Indication	For the treatment of hormone-receptor positive, HER2-negative, locally advanced or metastatic breast cancer in patients previously treated with a CDK4/6 inhibitor and an aromatase inhibitor where a PIK3CA mutation has been identified in a tumour or plasma specimen using a validated test. NB: No prior treatment with fulvestrant for any indication permitted.
Treatment Intent	Palliative
Frequency and number of cycles	28 days Until disease progression or excessive toxicity or patient choice to discontinue.
Monitoring Parameters pre-treatment	• **Virology screening:** All new patients referred for systemic anti-cancer treatment should be screened for hepatitis B and C and the result reviewed prior to the start of treatment. Patients not previously tested who are starting a new line of treatment, should also be screened for hepatitis B and C. Further virology screening will be performed following individual risk assessment and clinician discretion. • Baseline fasting glucose and HbA1c should be undertaken 1 week prior to start of treatment and if abnormal, treatment will need to be delayed until specialist diabetic advise has been obtained. HbA1c should be repeated 4 weeks after the start of treatment and every 3 months thereafter. • Monitor FBC, U&Es, LFTs and fasting glucose at baseline, day 8, 15 and 22 of cycle 1 and day 1 and 15 of cycle 2 and at the beginning of each cycle for 6 months and then, if clinically indicated, every 3 months thereafter. **See table 5 for monitoring of fasting glucose (including HbA1c test).** Patients should also self-monitor for hyperglycaemia as directed by the clinician in the first 4 weeks of treatment. • **NB**: Platelets should be >/=50 for intramuscular injection with fulvestrant. • If neutrophils <1.5 and / or PLT <100 prior to the start of treatment d/w consultant. • During treatment, if neutrophils 0.5 - <1.0 omit dose of alpelisib until neutrophils >/=1.5, then reduce by one dose level. If neutrophils <0.5 discontinue alpelisib. If platelets 25 - <50 omit dose until platelets >/=75, then reduce by one dose level. If PLT <25 discontinue alpelisib. • **Febrile neutropenia** (ANC < 1.0 x 10^9/L, with a single temperature of >/= 38.3 °C or a sustained temperature of >/= 38 °C for more than one hour) omit dose until resolved, then reduce by one dose level. • For grade 2 total **bilirubin elevation** (> 1.5 - 3.0 x ULN), interrupt Alpelisib dose until recovery to grade </=1 (</=1.5 x ULN) and resume at the same dose if resolved in </=14 days or resume at the next lower dose level if resolved in >14 days. Grade 3 (> 3.0 - 10.0 x ULN) interrupt Alpelisib dose until improvement to grade </=1, then resume Alpelisib at the next lower dose level. Grade 4 (>10 x ULN), permanently discontinue alpelisib. • If the patient is female they should either be post-menopausal, or if pre- or peri-menopausal, should have undergone ovarian ablation or suppression with LHRH agonist treatment. • **Dose Modifications**: • A dose of 300mg alpelisib should not be exceeded. • First dose reduction of alpelisib to 250mg each day, second dose reduction to 200mg each day. A maximum of two dose reductions recommended with the exception of pancreatitis, where only one dose reduction is permitted. • For management of toxicities see tables 1 to 4.

- **Hepatic impairment:**
  - Alpelisib: No dose adjustment required for patients with mild, moderate or severe hepatic impairment (Child-Pugh classes A, B or C).
  - Fulvestrant: no dose adjustment required for patients with mild or moderate hepatic impairment (Child-Pugh classes A and B), although use fulvestrant with caution. No data for the use of fulvestrant in severe hepatic impairment.
- **Renal impairment:**
  - Alpelisib: No dose adjustment required for patients with mild, or moderate renal impairment (CrCl >/=30 mL/min). Insufficient data are available in severe renal impairment <30ml/min, use with caution.
  - Fulvestrant: No dose adjustment required for patients with mild or moderate renal impairment (CrCl >/=30 mL/min). Insufficient data are available in patients with severe renal impairment to provide any dose adjustment recommendation, administer with caution.
- **Pneumonitis/ interstitial lung disease (ILD)**
  Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis (e.g. hypoxia, cough, dyspneoa). In patients who have new or worsening respiratory symptoms and are suspected to have developed ILD/pneumonitis, interrupt alpelisib immediately and evaluate the patient. Permanently discontinue in patients with severe ILD or pneumonitis.
- **Hyperglycaemia**
  Patients with a diagnosis of diabetes mellitus must have a treatment consultation with a diabetic specialist or a healthcare professional experienced in the management of hyperglycaemia prior to the start of treatment with alpelisib (in the phase III trials, patients with a history of diabetes mellitus intensified use of antidiabetic medicinal products while on treatment with Alpelisib).
  In addition, a consultation 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 or for nondiabetic patients who develop hyperglycaemia.
  All patients should self-monitor frequently in the first 4 weeks and especially within the first 2 weeks of treatment, as directed by the clinician, and all patients should be advised on the signs and symptoms of hyperglycaemia. A specific schedule for fasting glucose monitoring is recommended in table 5. Patients should be instructed on lifestyle changes that may reduce hyperglycaemia (e.g. dietary restrictions and physical activity).
- **Rash**
  Oral antihistamines may be given prophylactically or 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. See table 2.
- **Hypersensitivity reactions**
  Alpelisib should be permanently discontinued and should not be re-introduced in patients with serious hypersensitivity reactions.
- **Severe cutaneous reactions** (Stevens-Johnson syndrome (SJS), erythema multiforme (EM), DRESS)
  Alpelisib 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, alpelisib 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, alpelisib should be permanently discontinued. If a severe cutaneous reaction is not confirmed, see table 2. • **Diarrhoea** See table 3. Patients should be advised to start antidiarrhoeal treatment, increase oral fluids and notify the chemotherapy team as soon as diarrhoea occurs. • **Osteonecrosis of the jaw** Caution should be exercised when alpelisib and bisphosphonates or denosumab are used either simultaneously or sequentially. Alpelisib treatment should not be initiated in patients with ongoing osteonecrosis of the jaw from previous or concurrent treatment with bisphosphonates/denosumab. Patients should be advised to promptly report any new or worsening oral symptoms (such as dental mobility, pain or swelling, non-healing of mouth sores, or discharge) during treatment with alpelisib. • **Common drug interactions: (for comprehensive list refer to BNF/SPC)** Alpelisib plasma concentrations may be increased by BCRP inhibitors (e.g. eltrombopag, lapatinib, pantoprazole), monitor patient for toxicities. Alpelisib plasma concentrations may be decreased by Acid-reducing agents and as such, alpelisib must be taken immediately after food. Caution is recommended when alpelisib is used in combination with CYP3A4 substrates that also possess an additional time-dependent inhibition and induction potential on CYP3A4 that affects their own metabolism (e.g. rifampicin, ribociclib, encorafenib). Caution is recommended when CYP2C9 substrates are co-administered; pharmacological activity of CYP2C9 substrates with a narrow therapeutic index such as warfarin may be reduced by the CYP2C9 induction effects of alpelisib. Sensitive CYP2B6 substrates (e.g. bupropion) or CYP2B6 substrates with a narrow therapeutic window should be used with caution in combination with alpelisib, as alpelisib may reduce the clinical activity of such medicinal products. Alpelisib has the ability to inhibit OAT3 drug transporters and intestinal BCRP and P-gp; use with caution in combination with sensitive substrates of these transporters which exhibit a narrow therapeutic index (possible increased systemic exposure of the substrates). • **Driving / using machines** Alpelisib has minor influence on the ability to drive and use machines. Caution when driving or using machines in case of fatigue or blurred vision during treatment. • **Missed Dose**: The alpelisib dose should be taken within 9 hours after the time it is usually administered. After more than 9 hours, the dose should be skipped for that day. On the next day, alpelisib should be taken at the usual time. • **For oral self-administration**: refer to local Trust policy on oral anti-cancer medicines and supply Patient Information Leaflet and Macmillan information sheet.
References	SPC accessed online 19/7/22 Blueteq form accessed online 19/7/22 SOLAR-1 Phase III clinical protocol, accessed online https://clinicaltrials.gov/ProvidedDocs/18/NCT02437318/Prot_000.pdf

NB For funding information, refer to CDF and NICE Drugs Funding List

Table 1 Dose modification and management for hyperglycaemia[1]

Fasting glucose (FG) values[1]	**Recommendation**
Dose modification and management should only be based on fasting glucose (plasma/blood) values.	
>ULN-160 mg/dl or >ULN-8.9 mmol/l	No Alpelisib dose adjustment required. Initiate or intensify oral antidiabetic treatment[2].
>160-250 mg/dl or >8.9-13.9 mmol/l	No Alpelisib dose adjustment required. Initiate or intensify oral antidiabetic treatment[2]. If FG does not decrease to ≤160 mg/dl or 8.9 mmol/l within 21 days with appropriate oral antidiabetic treatment[2,3], reduce Alpelisib dose by 1 dose level and follow FG-value-specific recommendations.
>250-500 mg/dl or >13.9-27.8 mmol/l	Interrupt Alpelisib. Initiate or intensify oral antidiabetic treatment[2] and consider additional antidiabetic medicinal products such as insulin[3] for 1-2 days until hyperglycaemia resolves, as clinically indicated. Administer intravenous hydration and consider appropriate treatment (e.g. intervention for electrolyte / ketoacidosis / hyperosmolar disturbances). If FG decreases to ≤160 mg/dl or 8.9 mmol/l within 3 to 5 days under appropriate antidiabetic treatment, resume Alpelisib at next lower dose level. If FG does not decrease to ≤160 mg/dl or 8.9 mmol/l within 3 to 5 days under appropriate antidiabetic treatment, consultation with a healthcare professional with expertise in the treatment of hyperglycaemia is recommended. • If FG does not decrease to ≤160 mg/dl or 8.9 mmol/l within 21 days following appropriate antidiabetic treatment[2,3], permanently discontinue Alpelisib treatment.
>500 mg/dl or ≥27.8 mmol/l	Interrupt Alpelisib. Initiate or intensify appropriate antidiabetic treatment[2,3] (administer intravenous hydration and consider appropriate treatment [e.g. intervention for electrolyte / ketoacidosis / hyperosmolar disturbances]), re-check within 24 hours and as clinically indicated. • If FG decreases to ≤500 mg/dl or ≤27.8 mmol/l, then follow FG-value-specific recommendations for <500 mg/dl. If FG is confirmed at >500 mg/dl or ≥27.8 mmol/l after 24 hours, permanently discontinue Alpelisib treatment.

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

[2] Applicable antidiabetic medicinal products, such as metformin, SGLT2 inhibitors or insulin sensitisers (such as thiazolidinediones or dipeptidyl peptidase-4 inhibitors), should be initiated and the respective prescribing information should be reviewed for dosing and dose titration recommendations, including local diabetic treatment guidelines. Metformin was recommended in the phase III clinical study with the following guidance: Metformin should be initiated at 500 mg once daily. Based on tolerability, the metformin dose may be increased to 500 mg twice daily, followed by 500 mg with breakfast, and 1000 mg with the evening meal, followed by further increase to 1000 mg twice daily if needed.

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

Table 2 Dose modification and management for rash[1]

Grade	**Recommendation**
All grades	Consultation with a dermatologist should always be considered.
Grade 1 (<10% body surface area [BSA] with active skin toxicity)	No Alpelisib 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 Alpelisib 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 Alpelisib until rash improves to grade ≤1. Initiate or intensify topical/systemic corticosteroid and antihistamine treatment. Once rash improves to grade ≤1, resume Alpelisib 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 Alpelisib.
[1] Grading according to CTCAE Version 5.0	

Table 3 Dose modification and management for diarrhoea

Grade[1]	**Recommendation**
Grade 1	No Alpelisib dose adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated.
Grade 2	Interrupt Alpelisib dose. Initiate or intensify appropriate medical therapy and monitor as clinically indicated. If diarrhoea improves to grade ≤1, then resume Alpelisib at same dose level. If diarrhoea recurs as grade ≥2, interrupt Alpelisib dose until improvement to grade ≤1, then resume Alpelisib at the next lower dose level.
Grade 3[2]	Interrupt Alpelisib dose. Initiate or intensify appropriate medical therapy and monitor as clinically indicated. If diarrhoea improves to grade ≤1, then resume Alpelisib at the next lower dose level.
Grade 4[2]	Permanently discontinue Alpelisib.
[1] Grading according to CTCAE Version 5.0. [2] Patients should additionally be managed according to local standard of care, including electrolyte monitoring, administration of antiemetics and antidiarrhoeal medicinal products and/or fluid replacement and electrolyte supplements, as clinically indicated.	

Table 4 Dose modification and management for other toxicities (excluding hyperglycaemia, rash and diarrhoea)[1]

Grade	Recommendation
Grade 1 or 2	No Alpelisib dose adjustment required. Initiate appropriate medical therapy and monitor as clinically indicated[2,3].
Grade 3	Interrupt Alpelisib dose until improvement to grade ≤1, then resume Alpelisib at the next lower dose level[2].
Grade 4	Permanently discontinue Alpelisib[3].
[1] Grading according to CTCAE Version 5.0 [2] For grade 2 and 3 pancreatitis, interrupt Alpelisib dose until improvement to grade ≤1 and resume at next lower dose level. Only one dose reduction is permitted. If toxicity recurs, permanently discontinue Alpelisib treatment. [3] For grade 2 total bilirubin elevation, interrupt Alpelisib 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.	

Table 5 Schedule of fasting glucose monitoring

	Recommended schedule for the monitoring of fasting glucose and HbA1c levels in all patients treated with Alpelisib	**Recommended schedule of monitoring of fasting glucose and HbA1c levels in patients with diabetes, pre-diabetes, BMI ≥30 or age ≥75 years treated with Alpelisib**
At screening, before initiating treatment with Alpelisib	Test for fasting plasma glucose (FPG), HbA1c, and optimise the patient's level of blood glucose (see Table 1).	
After initiating treatment with Alpelisib	Monitor fasting glucose at weeks 1, 2, 4, 6 and 8 after treatment start and monthly thereafter.	
	Monitor/self-monitor fasting glucose regularly, more frequently in the first 4 weeks and especially within the first 2 weeks of treatment, according to the instructions of a healthcare professional*.	Monitor/self-monitor fasting glucose daily for the first 2 weeks of treatment. Then continue to monitor fasting glucose as frequently as needed to manage hyperglycaemia according to the instructions of a healthcare professional*.
	HbA1c should be monitored after 4 weeks of treatment and every 3 months thereafter.	
If hyperglycaemia develops after initiating treatment with Alpelisib	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.		

Cycle 1: Cycle length- 28 days

Day	Drug	Dose	Route	Infusion Duration	Administration
Day 1	**FULVESTRANT**	**500mg**	intramuscular	Each 5ml (250mg) injection over 1-2 minutes	Administered as 2 x 250mg (5ml) injections, one in each buttock.
Day 15	**FULVESTRANT**	**500mg**	intramuscular	Each 5ml (250mg) injection over 1-2 minutes	Administered as 2 x 250mg (5ml) injections, one in each buttock.

TTO	Drug	Dose	Route	Directions
Day 1	**ALPELISIB**	**300mg**	PO	Once a day taken immediately after food and at approximately the same time each day. Available as 50mg, 150mg, 200mg tablets
	Metoclopramide	10mg	PO	10mg TDS PRN. Do not take for more than 5 days continuously. Dispense with cycle 1 and then only if required.
	Loperamide	2mg-4mg	PO	Take 4mg (2 capsules) initially, then 2mg (1 capsule) after each loose stool when required. Maximum 16mg (8 capsules) a day. Dispense on cycle 1 and then only if required.
	Cetirizine	10mg	po	Once a day. May be given prophylactically or to manage symptoms.
	Hydrocortisone 1% cream		TOPICAL	Apply 1-2 times a day at the first sign of rash. Dispense on cycle 1 and then only if required.

Cycle 2 onwards: repeat every 28 days

Day	Drug	Dose	Route	Infusion Duration	Administration
1	**FULVESTRANT**	**500mg**	intramuscular	Each 5ml (250mg) injection over 1-2 minutes	Administered as 2 x 250mg (5ml) injections, one in each buttock.
TTO	Drug	Dose	Route	Directions	
1	**ALPELISIB**	**300mg**	PO	Once a day taken immediately after food and at approximately the same time each day. Available as 50mg, 150mg, 200mg tablets	
	Metoclopramide	10mg	PO	10mg TDS PRN. Do not take for more than 5 days continuously. Only supply if required.	
	Loperamide	2mg-4mg	PO	Take 4mg (2 capsules) initially, then 2mg (1 capsule) after each loose stool when required. Maximum 16mg (8 capsules) a day. Dispense on cycle 1 and then only if required.	
	Cetirizine	10mg	po	Once a day May be given prophylactically or to manage symptoms.	
	Hydrocortisone 1% cream		TOPICAL	Apply 1-2 times a day at the first sign of rash. Dispense on cycle 1 and then only if required.	