9%) of all patients, 83.3% of adult patients and 76.9% of paediatric patients received Vijoice for more than 12 months.

The main efficacy endpoint for the study was the proportion of patients with radiological response at week 24 as determined by independent central radiology review (ICRR), defined by achieving ≥ 20% reduction from baseline in the sum of measurable target lesion volume (1 to 3 lesions), provided that none of the individual target lesions had ≥ 20% increase from baseline and in the absence of progression of non-target lesions and without new lesions.

Additional efficacy endpoints included duration of response (DOR), defined as the time from the first documented response to the date of the first documented disease progression or death due to any cause.

Efficacy results for adult, paediatric and all patients are presented in Table 9. The primary analysis was performed on a subset of the efficacy population (N=37), comprising 32 patients without a missing response at week 24 (complete case analysis).

**Table 9 Summary of efficacy results in EPIK-P1**

| Efficacy parameters | Adult patients | Paediatric patients | All patients |
|---|---|---|---|
| **Primary analysis[1, 2]** | | | |
| Responders at week 24, % (n/N)<br>95% CI | 55.6 (5/9)<br>21.2, 86.3 | 30.4 (7/23)<br>13.2, 52.9 | 37.5 (12/32)<br>21.1, 56.3 |
| **Duration of response (DOR)** | | | |
| Median in months (range) | NR (2.8+, 29.7+) | NR (0.03+, 42.9+) | NR (0.03+, 42.9+) |
| % ≥ 6 months | 40 | 71 | 58 |
| % ≥ 12 months | 20 | 71 | 50 |

NR: Not reached
+: censored observation
[1] At baseline, 81% of patients had 1 target lesion, 16% had 2 target lesions, and 3% had 3 target lesions.
[2] As determined by ICRR.

Two paediatric patients required surgery due to clinical disease progression (not radiologically confirmed) after week 24. No patients developed a new lesion while receiving Vijoice during the study. At the end of the study, 91.2% of all patients (88.9% of adult patients and 92.3% of paediatric patients) were still receiving Vijoice.

*EPIK-P3*
EPIK-P3 is a phase II multicentre, open-label, interventional study (preceded by a retrospective non-interventional period) in adult and paediatric patients with severe or life-threatening complications of PROS who were treated with Vijoice as part of a compassionate use programme, participated in EPIK-P1, and continued to receive treatment with alpelisib after the end of EPIK-P1. This was mainly a safety study which included some efficacy outcomes as secondary endpoints. The median duration of exposure to Vijoice was 6.7 years (range: 0.4 to 9.5).

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Vijoice in one or more subsets of the paediatric population in the treatment of PROS as per paediatric investigation plan (PIP) P/0412/2022, for the granted indication (see section 4.2 for information on paediatric use).

Conditional approval

This medicinal product has been authorised under a so-called 'conditional approval' scheme. This means that further evidence on this medicinal product is awaited.
The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

## 5.2 Pharmacokinetic properties

The pharmacokinetics of alpelisib film-coated tablets have been studied in patients 2 years of age and older with PROS under an oral dosing regimen ranging from 50 mg to 250 mg daily under fed conditions.

Absorption

Following oral administration of alpelisib with food, the median time to reach peak plasma concentration ($T_{max}$) was 3.0 hours. Food affects alpelisib absorption at high doses and Vijoice should be taken immediately after food at approximately the same time each day (see sections 4.2 and 6.6).

*Relative bioavailability*
A crushed film-coated tablet administered as an oral suspension in water has not been demonstrated to be bioequivalent to an intact film-coated tablet. However, in a comparative study of relative bioavailability at a dose of 300 mg recommended in the oncology setting, the crushed suspension showed similar exposure to the intact tablets ($C_{max}$ ratio 1.00; AUC ratio 0.96), indicating no clinically meaningful differences in exposure.

Alpelisib 50 mg granules are bioequivalent to alpelisib 50 mg film-coated tablets in the fed state following a LFLC meal, indicating there is no clinically relevant difference in the rate and extent of absorption of alpelisib from these two pharmaceutical forms when administered with food.

*Food effect*
Alpelisib absorption is affected by food at high doses. In healthy adult volunteers after a single 300 mg oral dose of alpelisib recommended in the oncology setting, compared to the fasted state, a high-fat high-calorie (HFHC) meal increased $AUC_{inf}$ by 73% and $C_{max}$ by 84%, and a LFLC meal increased $AUC_{inf}$ by 77% and $C_{max}$ by 145%. The increase in gastrointestinal solubility by bile, secreted in response to food intake independent of the fat or calories content of the meal, is the potential cause of the food effect.

No clinically relevant food effect on alpelisib pharmacokinetics was observed after a single 50 mg oral dose of alpelisib as granules taken with a LFLC meal as compared to fasted administration.

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. Alpelisib steady-state distribution volume following oral dosing (Vss/F) was estimated by population PK modelling to be approximately 136 litres in a reference patient with PROS (female, normal renal function, 61 kg).

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

The half-life of alpelisib was estimated by population PK modelling to be 7.7 hours for a reference patient with PROS (female, normal renal function, 61 kg).

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 [$^{14}$C]-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 significant PK interaction. The data for the 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 rifampicin, a strong CYP3A4 inducer, confirmed that there is a clinically significant PK 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 ruled out 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 the 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 and gender*
Population PK analyses based on data from adult cancer patients and adult and paediatric patients with PROS indicated that the effects of age and gender on the systemic exposure of alpelisib are not predicted to require dose adjustment.

*Effect of body weight*
Population PK analyses based on data from adult patients with cancer and adult and paediatric patients with PROS indicate that alpelisib apparent clearance and volume of distribution increase with body weight. As a result, lower body weight is associated with higher systemic exposure, whereas higher body weight is associated with lower exposure for the same dose. Based on the available data, the magnitude of this effect is not considered clinically relevant and does not warrant dose adjustment in adult patients with PROS.

*Paediatric population (below 18 years)*
Observed steady-state PK data in paediatric patients with PROS indicate a clear effect of body weight on alpelisib exposure. In paediatric patients 6 to < 18 years old treated with alpelisib 50 mg once daily, mean steady-state $AUC_{24h}$ decreased from approximately 7 250 ng·h/ml in patients < 30 kg to 2 540 ng·h/ml in patients ≥ 60 kg (≈65% decrease), while mean $C_{max,ss}$ decreased from about 747 ng/ml to 300 ng/ml (≈60% decrease).

The pharmacokinetics of alpelisib in paediatric patients below the age of 2 years have not been established.

*Elderly*
Based on a population PK analysis in patients with cancer and patients with PROS that included 174 patients with cancer aged 65 years or older, with a maximum age of 87 years, no clinically relevant effect of age on the systemic exposure of alpelisib is predicted. No PK data are available for elderly patients with PROS.

*Race/Ethnicity*
The population PK analysis of data from adult patients with cancer and adult and paediatric patients with PROS that included 542 White patients, 107 Asian patients, 12 Black or African American patients, 21 patients of other race and 15 patients of unknown race indicates no clinically relevant effect of race on the systemic exposure of alpelisib.

The population PK analysis of data from adult patients with cancer and adult and paediatric patients with PROS that included 105 patients of Hispanic or Latino ethnicity, 523 patients not of Hispanic or Latino ethnicity and 69 patients of unknown ethnicity indicates no clinically relevant effect of ethnicity on the systemic exposure of alpelisib.

*Hepatic impairment*
A PK study in adult participants with normal or impaired hepatic function indicated that moderate and severe hepatic impairment have no clinically meaningful effect on the exposure of alpelisib (see section 4.2). In participants with severe hepatic impairment, peak alpelisib exposure was comparable to that in healthy participants ($C_{max}$ GMR [geometric mean ratio]=1.00) and total alpelisib exposure was approximately 26% higher ($AUC_{last}$ GMR=1.26, $AUC_{inf}$ GMR=1.25).

*Renal impairment*
The population PK analysis of data from adult patients with cancer and adult and paediatric patients with PROS that included 433 patients with normal renal function (eGFR ≥ 90 ml/min/1.73 $m^2$) / (CLcr ≥ 90 ml/min), 198 patients with mild renal impairment (eGFR 60 to < 90 ml/min/1.73 $m^2$) / (CLcr 60 to < 90 ml/min), and 66 patients with moderate renal impairment (eGFR 30 to < 60 ml/min/1.73 $m^2$), indicates that mild and moderate renal impairment have no effect on the exposure to alpelisib that would require dose adjustment. No PK data are available for patients with severe renal impairment (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. In 4- or 13-week repeated dose toxicity studies initiated in 8- to 10-week-old rats, degenerative effects were seen in the incisors and growth plates of bones. At the no observed adverse effect level (NOAEL), in 4-week repeated dose toxicity studies, exposure levels were 1.3 and 2.5 times the estimated exposure (AUC) in adult and paediatric patients at the recommended dose of 250 and 50 mg/day, respectively. In 13-week repeated dose toxicity studies, exposure levels were 0.2 and 0.3 times the estimated exposure (AUC) in adult and paediatric patients at the recommended dose of 250 and 50 mg/day, respectively. Effects on bone marrow, growth plates of bones, incisors 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. In repeated dose toxicity studies, adverse events were observed at clinically relevant doses based on AUC.

Cardiovascular safety pharmacology

*In vitro* inhibition of hERG channels ($IC_{50}$ of 9.4 µM, corresponding to approximately 4.2 µg/ml free drug) was shown at concentrations ~21-fold and ~31-fold higher than the estimated maximum (peak) plasma concentration of unbound alpelisib in humans at the recommended maximum alpelisib adult and paediatric doses of 250 mg/day (adult) or 50 mg/day (ages 2 to 5 years), respectively. No relevant electrophysiological effect was seen in dogs.

Carcinogenicity and genotoxicity

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 0.3 times the clinical exposure in patients at the highest recommended dose of 250 mg/day based on AUC).

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 2.6 and 5.0 times the estimated exposure (AUC) in humans at the recommended alpelisib dose of 250 or 50 mg/day, respectively.

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 at exposures below the average exposure expected for adult patients treated with 250 mg/day alpelisib, 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 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 two times the recommended adult dose of 250 mg/day. In males, fertility and reproductive performance, including sperm count and motility parameters, were unaffected at exposure levels equivalent to the estimated exposure (AUC) in humans at the recommended adult dose of 250 mg/day. However, at exposure levels (AUC) at or below the adult human dose of 250 mg/day, 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.

Juvenile animal studies

In a 9-week rat juvenile toxicity study initiated in 7-day-old animals, the NOAEL of 6 mg/kg/day resulted in lower exposure levels (AUC) than in paediatric patients at the recommended dose of 50 mg/day. At the dose of 20 mg/kg/day (2.2 to 4.2 times the estimated exposure [AUC] in paediatric patients at the recommended dose of 50 mg/day), adverse and non-reversible kidney effects were observed and included minimal to moderate increased vascular/perivascular extracellular matrix deposition in small vessels and minimal to moderate tubular degeneration/regeneration in the renal papilla and medulla. Correlating minimally higher urea nitrogen concentrations were observed at the end of the recovery period. These effects are not anticipated to be clinically relevant for patients aged 2 years and older based on interspecies comparison of postnatal renal development.

In addition, lower body weights, reduced body weight gains, delayed sexual maturation in the males and reduced femur lengths were observed at 20 mg/kg/day. No histopathological findings in the bone (including the growth plate) were reported.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Cellulose microcrystalline (E460)
Mannitol (E421)
Sodium starch glycolate
Hypromellose (E464)
Magnesium stearate (E470b)

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years.

### 6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.

Store in the original sachet in order to protect from light.

### 6.5 Nature and contents of container

PET/alu/PE (polyethylene terephthalate/aluminium/polyethylene) foil sachets.

Packs containing 28 sachets.

### 6.6 Special precautions for disposal and other handling

Instructions for preparation and administration of granules for oral use

For patients for whom a daily dose of 50 mg is prescribed, Vijoice granules should be administered in one of the following ways:

- Pour the contents of one sachet directly onto the tongue and swallow with approximately 50 to 150 ml water. If needed, rinse the mouth with additional water and swallow to ensure no particles remain in the mouth.
- Pour the contents of one sachet into a cup. Add 5 to 15 ml of a drink (water, milk or apple juice only) or soft food (puréed apple or yogurt only) and administer the mixture immediately. Rinse the cup with approximately 10 to 40 ml of the same drink or soft food. Administer the mixture immediately and ensure the entire dose is administered. If particles remain, repeat until the full dose is administered.

Discard the mixture if not administered within 2 hours after preparation.

Instructions for preparation and administration of granules via feeding tube

For patients who are not able to swallow, Vijoice can be administered via a feeding tube. Vijoice granules should be administered via a 8-12 Fr diameter silicone or polyurethane nasogastric tube (maximum tube length evaluated: 160 cm) or via a 12-24 Fr diameter silicone gastric tube (maximum tube length evaluated: 3.5 cm) (see section 4.2).

Vijoice granules should be prepared and administered in the following way:

- Pour the contents of one sachet into a cup. Add 20 ml water and stir with a spoon until a mixture is obtained. Make the mixture with water only.

- Immediately after preparation, withdraw the mixture from the cup into a syringe and administer it via the feeding tube.
- After administration of the granules via the feeding tube, add 20 ml water to the same cup. Stir the liquid with the same spoon to re-suspend any remaining particles. Withdraw the contents of the cup into the same syringe and administer it via the feeding tube. If particles remain, repeat this step.
- Discard the mixture if it is not administered within 60 minutes after preparation.

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

## 7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/26/2042/004

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

# ANNEX II

**A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE**

**B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

**D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

**E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION**

## A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Novartis Pharmaceutical Manufacturing LLC
Verovškova Ulica 57
1000 Ljubljana
Slovenia

Novartis Pharma GmbH
Sophie-Germain-Strasse 10
90443 Nuremberg
Germany

Novartis Farmacéutica S.A.
Gran Via de les Corts Catalanes 764
08013 Barcelona
Spain

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

## B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

## C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in Article 9 of Regulation (EC) No 507/2006 and, accordingly, the marketing authorisation holder (MAH) shall submit PSURs every 6 months.

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

## D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

## E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

| Description | Due date |
|---|---|
| In order to further confirm the efficacy, safety and pharmacokinetics of alpelisib in the treatment of adult and paediatric patients with PIK3CA-related overgrowth spectrum (PROS), the MAH should submit the final results of the phase II single-arm study CBYL719F12202 (EPIK-P4). | 31 December 2032 |

**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

# A. LABELLING

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON OF PACKS CONTAINING 50 MG TABLETS**

## 1. NAME OF THE MEDICINAL PRODUCT

Vijoice 50 mg film-coated tablets
alpelisib

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 50 mg alpelisib.

## 3. LIST OF EXCIPIENTS

## 4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

28 tablets
28-day supply for a **50 mg daily dose**.

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/26/2042/001 28 film-coated tablets of 50 mg

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Vijoice 50 mg

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER CARD OF PACKS CONTAINING 50 MG TABLETS**

## 1. NAME OF THE MEDICINAL PRODUCT

Vijoice 50 mg tablets
alpelisib

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. OTHER

Mon.
Tue.
Wed.
Thu.
Fri.
Sat.
Sun.

Take one tablet immediately after food on the day indicated.

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON OF PACKS CONTAINING 125 MG TABLETS**

## 1. NAME OF THE MEDICINAL PRODUCT

Vijoice 125 mg film-coated tablets
alpelisib

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 125 mg alpelisib.

## 3. LIST OF EXCIPIENTS

## 4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

28 tablets
28-day supply for a **125 mg daily dose**.

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/26/2042/002 28 film-coated tablets of 125 mg

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Vijoice 125 mg

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER CARD OF PACKS CONTAINING 125 MG TABLETS**

## 1. NAME OF THE MEDICINAL PRODUCT

Vijoice 125 mg tablets
alpelisib

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. OTHER

Mon.
Tue.
Wed.
Thu.
Fri.
Sat.
Sun.

Take one tablet immediately after food on the day indicated.

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON OF PACKS CONTAINING 50 MG AND 200 MG TABLETS**

## 1. NAME OF THE MEDICINAL PRODUCT

Vijoice 50 mg film-coated tablets
Vijoice 200 mg film-coated tablets
alpelisib

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 50 mg or 200 mg alpelisib.

## 3. LIST OF EXCIPIENTS

## 4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

28 tablets of 50 mg
28 tablets of 200 mg
28-day supply for a **250 mg daily dose**.

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/26/2042/003 28 film-coated tablets of 50 mg + 28 film-coated tablets of 200 mg

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Vijoice 50 mg + 200 mg

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER CARD OF PACKS CONTAINING 50 MG AND 200 MG TABLETS**

## 1. NAME OF THE MEDICINAL PRODUCT

Vijoice 50 mg tablets
Vijoice 200 mg tablets
alpelisib

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. OTHER

Mon.
Tue.
Wed.
Thu.
Fri.
Sat.
Sun.

Take both tablets in the coloured row immediately after food on the day indicated.

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON OF PACKS CONTAINING 50 MG GRANULES IN SACHET**

## 1. NAME OF THE MEDICINAL PRODUCT

Vijoice 50 mg granules in sachet
alpelisib

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sachet contains 50 mg alpelisib.

## 3. LIST OF EXCIPIENTS

## 4. PHARMACEUTICAL FORM AND CONTENTS

Granules in sachet

28 sachets
28-day supply for a **50 mg daily dose**.

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store in the original sachet in order to protect from light.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/26/2042/004 28 sachets

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Vijoice 50 mg

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**SACHETS**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Vijoice 50 mg granules
alpelisib
Oral use

## 2. METHOD OF ADMINISTRATION

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

## 6. OTHER

# B. PACKAGE LEAFLET

**Package leaflet: Information for the patient**

**Vijoice 50 mg film-coated tablets**
**Vijoice 125 mg film-coated tablets**
**Vijoice 200 mg film-coated tablets**
alpelisib

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, or pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, or pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**



## 1. What Vijoice is and what it is used for

**What Vijoice is**
Vijoice contains the active substance alpelisib, which belongs to a group of medicines called phosphatidylinositol-3-kinase (PI3K) inhibitors.

**What Vijoice is used for**
Vijoice is used to treat adults, adolescents and children from 2 years of age with severe or life-threatening PIK3CA-related overgrowth spectrum (PROS). PROS includes a broad range of rare disorders which cause uncontrollable overgrowth of parts of the body due to certain changes (mutations) in a gene called PIK3CA.

This gene leads to the production of a protein that instructs the body's cells to grow and multiply. The changes in the gene cause this protein to function irregularly and, as a consequence, help cells to grow and multiply in an abnormal way.

**How Vijoice works**
Vijoice works by blocking the effects of enzymes (proteins) called phosphatidylinositol-3-kinases (PI3K). These enzymes help abnormal cells to grow and multiply. By blocking their action, Vijoice can reduce uncontrollable growth and spread of the abnormal cells and help to reduce overgrown tissue and signs and symptoms of the disease in patients.

If you have any questions about how Vijoice works or why this medicine has been prescribed for you, ask your doctor, pharmacist or nurse.

## 2. What you need to know before you take Vijoice

Follow all of your doctor's instructions carefully, as they may differ from the general information in this leaflet. Check with your doctor if you are not sure.

**Do not take Vijoice**
- if you are allergic to alpelisib or any of the other ingredients of this medicine (listed in section 6). If you think you may be allergic, ask your doctor for advice.

**Warnings and precautions**
Talk to your doctor or pharmacist before taking Vijoice.

If any of the following apply to you before taking Vijoice, tell your doctor or pharmacist:
- if you have ever had a severe allergic reaction, including
  - Stevens-Johnson syndrome (SJS, a highly serious reaction with flu-like symptoms and painful rash affecting the skin, mouth, eyes and genitals);
  - erythema multiforme (EM, a skin reaction that causes red spots or patches on the skin, and that may look like a target or "bull's-eye" with a dark red centre surrounded by paler red rings);
  - drug reaction with eosinophilia and systemic symptoms (DRESS, a skin reaction combined with fever, facial swelling, enlarged lymph nodes and kidney or liver injury), or
  - toxic epidermal necrolysis (TEN, a serious skin reaction; possible symptoms include red skin, blistering of the lips, eyes or mouth, skin peeling, fever, rash).
- if you have, or have ever had, high levels of sugar in your blood or diabetes (or signs of increased sugar levels, such as excessive thirst and dry mouth, needing to pass urine more often than usual, producing greater amounts of urine than usual, tiredness, nausea, increased appetite with weight loss).

If any of the following apply to you during your treatment with Vijoice, tell your doctor or pharmacist immediately:
- Rash, itching, hives, breathlessness, difficulty breathing, wheezing, cough, light-headedness, dizziness, changes in levels of consciousness, low blood pressure, reddening of the skin, swelling of the face or throat, blue discolouration of the lips, tongue or skin (possible signs of severe allergic reactions).
- New or changing breathing problems such as difficult or painful breathing, cough, rapid breathing, blue discolouration of the lips, tongue or skin, hiccups (possible signs of non-infectious pneumonitis or pneumonia).
- Increased thirst and dry mouth, passing urine more often than usual, tiredness, increased appetite with weight loss, confusion, nausea, vomiting, fruity odour on breath, difficulty breathing, dry or flushed skin, which may be signs of increased blood sugar levels (hyperglycaemia) and its complications.
- Rash, reddening of the skin, blistering of the lips, eyes or mouth, skin peeling, sometimes with fever (possible signs of one of the following skin conditions: Stevens-Johnson syndrome (SJS), erythema multiforme (EM), drug reaction with eosinophilia and systemic symptoms (DRESS) or toxic epidermal necrolysis (TEN)).
- Severe diarrhoea, severe abdominal pain or stools with mucus or blood, which may be signs of inflammation of your intestine (colitis).

Your doctor may need to treat these symptoms, temporarily interrupt your treatment, reduce your dose, or permanently stop your treatment with Vijoice (see "How much Vijoice to take" in section 3).

**Make sure that you regularly test your blood sugar before you start treatment, during treatment and after you stop treatment with Vijoice.**
- Your doctor will advise you on how, when and where to carry out blood tests before starting and regularly during treatment with Vijoice to monitor your blood sugar levels. Based on the results, your doctor may prescribe a medicine to lower blood sugar levels, temporarily interrupt or reduce your Vijoice dose, or stop Vijoice treatment permanently.

- Treatment with Vijoice may only begin if your blood sugar levels are appropriate, as Vijoice can increase blood sugar (hyperglycaemia), which could be serious and require treatment.
- If you have certain conditions before you start treatment with Vijoice, such as high levels of sugar in your blood, diabetes, obesity, or age over 75 years, your blood sugar will need to be monitored more frequently during the first weeks of treatment with Vijoice. Afterwards, blood tests will be needed at least once a month, depending on your blood sugar levels.

**Children and adolescents**
Vijoice is not to be used in children under 2 years of age. The long-term effects of Vijoice on growth and development in children from 2 years of age and adolescents are not known.

**Other medicines and Vijoice**
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes in particular:
- ciclosporin, a medicine used to affect your immune system
- rifampicin, a medicine to treat tuberculosis and some other serious infections
- carbamazepine and phenytoin, medicines used to treat seizures or fits
- St. John's wort (also known as *Hypericum perforatum*), a herbal medicine used to treat depression and other conditions

Ask your doctor or pharmacist if you are not sure whether your medicine is one of the medicines listed above.

**Pregnancy**
Vijoice should not be used by women who are, or may be, pregnant. Vijoice may harm an unborn baby. If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

If you are a woman who could become pregnant, your doctor will check with you if you are pregnant and may perform a pregnancy test if necessary before starting treatment with Vijoice.

**Breast-feeding**
It is not known if Vijoice passes into breast milk. Therefore, you should not breast-feed during treatment with this medicine and for at least 1 week after the last dose.

**Contraceptive advice for women**
Women who could become pregnant should use an effective method of birth control during treatment and for at least 1 week after stopping Vijoice. It is not known if Vijoice reduces how well hormonal contraceptives work. If you use hormonal contraceptives, you should also use a barrier method. Ask your doctor about suitable methods. If you think you may be pregnant after starting treatment with Vijoice, tell your doctor immediately.

**Contraceptive advice for men**
During treatment and for at least 1 week after stopping treatment, male patients should use a condom for intercourse with female partners who could become pregnant. If the partner of a male patient suspects that she has become pregnant during this time, she should inform a doctor immediately.

**Driving and using machines**
Treatment with Vijoice may lead to tiredness or blurred vision. You should therefore be cautious when driving or using machines during your treatment with Vijoice.

**Vijoice contains sodium**
This medicine contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially "sodium-free".

## 3. How to take Vijoice

Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

**How much Vijoice to take**
The usual starting dose of Vijoice for adults is 250 mg once daily. The usual starting dose of Vijoice for adolescents and children (aged 2 years and older) is 50 mg once daily. Your doctor will decide on the right dose for you.

Depending on the dose prescribed, the number of tablets to take is as follows:
- 50 mg dose: one 50 mg tablet
- 125 mg dose: one 125 mg tablet
- 250 mg dose: one 200 mg tablet and one 50 mg tablet

Depending on how your body responds to the treatment with Vijoice, your doctor may want to adjust your Vijoice dose (see section 2). It is very important to follow your doctor's instructions. If you have certain side effects, your doctor may ask you to change to a lower dose, to interrupt treatment for a time, or to stop treatment.

**When to take Vijoice**
Vijoice tablets are supplied in packs containing blister cards. Each blister card shows the tablet(s) to be taken on each day of the week. Follow the instructions on the blister card.

Take Vijoice once a day, immediately after food. Taking Vijoice at the same time each day will help you to remember when to take your medicine.

**How to take Vijoice**
Vijoice tablets should be swallowed whole and should not be chewed or split before swallowing. You should not swallow any tablet that is broken, cracked or otherwise damaged as you may not be taking the full dose. If you cannot swallow tablets, you can take Vijoice as a suspension (this means mixed with water) as follows:
- Place the Vijoice tablet(s) in a cup containing 50 to 150 ml of water and let stand for about 5 minutes before crushing. **Use water only.**
- Crush the tablet(s) with a spoon and stir to dissolve. The suspension will be cloudy and you may see tablet pieces.
- **Swallow the suspension right away.**
- Add about 20 to 50 ml of water to the same cup and stir with the same spoon. Then swallow the entire contents of the cup to ensure the entire dose is consumed. Repeat this step if necessary.
- Throw away any Vijoice suspension that is not consumed within 60 minutes after it is prepared.

**Administration of Vijoice via feeding tube**
Patients who cannot swallow Vijoice as tablets or as a suspension can be given Vijoice via certain feeding tubes. The type of tube will be determined by the doctor. The tablets have to be prepared as a suspension (this means mixed with water) as follows:
- Place the Vijoice tablet(s) in a cup containing 40 ml of water and let it stand for about 5 minutes before crushing. **Use water only.**
- Crush the tablet(s) with a spoon and stir to dissolve. The suspension will be cloudy and you may see tablet pieces.
- Draw up the mixture from the cup into a syringe and give it through the feeding tube right away.
- Add about 40 ml of water to the same cup and stir with the same spoon. Then draw up the entire contents from the cup into the same syringe and give through the feeding tube. Repeat this step if there are tablet pieces remaining in the syringe or in the cup.
- Throw away any Vijoice suspension that is not administered within 60 minutes after it is prepared.

**How long to take Vijoice**
Take Vijoice for as long as your doctor tells you to.

This is a long-term treatment, possibly lasting for months or years. Your doctor will regularly monitor your condition to check that the treatment is having the desired effect.

If you have questions about how long to take Vijoice, talk to your doctor or to your pharmacist.

**If you take more Vijoice than you should**
People who have taken too many Vijoice tablets have experienced effects that are known side effects of alpelisib, including high blood sugar levels, nausea, tiredness and rash. If you accidentally take too many tablets, or if someone else accidentally takes your medicine, contact a doctor or hospital for advice immediately. Medical treatment may be necessary.

**If you forget to take Vijoice**
If you forget to take a dose of Vijoice, you may still take it, immediately after food, up to 9 hours after the time you should have taken it. If you only remember more than 9 hours after you should have taken it, skip the dose for that day. The next day, take the dose at your usual time. Do not take a double dose to make up for the one that you missed.

**If you vomit after a dose of Vijoice**
If you vomit after you take the Vijoice tablet(s), do not take any more tablets until your next scheduled dose.

**If you stop taking Vijoice**
Stopping your treatment with Vijoice may cause your condition to become worse. Do not stop taking Vijoice unless your doctor tells you to stop.

If you have any further questions on the use of Vijoice, ask your doctor or pharmacist.

## 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

**Serious side effects**
If you get any serious side effects, **stop taking this medicine and tell your doctor immediately**.

**Very common** (*may affect more than 1 in 10 people)*:
- High levels of sugar in the blood, also called hyperglycaemia. Possible symptoms include: feeling very thirsty, passing urine more often than usual or passing greater amounts of urine than usual, increased appetite with weight loss

**Common** *(may affect up to 1 in every 10 people)*:
- Severe allergic reactions. Possible signs include: rash, itching, hives, breathlessness, difficulty breathing, wheezing, cough, light-headedness, dizziness, changes in levels of consciousness, low blood pressure, reddening of the skin, swelling of the face and/or throat, blue discolouration of the lips, tongue or skin

**Other possible side effects**
Other side effects include the following listed below. If these side effects become severe, tell your doctor, pharmacist or nurse.

**Very common** (*may affect more than 1 in 10 people)*:
- Decreased appetite
- Headache
- Diarrhoea

- Vomiting
- Mouth sores or ulcers with gum inflammation (stomatitis)
- Nausea
- Abdominal pain
- Rash
- Skin inflammation with rash (dermatitis)
- Dry skin
- Hair loss and hair thinning (alopecia)

**Common** *(may affect up to 1 in every 10 people)*:
- Dehydration
- Acne
- Itching (pruritus)
- Mucosal dryness

During Vijoice treatment, the results of some blood tests may be abnormal, as follows:

**Very common:**
- Low level of phosphorous or calcium in the blood (decreased phosphorous, decreased calcium)
- High level of creatinine or sugar in the blood (increased creatinine, increased glucose)
- High blood level of glycosylated haemoglobin (a marker of blood sugar level over the last 8 to 12 weeks)
- High blood levels of the lipase enzyme (lipase increased)

**Reporting of side effects**
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store Vijoice

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the blister card after "EXP". The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not take this medicine if you notice any damage to the packaging or if there are any signs of tampering.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## 6. Contents of the pack and other information

**What Vijoice contains**
- The active substance of Vijoice is alpelisib.
- Each Vijoice 50 mg film-coated tablet contains 50 mg alpelisib.
- Each Vijoice 125 mg film-coated tablet contains 125 mg alpelisib.
- Each Vijoice 200 mg film-coated tablet contains 200 mg alpelisib.

- The other ingredients are:
  - Tablet core: cellulose microcristalline (E460), mannitol (E421), sodium starch glycolate (see section 2 “Vijoice contains sodium”), hypromellose (E464), magnesium stearate (E470b).
  - Coating material: Hypromellose (E464), iron oxide red (applicable only to 50 mg and 200 mg strengths) and yellow (E172), titanium dioxide (E171), macrogol (E1521), talc (E553b).

**What Vijoice looks like and contents of the pack**
Vijoice 50 mg film-coated tablets are light yellow, round tablets, debossed with “C7” on one side and “NVR” on the other side. Approximate diameter: 7 mm.

Vijoice 125 mg film-coated tablets are dark yellow, ovaloid tablets, debossed with “Y7” on one side and “NVR” on the other side. Approximate size: 13 mm x 6 mm.

Vijoice 200 mg film-coated tablets are pale yellow, ovaloid tablets, debossed with “CL7” on one side and “NVR” on the other side. Approximate size: 16 mm x 7 mm.

Vijoice is supplied as film-coated tablets in blisters. Vijoice is available in the following pack sizes:

- Packs containing 50 mg film-coated tablets (for patients on 50 mg daily dose)
  - Packs containing 28-day supply: 28 film-coated tablets.

- Packs containing 125 mg film-coated tablets (for patients on 125 mg daily dose)
  - Packs containing 28-day supply: 28 film-coated tablets.

- Packs containing 50 mg and 200 mg film-coated tablets (for patients on 250 mg daily dose)
  - Packs containing 28-day supply: 56 film-coated tablets (28 tablets of 50 mg and 28 tablets of 200 mg).

Not all pack sizes may be marketed.

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**This leaflet was last revised in**

This medicine has been given ‘conditional approval’. This means that there is more evidence to come about this medicine.
The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

**Other sources of information**
Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

**Package leaflet: Information for the patient**

**Vijoice 50 mg granules in sachet**
alpelisib

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, or pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, or pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**



## 1. What Vijoice is and what it is used for

**What Vijoice is**
Vijoice contains the active substance alpelisib, which belongs to a group of medicines called phosphatidylinositol-3-kinase (PI3K) inhibitors.

**What Vijoice is used for**
Vijoice is used to treat adults, adolescents and children from 2 years of age with severe or life-threatening PIK3CA-related overgrowth spectrum (PROS). PROS includes a broad range of rare disorders which cause uncontrollable overgrowth of parts of the body due to certain changes (mutations) in a gene called PIK3CA.

This gene leads to the production of a protein that instructs the body's cells to grow and multiply. The changes in the gene cause this protein to function irregularly and, as a consequence, help cells to grow and multiply in an abnormal way.

**How Vijoice works**
Vijoice works by blocking the effects of enzymes (proteins) called phosphatidylinositol-3-kinases (PI3K). These enzymes help abnormal cells to grow and multiply. By blocking their action, Vijoice can reduce uncontrollable growth and spread of the abnormal cells and help to reduce overgrown tissue and signs and symptoms of the disease in patients.

If you have any questions about how Vijoice works or why this medicine has been prescribed for you, ask your doctor, pharmacist or nurse.

## 2. What you need to know before you take Vijoice

Follow all of your doctor's instructions carefully, as they may differ from the general information in this leaflet. Check with your doctor if you are not sure.

**Do not take Vijoice**
- if you are allergic to alpelisib or any of the other ingredients of this medicine (listed in section 6). If you think you may be allergic, ask your doctor for advice.

**Warnings and precautions**
Talk to your doctor or pharmacist before taking Vijoice.

If any of the following apply to you before taking Vijoice, tell your doctor or pharmacist:
- if you have ever had a severe allergic reaction, including
  - Stevens-Johnson syndrome (SJS, a highly serious reaction with flu-like symptoms and painful rash affecting the skin, mouth, eyes and genitals);
  - erythema multiforme (EM, a skin reaction that causes red spots or patches on the skin, and that may look like a target or "bull's-eye" with a dark red centre surrounded by paler red rings);
  - drug reaction with eosinophilia and systemic symptoms (DRESS, a skin reaction combined with fever, facial swelling, enlarged lymph nodes and kidney or liver injury), or
  - toxic epidermal necrolysis (TEN, a serious skin reaction; possible symptoms include red skin, blistering of the lips, eyes or mouth, skin peeling, fever, rash).
- if you have, or have ever had, high levels of sugar in your blood or diabetes (or signs of increased sugar levels, such as excessive thirst and dry mouth, needing to pass urine more often than usual, producing greater amounts of urine than usual, tiredness, nausea, increased appetite with weight loss).

If any of the following apply to you during your treatment with Vijoice, tell your doctor or pharmacist immediately:
- Rash, itching, hives, breathlessness, difficulty breathing, wheezing, cough, light-headedness, dizziness, changes in levels of consciousness, low blood pressure, reddening of the skin, swelling of the face or throat, blue discolouration of the lips, tongue or skin (possible signs of severe allergic reactions).
- New or changing breathing problems such as difficult or painful breathing, cough, rapid breathing, blue discolouration of the lips, tongue or skin, hiccups (possible signs of non-infectious pneumonitis or pneumonia).
- Increased thirst and dry mouth, passing urine more often than usual, tiredness, increased appetite with weight loss, confusion, nausea, vomiting, fruity odour on breath, difficulty breathing, dry or flushed skin, which may be signs of increased blood sugar levels (hyperglycaemia) and its complications.
- Rash, reddening of the skin, blistering of the lips, eyes or mouth, skin peeling, sometimes with fever (possible signs of one of the following skin conditions: Stevens-Johnson syndrome (SJS), erythema multiforme (EM), drug reaction with eosinophilia and systemic symptoms (DRESS) or toxic epidermal necrolysis (TEN)).
- Severe diarrhoea, severe abdominal pain or stools with mucus or blood, which may be signs of inflammation of your intestine (colitis).

Your doctor may need to treat these symptoms, temporarily interrupt your treatment, reduce your dose, or permanently stop your treatment with Vijoice (see "How much Vijoice to take" in section 3).

**Make sure that you regularly test your blood sugar before you start treatment, during treatment and after you stop treatment with Vijoice.**
- Your doctor will advise you on how, when and where to carry out blood tests before starting and regularly during treatment with Vijoice to monitor your blood sugar levels. Based on the results, your doctor may prescribe a medicine to lower blood sugar levels, temporarily interrupt or reduce your Vijoice dose, or stop Vijoice treatment permanently.

- Treatment with Vijoice may only begin if your blood sugar levels are appropriate, as Vijoice can increase blood sugar (hyperglycaemia), which could be serious and require treatment.
- If you have certain conditions before you start treatment with Vijoice, such as high levels of sugar in your blood, diabetes, obesity, or age over 75 years, your blood sugar will need to be monitored more frequently during the first weeks of treatment with Vijoice. Afterwards, blood tests will be needed at least once a month, depending on your blood sugar levels.

**Children and adolescents**
Vijoice is not to be used in children under 2 years of age. The long-term effects of Vijoice on growth and development in children from 2 years of age and adolescents are not known.

**Other medicines and Vijoice**
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes in particular:
- ciclosporin, a medicine used to affect your immune system
- rifampicin, a medicine to treat tuberculosis and some other serious infections
- carbamazepine and phenytoin, medicines used to treat seizures or fits
- St. John's wort (also known as *Hypericum perforatum*), a herbal medicine used to treat depression and other conditions

Ask your doctor or pharmacist if you are not sure whether your medicine is one of the medicines listed above.

**Pregnancy**
Vijoice should not be used by women who are, or may be, pregnant. Vijoice may harm an unborn baby. If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

If you are a woman who could become pregnant, your doctor will check with you if you are pregnant and may perform a pregnancy test if necessary before starting treatment with Vijoice.

**Breast-feeding**
It is not known if Vijoice passes into breast milk. Therefore, you should not breast-feed during treatment with this medicine and for at least 1 week after the last dose.

**Contraceptive advice for women**
Women who could become pregnant should use an effective method of birth control during treatment and for at least 1 week after stopping Vijoice. It is not known if Vijoice reduces how well hormonal contraceptives work. If you use hormonal contraceptives, you should also use a barrier method. Ask your doctor about suitable methods. If you think you may be pregnant after starting treatment with Vijoice, tell your doctor immediately.

**Contraceptive advice for men**
During treatment and for at least 1 week after stopping treatment, male patients should use a condom for intercourse with female partners who could become pregnant. If the partner of a male patient suspects that she has become pregnant during this time, she should inform a doctor immediately.

**Driving and using machines**
Treatment with Vijoice may lead to tiredness or blurred vision. You should therefore be cautious when driving or using machines during your treatment with Vijoice.

**Vijoice contains sodium**
This medicine contains less than 1 mmol sodium (23 mg) per sachet, that is to say essentially "sodium-free".

## 3. How to take Vijoice

Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

**How much Vijoice to take**
The usual starting dose of Vijoice for adults is 250 mg once daily. The usual starting dose of Vijoice for adolescents and children (aged 2 years and older) is 50 mg once daily. Your doctor will decide on the right dose for you.

For a prescribed dose of 50 mg, take one sachet of 50 mg granules.

Depending on how your body responds to the treatment with Vijoice, your doctor may want to adjust your Vijoice dose (see section 2). It is very important to follow your doctor's instructions. If you have certain side effects, your doctor may ask you to interrupt treatment for a time, or to stop treatment.

**When to take Vijoice**
Take Vijoice once a day, immediately after food. Taking Vijoice at the same time each day will help you to remember when to take your medicine.

**How to take Vijoice**
Each sachet is for single use only. Do not use the sachet if the sachet seal is broken.

Take Vijoice granules as follows:
- Hold the sachet of granules with the cut line at the top.
- Shake the sachet gently to ensure the Vijoice granules are in the lower part of the sachet.
- Using scissors, open the sachet along the cut line.
- Take the granules out of the sachet in **one** of the following ways:
    - Pour the granules from one sachet directly onto your tongue, tapping the side and top of the sachet as necessary to ensure that it is completely empty. Swallow with about 50 to 150 ml of water only. If there are any granules left in your mouth, rinse your mouth with additional water and swallow to make sure that you have taken the full dose.

    **or**
    - Pour the granules from one sachet into a cup, tapping the side and top of the sachet as necessary to ensure that it is completely empty. Add 5 to 15 ml of a drink (water, milk or apple juice only) or soft food (puréed apple or yogurt only) and take the mixture right away. Rinse the cup with approximately 10 to 40 ml of the same drink or soft food. Take the mixture right away and ensure that you have taken the full dose. Repeat this step until there is no mixture remaining in the cup.
- Throw away any Vijoice granules mixed with water, milk, apple juice, puréed apple, or yogurt that is not taken within 2 hours after it is prepared.

**Administration of Vijoice via feeding tube**
Patients who cannot swallow Vijoice granules directly or as a mixture can be given Vijoice via certain feeding tubes. The type of tube will be determined by the doctor. The granules have to be prepared as follows:
- Pour the granules from one sachet into a cup, tapping the side and top of the sachet as necessary to ensure that it is completely empty.
- Add 20 ml of water to the same cup and stir with a spoon. Then draw up the entire contents from the cup into a syringe and give through the feeding tube. Repeat this step until there is no mixture remaining in the cup or in the syringe.
- Throw away any Vijoice mixture that is not taken within 60 minutes after it is prepared.

**How long to take Vijoice**
Take Vijoice for as long as your doctor tells you to.

This is a long-term treatment, possibly lasting for months or years. Your doctor will regularly monitor your condition to check that the treatment is having the desired effect.

If you have questions about how long to take Vijoice, talk to your doctor or to your pharmacist.

**If you take more Vijoice than you should**
People who have taken too many Vijoice granules may experience effects that are known side effects of alpelisib, including high blood sugar levels, nausea, tiredness and rash. If you accidentally take too many granules, or if someone else accidentally takes your medicine, contact a doctor or hospital for advice immediately. Medical treatment may be necessary.

**If you forget to take Vijoice**
If you forget to take a dose of Vijoice, you may still take it, immediately after food, up to 9 hours after the time you should have taken it. If you only remember more than 9 hours after you should have taken it, skip the dose for that day. The next day, take the dose at your usual time. Do not take a double dose to make up for the one that you missed.

**If you vomit after a dose of Vijoice**
If you vomit after you take the Vijoice granules, do not take any more granules until your next scheduled dose.

**If you stop taking Vijoice**
Stopping your treatment with Vijoice may cause your condition to become worse. Do not stop taking Vijoice unless your doctor tells you to stop.

If you have any further questions on the use of Vijoice, ask your doctor or pharmacist.

## 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

**Serious side effects**
If you get any serious side effects, **stop taking this medicine and tell your doctor immediately**.

**Very common** (*may affect more than 1 in 10 people)*:
- High levels of sugar in the blood, also called hyperglycaemia. Possible symptoms include: feeling very thirsty, passing urine more often than usual or passing greater amounts of urine than usual, increased appetite with weight loss

**Common** (*may affect up to 1 in every 10 people)*:
- Severe allergic reactions. Possible signs include: rash, itching, hives, breathlessness, difficulty breathing, wheezing, cough, light-headedness, dizziness, changes in levels of consciousness, low blood pressure, reddening of the skin, swelling of the face and/or throat, blue discolouration of the lips, tongue or skin

**Other possible side effects**
Other side effects include the following listed below. If these side effects become severe, tell your doctor, pharmacist or nurse.

**Very common** (*may affect more than 1 in 10 people)*:
- Decreased appetite
- Headache
- Diarrhoea
- Vomiting
- Mouth sores or ulcers with gum inflammation (stomatitis)
- Nausea

- Abdominal pain
- Rash
- Skin inflammation with rash (dermatitis)
- Dry skin
- Hair loss and hair thinning (alopecia)

**Common** *(may affect up to 1 in every 10 people)*:
- Dehydration
- Acne
- Itching (pruritus)
- Mucosal dryness

During Vijoice treatment, the results of some blood tests may be abnormal, as follows:

**Very common:**
- Low level of phosphorous or calcium in the blood (decreased phosphorous, decreased calcium)
- High level of creatinine or sugar in the blood (increased creatinine, increased glucose)
- High blood level of glycosylated haemoglobin (a marker of blood sugar level over the last 8 to 12 weeks)
- High blood levels of the lipase enzyme (lipase increased)

**Reporting of side effects**
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store Vijoice

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the sachet after "EXP". The expiry date refers to the last day of that month.

This medicine does not require any special temperature storage conditions.

Store in the original sachet in order to protect from light.

Do not take this medicine if you notice any damage to the packaging or if there are any signs of tampering.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## 6. Contents of the pack and other information

**What Vijoice contains**
- The active substance of Vijoice is alpelisib.
- Each Vijoice 50 mg granules sachet contains 50 mg alpelisib.
- The other ingredients are:
  - Cellulose microcrystalline (E460), mannitol (E421), sodium starch glycolate (see section 2 "Vijoice contains sodium"), hypromellose (E464), magnesium stearate (E470b).

**What Vijoice looks like and contents of the pack**
Vijoice 50 mg granules in sachet is a white to almost white free-flowing mixture of powder and granules in a sachet.

Each pack contains 28 sachets (28-day supply for patients on 50 mg daily dose).

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**Other sources of information**
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# ANNEX IV

# CONCLUSIONS ON THE GRANTING OF THE CONDITIONAL MARKETING AUTHORISATION PRESENTED BY THE EUROPEAN MEDICINES AGENCY

**Conclusions presented by the European Medicines Agency on:**

- **Conditional marketing authorisation**

The CHMP having considered the application is of the opinion that the risk-benefit balance is favourable to recommend the granting of the conditional marketing authorisation as further explained in the European Public Assessment Report.