NOVARTIS

Pivito®
(alpelisib)

50, 150 and 200 mg film-coated tablets

Professional Information

Document status: Final

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SCHEDULING STATUS: S4

1. NAME OF THE MEDICINAL PRODUCT

Pivikto® 50 mg film-coated tablets

Pivikto® 150 mg film-coated tablets

Pivikto® 200 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Pivikto 50 mg film-coated tablets

Each film-coated tablet contains 50 mg of alpelisib.

Pivikto 150 mg film-coated tablets

Each film-coated tablet contains 150 mg of alpelisib.

Pivikto 200 mg film-coated tablets

Each film-coated tablet contains 200 mg of alpelisib.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Pivikto 50 mg film-coated tablets

Light pink, unscored, round, curved film-coated tablet with bevelled edges, imprinted with “L7” on one side and “NVR” on the other side. Approximate diameter: 7.2 mm.

Pivikto 150 mg film-coated tablets

Pale red, unscored, ovaloid, curved film-coated tablet with bevelled edges, imprinted with “UL7” on one side and “NVR” on the other side. Approximate size: 14.2 mm (length); 5.7 mm (width).

Pivikto 200 mg film-coated tablets

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Pivikto is indicated in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated, advanced or metastatic breast cancer following progression on or after an endocrine-based regimen (see section 5.1).

4.2 Posology and method of administration

Treatment with Pivikto should be initiated by a medical practitioner experienced in the use of anticancer therapies.

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

Posology

The recommended dose of Pivikto is 300 mg (2 x 150 mg film-coated tablets) taken once daily on a continuous basis. Pivikto should be taken immediately after food, at approximately the same time each day (see section 5.2).

Swallow Pivikto tablets whole (tablets should not be chewed, crushed or split prior to swallowing). No tablet should be ingested if it is broken, cracked, or otherwise not intact.

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

When given with Pivikto, the recommended dose of fulvestrant is 500 mg administered on Days 1, 15, and 29, and once monthly thereafter. Please refer to the full prescribing information for fulvestrant.

Dose modifications

The recommended dose modifications for adverse reactions (ARs) are listed in Table 1.

Table 1 Pivikto dose reduction guidelines for adverse reactions (ARs)[1]

Pivikto dose level	Dose and schedule	Number and strength of tablets
Starting dose	300 mg once daily	Two 150 mg tablets
First dose reduction	250 mg once daily	One 200 mg tablet and one 50 mg tablet
Second dose reduction	200 mg once daily[2]	One 200 mg tablet
[1] Only one dose reduction is permitted for pancreatitis. [2] If further dose reduction below 200 mg once daily is required, discontinue Pivikto		

Tables 2 - 5 summarise the recommendations for dose interruption, reduction or discontinuation of Pivikto in the management of specific ARs.

Hyperglycaemia

In patients with risk factors for hyperglycaemia, monitor fasting glucose more closely and as clinically indicated (see section 4.4).

Prophylactic use of metformin has been shown to decrease the incidence and severity of hyperglycaemia when metformin is initiated 7 days prior to the start of treatment with Pivikto and

metformin dose titrated to the maximum tolerated dose (see section 4.4 and 4.8).

Table 2 Dose modification and management for hyperglycaemia

Fasting Glucose	**Recommendation**
Dose modifications and management should only be based on fasting glucose (plasma/blood) values	
Grade 1 >ULN-160 mg/dl or > ULN-8.9 mmol/l	No Pivikto dose adjustment required. Initiate or intensify oral anti-diabetic treatment[2].
Grade 2 >160-250 mg/dl or > 8.9-13.9 mmol/l	No Pivikto dose adjustment required. Initiate or further intensify oral antidiabetic treatment[2]. If FG does not decrease to ≤ 160 mg/dl or 8.9 mmol/l within 21 days with appropriate antidiabetic treatment, reduce Pivikto dose by 1 dose level and follow FG value specific recommendations.
Grade 3 > 250-500 mg/dl or > 13.9-27.8 mmol/l	Interrupt Pivikto. Initiate or intensify oral antidiabetic treatment[2] and consider additional antidiabetic medications[3] for 1 - 2 days until hyperglycaemia improves. Administer intravenous hydration and consider appropriate treatment (e.g. intervention for

	electrolyte/ketoacidosis/hyperosmolar disturbances). If FG decreases to ≤ 160 mg/dl or 8.9 mmol/l within 3 to 5 days under appropriate antidiabetic treatment, resume Pivikto at next lower dose level. If FG does not decrease to ≤ 160 mg/dl or 8.9 mmol/l within 3 to 5 days under appropriate antidiabetic treatment, consultation with a healthcare professional with expertise in the treatment of hyperglycaemia is recommended. If FG does not decrease to ≤ 160 mg/dl or 8.9 mmol/l within 21 days following appropriate antidiabetic treatment[2], permanently discontinue Pivikto treatment.
Grade 4 > 500 mg/dl or ≥ 27.8 mmol/l	Interrupt Pivikto. Initiate or intensify appropriate antidiabetic treatment[2] (e.g. intervention for electrolyte/ketoacidosis/hyperosmolar disturbances), re-check FG within 24 hours and as clinically indicated. If FG decreases to ≤ 500 mg/dl or ≤ 27.8 mmol/l, then follow FG value specific recommendations for Grade 3. If FG is confirmed at > 500 mg/dl or ≥ 27.8 mmol/l, permanently discontinue Pivikto treatment.
[1] FG- Grade levels reflect hyperglycaemia grading according to CTCAE Version 4.03 (CTCAE = Common Terminology Criteria for Adverse Events). [2] Initiate applicable anti-diabetic medications, including metformin and insulin sensitizers (such as thiazolidinediones or dipeptidyl peptidase-4 inhibitors), and review respective	

prescribing information for dosing and dose titration recommendations, including local diabetic treatment guidelines. Metformin was recommended in the SOLAR-1 trial with the following guidance: *Initiate metformin 500 mg once daily. Based on tolerability, metformin dose may be increased to 500 mg twice daily, followed by 500 mg with breakfast, and 1000 mg with dinner, followed by further increase to 1000 mg twice daily if needed* (see section 4.4). Currently metformin is the only oral antidiabetic medication that has been clinically evaluated in combination with Pivikto.

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

Rash

Table 3 Dose modification and management for rash Grade[1,2]	**Recommendation[3]**
Grade 1 (< 10 % body surface area (BSA) with active skin toxicity)	No Pivikto dose adjustment required. Initiate topical corticosteroid treatment. Consider adding oral antihistamine treatment to manage symptoms. If active rash is not improved within 28 days of appropriate treatment, add a low dose systemic corticosteroid.

Grade 2 (10 - 30 % BSA with active skin toxicity)	No Pivikto dose adjustment required. Initiate or intensify topical corticosteroid and oral antihistamine treatment. Consider low-dose systemic corticosteroid treatment. If rash improves to Grade ≤ 1 within 10 days, systemic corticosteroid may be discontinued.
Grade 3 (e.g. severe rash not responsive to medical management) (> 30 % BSA with active skin toxicity)	Interrupt Pivikto until rash improves to Grade ≤ 1. Initiate or intensify topical / systemic corticosteroid and antihistamine treatment. Once rash improves to Grade ≤ 1, then resume Pivikto at next lower dose level.
Grade 4 (e.g. severe bullous, blistering or exfoliating skin conditions) (any % BSA associated with extensive superinfection, with intravenous antibiotics indicated; life-threatening consequences)	Permanently discontinue Pivikto.

[1] Grading according to CTCAE Version 5.0

[2] For all grades of rash, consider consultation with a dermatologist.

[3] Antihistamines administered prior to rash onset may decrease incidence and severity of rash based on the SOLAR-1 trial.

Diarrhoea or colitis

Table 4 Dose modification and management for diarrhoea or colitis

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

[1] Grading according to 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 additionally be managed according to local standard of care, including electrolyte monitoring, administration of antiemetics and antidiarrheal medicinal products and/or fluid replacement and electrolyte supplements, as clinically indicated.

Other toxicities

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

Grade[1]	Recommendation
Grade 1 or 2	No Pivikto dose adjustment required. Initiate appropriate medical therapy and monitor as clinically indicated[2,3].
Grade 3	Interrupt Pivikto dose until recovery to Grade ≤ 1, then resume Pivikto at the next lower dose level[2].
Grade 4	Permanently discontinue Pivikto.

[1] Grading according to CTCAE Version 5.0

[2] For Grade 2 and 3 pancreatitis, interrupt Pivikto dose until recovery to Grade < 2 and resume at next lower dose level. Only one dose reduction is permitted. If toxicity recurs, permanently discontinue Pivikto treatment.

[3] For Grade 2 total bilirubin elevation, interrupt Pivikto dose until recovery to Grade ≤ 1 and resume at the same dose if resolved in ≤ 14 days or resume at the next lower dose level if resolved in > 14 days.

Special populations

Elderly

No dose regimen adjustment is required in patients aged 65 years or above (see section 5.2).

Renal impairment

Based on population pharmacokinetic analysis, no dose adjustment is necessary in patients with mild or moderate renal impairment (CrCl 30 to < 90 ml/min) (see section 5.2). Caution should be used in patients with severe renal impairment (CrCl < 30 ml/min) as there is no experience with Pivikto in this

population.

Hepatic impairment

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

Paediatric population

The safety and efficacy of Pivikto in paediatric patients have not been established.

Method of administration:

Pivikto tablets should be swallowed whole. They should not be chewed, crushed or split prior to swallowing. Tablets that are broken, cracked or otherwise not intact should not be ingested.

4.3 Contraindications

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

Pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

Hypersensitivity (including anaphylactic reaction)

Serious hypersensitivity reactions (including anaphylactic reaction and anaphylactic shock), manifested

by symptoms including, but not limited to, dyspnoea, flushing, rash, fever or tachycardia, were reported in patients treated with Pivikto in clinical studies. Angioedoema has been reported in the post-marketing setting in patients treated with Pivikto (see section 4.8). Pivikto should be permanently discontinued in patients with serious hypersensitivity reactions. Appropriate treatment should be promptly initiated.

Severe cutaneous reactions

Severe cutaneous reactions have been reported with Pivikto. In the Phase III clinical study, Stevens-Johnson syndrome (SJS) and erythema multiforme (EM) were reported in 0.4 % and 1.1 % of patients, respectively. Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported in the post-marketing setting (see section 4.8).

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

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

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

Hyperglycaemia

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

Hyperglycaemia was reported in 65 % of patients treated with Pivikto in the Phase III clinical study. Grade 2 (FPG 160 – 250 mg/dl), 3 (FPG >250 – 500 mg/dl) or 4 (FPG > 500 mg/dl) hyperglycaemia were reported in 15,8 %, 33,1 % and 3,9 % of patients, respectively, in the Phase III clinical study. Patients should be advised of the signs and symptoms of hyperglycaemia (e.g. excessive thirst, urinating more often than usual or higher amount of urine than usual, increased appetite with weight loss).

In the phase III clinical study, patients with a history of diabetes mellitus intensified anti-diabetic medication(s) while on treatment with Pivikto; therefore, these patients require monitoring and possibly intensified anti-diabetic treatment. Patients with poor glycaemic control may be at a higher risk of developing severe hyperglycaemia and associated complications. Patients with risk factors for hyperglycaemia such as obesity (BMI ≥ 30), elevated FG or HbA1c at or above the upper limit of normal, or age ≥ 75 are at a higher risk of developing severe hyperglycaemia. The schedule for monitoring fasting glucose is presented in Table 6-1.

Table 6-1 Schedule of fasting plasma glucose monitoring

	Recommended schedule for the monitoring of fasting plasma glucose and HbA1c levels in all patients treated with Pivikto	**Recommended schedule of monitoring of fasting plasma glucose and HbA1c levels in patients with diabetes, pre-diabetes, BMI ≥30 or age ≥75 years treated with Pivikto**
At screening, before initiating treatment with Pivikto	Test for fasting plasma glucose (FPG), HbA1c, and optimize the patient's level of blood glucose.	
After initiating treatment with Pivikto	Monitor/self-monitor fasting glucose 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*.	Monitor/self-monitor fasting glucose more frequently for the first few weeks of treatment. Then continue to monitor fasting glucose as frequently as needed to manage hyperglycaemia according to the instructions of a healthcare professional*.
	HbA1c should be monitored every 3 months as clinically indicated.	
If hyperglycaemia develops after initiating treatment with Pivikto	Monitor fasting glucose regularly, as per local standard of care and at least until fasting glucose decreases to normal levels.	

	During treatment with antidiabetic medication, continue monitoring fasting glucose at least once a week for 8 weeks, followed by once every 2 weeks, and monitor fasting glucose according to the instructions of a healthcare professional with expertise in the treatment of hyperglycaemia.
** All glucose monitoring should be performed at the physician's discretion as clinically indicated.*	

Prophylactic use of metformin has been shown to decrease the incidence and severity of hyperglycaemia when metformin is initiated 7 days prior to the start of treatment with Pivikto (see section 4.2 and section 4.8).

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

The safety of Pivikto in patients with Type 1 and uncontrolled Type 2 diabetes mellitus has not been established as these patients were excluded from the SOLAR-1 trial. Patients with a medical history of Type 2 diabetes mellitus were included. They may require intensified diabetic treatment and should be closely monitored.

Pneumonitis

Pneumonitis, including serious cases of pneumonitis/acute interstitial lung disease, have been reported in Pivikto-treated patients in clinical studies. Patients should be advised to report promptly any new or worsening respiratory symptoms. In patients who have new or worsening respiratory symptoms or are

suspected to have developed pneumonitis, Pivikto 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. Pivikto should be permanently discontinued in all patients with confirmed pneumonitis.

Diarrhoea or colitis

Severe diarrhoea, including dehydration and acute kidney injury, occurred in patients treated with Pivikto.

Most patients (58 %) experienced diarrhoea during treatment with Pivikto. Grade 3 diarrhoea occurred in 7 % (n = 19) of patients. Among patients with Grade 2 or 3 diarrhoea (n = 71), the median time to onset was 46 days (range: 1 to 442 days).

Colitis has been reported in the post-marketing setting in patients treated with Pivikto (see section 4.8).

Dose reductions of Pivikto were required in 5,6 % of patients and 2,8 % of patients discontinued Pivikto due to diarrhoea. In the 164 patients who experienced diarrhoea, antidiarrhoeal medications (e.g. loperamide) were required to manage symptoms in 63 % (104/164).

Patients should be monitored for diarrhoea and additional symptoms of colitis, such as abdominal pain and mucus or blood in stool. Based on the severity of the diarrhoea or colitis, Pivikto may require dose interruption, reduction, or discontinuation as described in Table 4 (see section 4.2).

Patients should be advised to notify their healthcare provider if diarrhoea or additional symptoms of colitis occur while taking Pivikto. Patients should be managed according to local standard of care medical management, including electrolyte monitoring, administration of anti-emetics and anti-diarrhoeal medications and/or fluid replacement and electrolyte supplements, as clinically indicated.

In case of colitis, additional treatment, such as steroids, may be considered as clinically indicated.

Osteonecrosis of the jaw (ONJ)

In the Phase III clinical study, ONJ was reported in 4,2 % patients (12/284) in the Pivikto plus fulvestrant arm compared to 1,4 % patients (4/287) in the placebo plus fulvestrant arm. All patients experiencing ONJ were also exposed to prior or concomitant bisphosphonates (e.g. zoledronic acid). Therefore, in patients receiving Pivikto and bisphosphonates, an increased risk of development of ONJ cannot be excluded.

4.5 Interaction with other medicinal products and other forms of interaction

Medicinal products that may increase alpelisib plasma concentrations

BCRP inhibitors

Coadministration of Pivikto with a BCRP (breast cancer resistance protein) inhibitor may increase alpelisib concentration, which may increase the risk of toxicities. Avoid the use of BCRP inhibitors in patients treated with Pivikto. If unable to use alternative drugs, when Pivikto is used in combination with BCRP inhibitors, closely monitor for increased adverse reactions.

Medicinal products that may decrease alpelisib concentrations

CYP3A4 Inducers

Coadministration of Pivikto with a strong CYP3A4 inducer may decrease alpelisib concentration, which may decrease alpelisib activity. Avoid coadministration of Pivikto with strong CYP3A4 inducers.

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

Medicinal products whose plasma concentrations may be altered by alpelisib

CYP3A4, CYP2C8, CYP2C9, CYP2C19 and CYP2B6 substrates

No dose adjustment is required when co-administering Pivikto with CYP3A4 substrates (e.g. everolimus, midazolam), CYP2C8 substrates (e.g. repaglinide), CYP2C9 substrates (e.g. warfarin), CYP2C19 (e.g. omeprazole) and CYP2B6 substrates (e.g. bupropion, efavirenz).

Effect of Alpelisib on Transporters:

Alpelisib is an inhibitor of P-gp. Alpelisib has a low potential to inhibit BCRP, MRP2, BSEP, OATP1B1,

OATP1B3, OCT1, OAT1, OAT3, OCT2, MATE1, and MATE2K at clinically relevant concentrations.

4.6 Fertility, pregnancy and lactation

Contraception in males and females

Females of reproductive potential should be advised that animal studies and the mechanism of action have shown that alpelisib can be harmful to the developing foetus.

Females of reproductive potential should use effective contraception during treatment with Pivikto and for 1 week after the last dose. It is currently unknown whether alpelisib may reduce the effectiveness of systemically acting hormonal contraceptives.

Male patients with sexual partners who are pregnant, possibly pregnant or who could become pregnant should use condoms and effective contraception during Pivikto treatment and for 1 week after the last dose.

Please refer to the full prescribing information of fulvestrant for pregnancy information.

Pregnancy

Pivikto should not be used during pregnancy (see section 4.3).

Based on animal data and its mechanism of action, Pivikto can cause foetal harm when administered to a pregnant woman.

Embryo-fetal development studies in rats and rabbits have demonstrated that oral administration of alpelisib during organogenesis induced embryo-toxicity, foeto-toxicity, and teratogenicity.

Breastfeeding

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

Because of the potential for serious adverse reactions in the breastfed infant, it is recommended that women should not breastfeed during treatment and for at least 1 week after the last dose of Pivikto.

Fertility

There are no data on the effects of alpelisib on fertility. Based on repeated dose toxicity 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

Patients should be advised to be cautious when driving or using machines in case they experience fatigue or blurred vision during treatment (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The safety profile is based on data from 284 patients in the Pivikto plus fulvestrant arm of the double-blind, placebo-controlled phase III study.

The most common adverse drug reactions (ADRs) (all grades, incidence ≥ 20 %) were glucose increased, creatinine increased, diarrhoea, gamma-glutamyltransferase increased, rash, lymphocyte count decreased, nausea, alanine aminotransferase increased, fatigue, haemoglobin increased, lipase increased, decreased appetite, stomatitis, vomiting, weight decreased, hypocalcaemia, glucose

decreased, activated partial thromboplastin time (aPTT) prolonged and alopecia.

METALLICA safety information:

Additional safety evaluation regarding hyperglycaemia was performed in the Phase II, multicenter, open-label, single-arm, two-cohort study which assessed the prophylactic use of metformin for prevention of alpelisib-induced Grade 3/4 hyperglycaemia in patients with HR-positive, HER2-negative advanced breast cancer harboring PIK3CA mutation(s).

In this Phase II study, metformin plus endocrine therapy (fulvestrant, letrozole or exemestane) was initiated 7 days prior to treatment with Pivikto in adult patients progressing on an aromatase inhibitor (AI)-based treatment (≤ 2 previous endocrine and ≤ 1 prior chemotherapy regimens for advanced breast cancer).

A total of 68 patients were enrolled to one of two cohorts. 48 patients with normal glycaemic status (FPG <100 mg/dL [<5.6 mmol/L] and HbA1c <5.7 %) were assigned to cohort A and 20 patients with impaired glycaemic status (FPG 100 to 140 mg/dL [5.6 to 7.8 mmol/L] or HbA1c 5.7 to 6.4 %) were assigned to cohort B. The majority of patients (63/68, 92.6 % [45 in cohort A, 18 in cohort B]) received fulvestrant as endocrine therapy during the study.

Metformin was initiated 7 days prior to the start of treatment with Pivikto as follows: metformin 500 mg twice daily from day 1 to day 3, thereafter increased up to 1,000 mg twice daily based on tolerability.

The most common AEs (reported in ≥30 % of patients) in the study were diarrhoea (67.6 %), nausea (67.6 %), fatigue (45.6 %), hyperglycaemia (44.1 %), rash (38.2 %) and vomiting (33.8 %). The most common Grade 3/4 AEs (reported in ≥ 5 % of patients) were rash (16.2 %), diarrhoea (13.2 %) and hyperglycaemia (5.9 %).

The incidence of diarrhoea observed in the study could be attributed to the initial GI intolerability caused by both metformin and Pivikto. The majority of the reported diarrhoea events were Grade 1 to 2. For

management recommendations of diarrhoea, see section 4.5.

Tabulated list of adverse reactions

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

Table 6 ADRs observed in phase III clinical study and during post-marketing experience

Blood and lymphatic system disorders	*Very common*: Anaemia (10 %; grade 3-4: 4 %) *Common*: Lymphopenia, thrombocytopenia
Eye disorders	*Common*: Blurred vision, dry eye
Gastrointestinal disorders	*Very common*: Diarrhoea (58 %; grade 3-4: 7 %), nausea (45 %; grade 3-4: 3 %), stomatitis (also includes aphthous ulcer and mouth ulceration) (30 %; grade 3-4: 3 %), vomiting (27 %; grade 3-4: 1 %), abdominal pain (17 %; grade 3-4: 1 %), dyspepsia (11 %; grade 3-4: 0 %) *Common*: Toothache, gingivitis, cheilitis, gingival pain, increased lipase* *Uncommon*: Pancreatitis

Hepatobiliary disorders	*Common*: Increased gamma-glutamyltransferase*, increased alanine aminotransferase*
General disorders and administration site conditions	*Very common*: Fatigue (42 %; grade 3-4: 5 %), mucosal inflammation (19 %; grade 3-4: 2 %), peripheral oedema (15 %; grade 3-4: 0 %), fever (14 %; grade 3-4: 1%), mucosal dryness (12 %; grade 3-4: <1 %) *Common*: Oedema (also includes facial oedema)
Immune system disorders	*Common*: Hypersensitivity (also includes allergic dermatitis, anaphylactic reactions and anaphylactic shock)
Infections and infestations	*Very common*: Urinary tract infection (also includes a single case of urosepsis) (10 %; grade 3-4: 1 %)
Metabolism and nutrition disorders	*Very common*: Hyperglycaemia (65 %; grade 3-4: 37 %), decreased appetite (36 %; grade 3-4: 1 %), decreased weight (27 %; grade 3-4: 4 %) *Common*: Hypokalaemia, hypocalcaemia, dehydration, increased glycosylated haemoglobin *Uncommon*: Ketoacidosis (also includes diabetic ketoacidosis)
Musculoskeletal and connective tissue disorders	*Common*: Muscle spasms, myalgia, osteonecrosis of the jaw
Nervous system disorders	*Very common*: Headache (18 %; grade 3-4: 1 %), dysgeusia (also includes ageusia, hypogeusia) (18 %; grade 3-4: < 1 %)

Psychiatric disorders	*Common*: Insomnia
Renal and urinary disorders	*Very common*: Increased blood creatinine (10 %; grade 3-4: 2 %) *Common*: Acute kidney injury
Respiratory, thoracic and mediastinal disorders	*Common*: Pneumonitis (also includes interstitial lung disease)
Skin and subcutaneous tissue disorders	*Very common*: Rash (52 %; grade 3-4: 20 %), alopecia (20 %; grade 3-4: 0 %), pruritus (18 %; grade 3-4: 1 %), dry skin (18 %; grade 3-4: < 1 %) *Common*: Erythema (includes generalised erythema), dermatitis (also includes acneiform dermatitis), palmar-plantar erythrodysaesthesia syndrome, erythema multiforme *Uncommon*: Stevens-Johnson syndrome
Vascular disorders	*Common*: Hypertension, lymphoedema

Post-marketing adverse effects

Eye disorders	Unknown: Uveitis
Gastrointestinal disorders	Unknown: Colitis
Metabolism and nutrition disorders	Unknown: Hyperglycaemic hyperosmolar nonketotic syndrome
Skin and subcutaneous tissue disorders	Unknown: Angioedema, Drug reaction with eosinophilia and systemic symptoms (DRESS)

Description of selected ADRs

Hyperglycaemia

In the Phase III clinical study hyperglycaemia (FPG > 160 mg/dl) was reported in 184 (64,8 %) patients. Hyperglycaemia resolved to grade ≤ 1 (FPG < 160 mg/dl) in 166 (88,8 %) of the 187 patients. Interruptions of treatment and dose adjustments due to hyperglycaemia were reported in 26,8 % and 28,9 % of patients, respectively, in the Pivikto plus fulvestrant arm. Hyperglycaemia leading to discontinuation of Pivikto and/or fulvestrant was reported in 19 (6,7 %) patients.

In the Phase II clinical study (Metallica) the primary objective was to assess the occurrence of Grade 3/4 hyperglycaemic events (defined using both fasting glucose values and reported adverse events) in the first two cycles of initiating Pivikto in patients who received prophylactic metformin.

The study met its primary objective, with 2.1 % (1/48; 95 % CI: 0.5, 11.1; p < 0.001) of patients in cohort A and 15.0 % (3/20; 95 % CI: 5.6, 37.8; p = 0.016) of patients in cohort B experiencing Grade 3/4 hyperglycaemia during the first two cycles of treatment with Pivikto plus any endocrine therapy (fulvestrant, letrozole or exemestane).

For patients on Pivikto with fulvestrant as endocrine therapy, Grade 3/4 hyperglycaemia incidence rates were 2.2 % (1/45 patients) and 16.7 % (3/18 patients) in cohorts A and B, respectively. No additional patients reported Grade 3/4 hyperglycaemia after the first two cycles of treatment with Pivikto. The overall incidence of any Grade hyperglycaemia adverse events was 33.3 % (16/48 patients) and 70.0 % (14/20 patients) in cohort A and cohort B, respectively.

Dose reduction of Pivikto due to AEs was reported in 27.9 % of patients, of which, it was due to hyperglycaemia in 5.9 % of patients.

No Pivikto treatment discontinuations were related to hyperglycaemia.

Rash

Rash events (including rash maculopapular, macular, generalised, papular and pruritic, dermatitis and dermatitis acneiform) were reported in 153 (53,9 %) patients. Rash was predominantly mild or moderate (grade 1 or 2) and responsive to therapy, and in some cases rash was accompanied by pruritus and dry skin.

Grade 2 and 3 events were reported in 13,7 % and 20,1 % of patients, respectively, with a median time to first onset of 12 days (range: 2 days to 220 days).

Topical corticosteroid treatment should be initiated at the first signs of rash and oral corticosteroid treatment should be considered for moderate to severe rashes. Additionally, antihistamines are recommended to manage symptoms of rash. In the Phase III study use of at least one topical corticosteroid was reported in 73,9 % (113/153) of patients who developed a rash and use of at least one oral antihistamine in 67,3 % (103/153). Systemic corticosteroids were administered in 23 % (66/284) of patients to treat rashes. Of the patients who received systemic corticosteroids 55 % (36/66) received oral corticosteroids to treat rash. At least one event of rash resolved in the majority of the patients (92 %, 141/153). Treatment with Pivikto and/or fulvestrant was discontinued due to rash in 12 patients (4,2 %).

A subgroup of 86 patients received antirash treatment, including antihistamines, prior to the onset of rash. In these patients, rash was reported less frequently than in the overall study population for all grades of rash (26,7 % vs 53.9 %), grade 3 rash (11,6 % vs 20,1 %) and rash leading to permanent discontinuation of Pivikto (3,5 % vs 4,2 %). Accordingly, antihistamines may be initiated prophylactically at the time of initiation of treatment with Pivikto. Based on the severity of the rash interruption of treatment with Pivikto, dose reduction or discontinuation of treatment may be required as described in Table 3 “Dose modification and management for rash” (see section 4.2).

Gastrointestinal toxicity (nausea, diarrhoea, vomiting)

Diarrhoea, nausea and vomiting were reported in 57,7 %, 44,7 % and 27,1 % of the patients, respectively, and led to discontinuation of Pivikto and/or fulvestrant in 8 (2,8 %), 5 (1,8 %) and 3 (1,1 %) patients, respectively.

Grade 2 and 3 diarrhoea events were reported in 18,3 % and 6,7 % of patients, respectively, with a median time to onset of grade ≥ 2 diarrhoea of 46 days (range: 1 day to 442 days).

Severe diarrhoea and clinical consequences, such as dehydration and acute kidney injury, have been reported during treatment with Pivikto and resolved with appropriate intervention (see Table 4). Antiemetics (e.g. ondansetron) and antidiarrhoeal medicinal products (e.g. loperamide) were used in 27/149 (18,1 %) and 104/164 (63,4 %) patients, respectively, to manage symptoms.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on the SAHPRA website.

4.9 Overdose

Symptoms

The adverse reactions associated with overdose have been consistent with the safety profile of Pivikto 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 Pivikto.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, other antineoplastic agents, ATC code: L01XX65

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-signaling, cellular transformation and the generation of tumours in a variety of preclinical models.

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

In vivo, alpelisib inhibited the PI3K/AKT signaling pathway and reduced tumour growth in xenograft models, including models of breast cancer.

PI3K inhibition by alpelisib treatment has been shown to induce an increase in oestrogen receptor (ER) transcription in breast cancer cells. The combination of alpelisib and fulvestrant demonstrated increased anti-tumour activity compared to either treatment alone in xenograft models derived from ER-positive, PIK3CA mutated breast cancer cell lines.

Cardiac Electrophysiology

Serial ECGs were collected following a single dose and at steady-state to evaluate the effect of alpelisib on the QTcF interval in patients with advanced cancer. An analysis of clinical ECG data demonstrates the absence of a large effect (i.e. > 20 ms) on QTcF prolongation at the recommended 300 mg dose with or without fulvestrant.

5.2 Pharmacokinetic properties

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

Absorption

Following oral administration of alpelisib, median time to reach peak plasma concentration (T_{max}) ranged between 2,0 to 4,0 hours, independent of dose, time or regimen. Steady-state plasma levels of alpelisib after daily dosing can be expected to be reached on day 3 following onset of therapy in most patients.

Food effect

Alpelisib absorption is affected by food.

A high-fat high-calorie meal (985 calories with 58,1 g of fat) increased alpelisib AUC by 73 % and C_{max} by 84 %, and a low-fat low-calorie meal (334 calories with 8,7 g of fat) increased alpelisib AUC by 77 % and C_{max} by 145 % following a single dose of Pivikto. No clinically significant differences in alpelisib AUC were observed between low-fat low-calorie and high-fat high-calorie meals.

Distribution

Alpelisib moderately binds to protein with a free fraction of 10,8 % regardless of concentration. Alpelisib was equally distributed between red blood cells and plasma with a mean *in vivo* blood-to-plasma ratio of 1.03. As alpelisib is a substrate of human efflux transporters, penetration of the blood-brain barrier is not expected to occur in humans. The volume of distribution of alpelisib at steady state (Vss/F) is estimated at 114 litres (intersubject CV % 46 %).

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 minor contribution of CYP3A4. Alpelisib hydrolysis occurs systemically by both chemical decomposition and enzymatic hydrolysis via ubiquitously expressed, high-capacity enzymes (esterases, amidases, choline esterase) not limited to the liver. CYP3A4-mediated metabolites and glucuronides amounted to ~15 % of the dose; BZG791 accounted for ~40 – 45 % of the dose. The rest of the absorbed fraction of the dose was excreted as alpelisib.

Elimination

Alpelisib exhibits low clearance with 9,2 l/h (CV % 21 %) based on population pharmacokinetic analysis under fed conditions. The population-derived half-life, independent of dose and time, was 8 to 9 hours at steady state with 300 mg once daily.

In a human mass-balance study, after oral administration, alpelisib and its metabolites were excreted in

the faeces (81,0 %), mainly through hepatobiliary export and/or intestinal secretion of alpelisib, or metabolised to BZG791.

Excretion in the urine is minor (13,5 %), with unchanged alpelisib (2 %). Following a single oral dose of [14C]-alpelisib, 94,5 % of the total administered radioactive dose was recovered within 8 days.

Linearity/non-linearity

The pharmacokinetics were found to be linear with respect to dose and time under fed conditions between 30 and 450 mg. After multiple doses, alpelisib exposure (AUC) at steady state is only slightly higher than that of a single dose, with an average accumulation of 1,3 to 1,5 with a daily dosing regimen.

Metabolic interaction

CYP3A4 substrates

In a drug-drug interaction study with the sensitive CYP3A4 substrate everolimus, AUC increased by 11,2 %. No clinically meaningful change is expected as a result of drug interaction with CYP3A4 substrates.

Effect of Alpelisib on CYP Enzymes:

Alpelisib inhibits CYP3A4 in a time-dependent manner and induces CYP2B6, CYP2C9 and CYP3A4.

Transporter-based interaction

Alpelisib showed only weak *in vitro* inhibition towards the ubiquitously expressed efflux transporters

(P-gp, BCRP, MRP2, BSEP), solute carrier transporters at the liver inlet (OATP1B1, OATP1B3, OCT1) and solute carrier transporters in the kidney (OAT1, OCT2, MATE1, MATE2K).

As unbound systemic steady-state concentrations (or concentrations at the liver inlet) at both the therapeutic dose and maximum tolerated dose are significantly lower than the experimentally determined unbound inhibition constants or IC_{50}, the inhibition will not translate into clinical significance.

Special populations

Effect of age, weight and gender

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

Paediatric patients (below 18 years)

The pharmacokinetics of Pivikto in paediatric patients have not been established.

Elderly (age 65 years or above)

Of 284 patients who received Pivikto in the phase III study, 117 patients were ≥ 65 years of age and 34 patients were ≥ 75 years of age. No overall differences in effectiveness of Pivikto were observed between these patients and younger patients (see section 4.2).

Race/Ethnicity

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

of Pivikto.

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

Renal impairment

No dose adjustment is necessary in patients with mild or moderate renal impairment. Based on a population pharmacokinetic analysis that included 117 patients with normal renal function (eGFR ≥ 90 ml/min/1.73 m^2) / (CLcr ≥ 90 ml/min), 108 patients with mild renal impairment (eGFR 60 to < 90 ml/min/1.73 m^2)/ (CLcr 60 to <9 0 ml/min), and 45 patients with moderate renal impairment (eGFR 30 to < 60 ml/min/1,73 m^2), mild and moderate renal impairment had no effect on the exposure of alpelisib (see section 4.2).

Hepatic impairment

No dose adjustment is necessary in patients with mild, moderate or severe hepatic impairment (Child-Pugh A, B and C). Based on a pharmacokinetic study in patients with hepatic impairment, moderate and severe hepatic impairment had negligible effect on the exposure of alpelisib (see section 4.2). The mean exposure for alpelisib was increased 1.26-fold in patients with severe (GMR: 1.00 for C_{max}; 1.26 for AUC_{last}/AUC_{inf}) hepatic impairment.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Cellulose microcrystalline

Mannitol

Sodium starch glycolate

Hypromellose

Magnesium stearate

Film coating

Hypromellose

Iron oxide, black (E172)

Iron oxide, red (E172)

Titanium dioxide (E171)

Macrogol

Polyethylene glycol

Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30 °C.

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

6.5 Nature and contents of container

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

Pivikto 50 mg and 200 mg film-coated tablets (Multipacks)

Packs containing 28 film-coated tablets (14 of 50 mg and 14 of 200 mg) or 56 film-coated tablets (28 of 50 mg and 28 of 200 mg).

Pivikto 50 mg

Packs containing 28 or 56 film-coated tablets.

Pivikto 150 mg film-coated tablets

Packs containing 28 or 56 film-coated tablets.

Pivikto 200 mg film-coated tablets

Packs containing 14 or 28 film-coated tablets.

Not all pack sizes may be marketed.

7. MARKETING AUTHORISATION HOLDER

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8. REGISTRATION NUMBER:

Pivikto® 50 mg: 55/26/0290

Pivikto® 150 mg: 55/26/0291

Pivikto® 200 mg: 55/26/0292

9. DATE OF FIRST AUTHORISATION

30 November 2021

10. DATE OF REVISION OF THE TEXT

25 June 2026