**TREZILENT™** (alpelisib)
50 mg, 150 mg and 200 mg Film-coated tablets

# LEAFLET

DISETUJUI OLEH BPOM: 19/12/2022

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**Serious Warnings and Precautions**

Treatment of Trezilent should be initiated by the physician experienced in the use of anti-cancer agents.

The following serious adverse reactions were reported in patients treated with Trezilent.

- Hypersensitivity, including anaphylactic reactions (see section 6 Warnings and precautions)
- Severe cutaneous reactions including Stevens-Johnson Syndrome, Drug Reaction with Eosinophilia and Systemic Symptoms and Erythema Multiforme (see section 6 Warnings and precautions)
- Hyperglycemia, including hyperglycaemic hyperosmolar non-ketocic syndrome and some fatal cases of diabetic ketoacidosis (see section 6 Warnings and precautions)
- Pneumonitis (see section 6 Warnings and precautions)

# 1 Tradename

TREZILENT™ 50 mg film-coated tablets

TREZILENT™ 150 mg film-coated tablets

TREZILENT™ 200 mg film-coated tablets

# 1 Description and composition

## Pharmaceutical form

**Film-coated tablets**

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

## Active substance

Film-coated tablets containing alpelisib

## Excipients

Film-coated tablet core: Microcrystalline cellulose, mannitol, sodium starch glycolate, hypromellose and magnesium stearate.

Coating material: Hypromellose, titanium dioxide, macrogol / polyethylene glycol (PEG), talc, iron oxide red, and iron oxide black.

Information might differ in some countries.

## 2 Indications

Trezilent is an alpha-specific class I phosphatidylinositol-3-kinase (PIK3CA) inhibitor indicated in combination with fulvestrant for the treatment of postmenopausal women, with hormone receptor positive, HER2-negative, advanced breast cancer with a PIK3CA mutation after disease progression following an endocrine-based regimen.

## 3 Dosage regimen and administration

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

### Dosage regimen

### General target population

Patients with HR (hormone receptor) positive, HER2 negative advanced breast cancer should be selected for treatment with Trezilent, based on the presence of a PIK3CA mutation in tumor or plasma specimens, using a validated test. If a mutation is not detected in a plasma specimen, test tumor tissue if available.

There was no treatment benefit demonstrated in patients without PIK3CA mutations, in the phase III clinical study (see section 12 clinical studies).

The recommended dose of Trezilent is 300 mg (2×150 mg film-coated tablets) taken orally, once daily on a continuous basis. Trezilent should be taken immediately following food, at approximately the same time each day (see section 11 Clinical pharmacology and section 8 Interactions). The maximum recommended daily dose of Trezilent is 300 mg. If a dose of Trezilent is missed, it can be taken immediately following food and within 9 hours after the time it is usually administered. After more than 9 hours, the dose should be skipped for that day. On the next day, Trezilent should be taken at its usual time. If the patient vomits after taking the Trezilent 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 co-administered with Trezilent, the recommended dose of fulvestrant is 500 mg administered intramuscularly on days 1, 15 and, 29, and once monthly thereafter. Please refer to the full prescribing information of fulvestrant.

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

### Dosing modifications

The recommended daily dose of Trezilent is 300 mg. Management of severe or intolerable adverse drug reactions (ADRs) may require temporary dosing interruption, reduction, and/or

discontinuation of Trezilent. If dosing reduction is required, the dosing reduction guidelines for ADRs are listed in Table 4-1. A maximum of 2 dosing reductions are recommended, after which the patient should be discontinued from treatment with Trezilent. Dosing reduction should be based on worst preceding toxicity.

**Table 4-1 Recommended dosing reduction guidelines for adverse drug reactions for Trezilent[1]**

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

*[1]Only one dose reduction is permitted for pancreatitis.*

Tables 4-2, 4-3, 4-4 and 4-5 summarize recommendations for dosing interruption, reduction or discontinuation of Trezilent in the management of specific ADRs. Clinical judgment 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 for treatment with Trezilent.

**Hyperglycemia**

Consultation with a Healthcare Professional (HCP) with experience in the management of hyperglycemia should be considered and lifestyle changes as per local guidelines (e.g. American Diabetes Association (ADA)), including exercise and dietary advice should be recommended/reinforced (e.g. small frequent meals, low carbohydrate, high fiber, low processed food intake, three macronutrient balanced meals and 2 optional small snacks rather than one large meal).

Fasting Plasma Glucose (FPG) and/or HbA1c (hemoglobin A1c) test should be performed before initiating treatment with Trezilent. Glucose levels should be corrected in patients with abnormal glucose levels which are in the range of pre-diabetic or diabetic before initiating Trezilent, and should be closely monitored to enable early detection and early treatment of hyperglycemia.

After initiating treatment with Trezilent, Fasting Glucose (FG; either plasma or blood) should be monitored at least once per week in the first 2 weeks, followed by every 4 weeks and as clinically indicated. HbA1c should be monitored every 3 months as clinically indicated.

If patient experiences hyperglycemia after initiating treatment with Trezilent, FG should be monitored as clinically indicated, and at least twice weekly until FG decreases to ≤160 mg/dL. During treatment with anti-diabetic medication, monitoring of FG should be continued at least once a week for 8 weeks, followed by once every 2 weeks and as clinically indicated.

**Table 4-2 Dosing modification and management for hyperglycemia[1]**

| Fasting Glucose (FG)[2] | Recommendation |
|---|---|
| **Dose modifications and management should only be based on fasting glucose (plasma/blood) values.** | |

| Fasting Glucose (FG)[2] | Recommendation |
|---|---|
| >ULN - 160 mg/dL or >ULN - 8.9 mmol/L | No Trezilent dose adjustment required.<br>Initiate or intensify oral anti-diabetic treatment[2]. |
| >160 to 250 mg/dL or >8.9 to 13.9 mmol/L. | No Trezilent dose adjustment required.<br>Initiate or intensify oral anti-diabetic treatment[2].<br>If FG does not decrease to ≤160 mg/dL or 8.9 mmol/L within 21 days with appropriate oral anti-diabetic treatment[2,3], reduce Trezilent dose by 1 dose level, and follow FG value specific recommendations. |
| >250 to 500 mg/dL or<br>>13.9 to 27.8 mmol/L | Interrupt Trezilent.<br>Initiate or intensify oral anti-diabetic treatment[2] and consider additional anti-diabetic medications such as insulin[3] for 1 to 2 days until hyperglycemia resolves, as clinically indicated<br>Administer intravenous hydration and consider appropriate treatment (e.g. intervention for electrolyte/ketoacidosis/hyperosmolar disturbances).<br>If FG decreases to ≤160 mg/dL or 8.9 mmol/L within 3 to 5 days under appropriate anti-diabetic treatment, resume Trezilent at 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 anti-diabetic treatment, consultation with a physician with expertise in the treatment of hyperglycemia is recommended.<br>If FG does not decrease to ≤160 mg/dL or 8.9 mmol/L within 21 days following appropriate anti-diabetic treatment[2,3], permanently discontinue Trezilent treatment. |
| >500 mg/dL or<br>≥27.8 mmol/L | Interrupt Trezilent.<br>Initiate or intensify appropriate anti-diabetic 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.<br>If FG decreases to (≤500 mg/dL) or (≤27.8 mmol/L), then follow FG value specific recommendations for (<500 mg/dL).<br>If FG is confirmed at >500 mg/dL or (≥27.8 mmol/L), permanently discontinue Trezilent treatment. |

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

*[2] Applicable anti-diabetic medications, like metformin, SGLT2 inhibitors or insulin sensitizers (such as thiazolidinediones or dipeptidyl peptidase-4 inhibitors), should be initiated and 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 500 mg once daily should be initiated. Based on tolerability, metformin dose may be increased to 500 mg bid, followed by 500 mg with breakfast, and 1,000 mg with dinner, followed by further increase to 1,000 mg bid if needed (see section 6 Warnings and precautions).*

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

## Rash

Oral antihistamine administration may be considered prophylactically, at the time of initiation of treatment with Trezilent. Based on the severity of rash, Trezilent may require dose interruption, reduction, or discontinuation as described in Table 4-3 (see section 7 Adverse drug reactions).

**Table 4-3 Dosing modification and management for rash[1]**

| Grade | Recommendation |
|---|---|
| All Grades | Consultation with a dermatologist should always be considered |
| Grade 1<br>(<10% body surface area (BSA) with active skin toxicity) | No Trezilent 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 to 30% BSA with active skin toxicity) | No Trezilent 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 Trezilent until rash improves to Grade ≤1.<br>Initiate or intensify topical/systemic corticosteroid and anti-histamine treatment.<br>Once rash improves to Grade ≤1, resume Trezilent at next lower dose level. |
| Grade 4 (e.g: severe bullous, blistering or exfoliating skin conditions).<br>(any % BSA associated with extensive superinfection, with IV antibiotics indicated; life-threatening consequences) | Permanently discontinue Trezilent. |

[1] *Grading according to CTCAE Version 5.0*

**Table 4-4 Dosing modification and management for diarrhea[1]**

| Grade[1] | Recommendation |
|---|---|
| Grade 1 | No Trezilent dose adjustment required.<br>Initiate appropriate medical therapy and monitor as clinically indicated. |
| Grade 2 | Interrupt Trezilent dose until improvement to Grade ≤1, then resume Trezilent at same dose level.<br>If diarrhea recurs as Grade ≥2, interrupt Trezilent dose until improvement to Grade ≤1, then resumeTrezilent at the next lower dose level.<br>Initiate or intensify appropriate medical therapy and monitor as clinically indicated. |
| Grade 3[2] | Interrupt Trezilent dose until improvement to Grade ≤1, then resume Trezilent at the next lower dose level.<br>Initiate or intensify appropriate medical therapy and monitor as clinically indicated. |
| Grade 4[2] | Permanently discontinue Trezilent. |

[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 antidiarrheal medicinal products and/or fluid replacement and electrolyte supplements, as clinically indicated.*

### Other toxicities

**Table 4-5 Dosing modification and management for other toxicities (excluding hyperglycemia, rash and diarrhea)[1]**

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

[1] *Grading according to CTCAE Version 5.0 .*

[2] *For Grade 2 and 3 pancreatitis, interrupt Trezilent dose until improvement to Grade ≤1 and resume at next lower dose level. Only one dose reduction is permitted. If toxicity recurs, permanently discontinue Trezilent treatment.*

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

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

## Special populations

### Renal impairment

Based on population pharmacokinetic analysis, no dose adjustment is necessary in patients with mild or moderate renal impairment (see section 11 Clinical pharmacology). Caution should be used in patients with severe renal impairment as there is no experience with Trezilent in this population (see section 11 Clinical pharmacology).

### 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 and severe hepatic impairment (Child-Pugh class A, B or C, respectively) (see section 11 Clinical pharmacology).

Refer to the full prescribing information of fulvestrant for dose modifications related to hepatic impairment.

### Pediatric patients (below 18 years)

The safety and efficacy of Trezilent in pediatric patients have not been established.

### Geriatric patients (65 years or above)

No dosage regimen adjustment is required in patients 65 years or above (see section 12 Clinical studies).

### Method of administration

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

## 4 Contraindications

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

## 5 Warnings and precautions

**Hypersensitivity (including anaphylactic reaction)**

Serious hypersensitivity reactions (including anaphylactic reaction and anaphylactic shock), manifested by symptoms including, but not limited to, dyspnea, flushing, rash, fever or tachycardia were reported in patients treated with Trezilent in clinical studies (see section 7 Adverse drug reactions). Trezilent should be permanently discontinued and should not be re-introduced in patients with serious hypersensitivity reactions. Appropriate treatment should be promptly initiated.

**Severe cutaneous reactions**

Severe cutaneous reactions have been reported with Trezilent. In the Phase III clinical study, Stevens-Johnson syndrome (SJS) and erythema multiforme (EM) were reported in 1 (0.4%) and 3 (1.1%) patients, respectively. Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported in the post marketing setting (see section 7 Adverse drug reactions).

Trezilent treatment should not be initiated in patients with 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, Trezilent should be interrupted until the etiology of the reaction has been determined. A consultation with a dermatologist is recommended. If a severe cutaneous reaction is confirmed, Trezilent should be permanently discontinued. Trezilent should not be reintroduced in patients who have experienced previous severe cutaneous reactions. If a severe cutaneous reaction is not confirmed, Trezilent may require treatment interruption, dose reduction, or treatment discontinuation as described in Table 4-3 Dose modification and management for rash (see section 4 Dosage regimen and administration).

**Hyperglycemia**

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

Hyperglycemia was reported in 64.8% of patients treated with Trezilent in the phase III clinical study. Grade 2 (FPG 160 to 250 mg/dL), 3 (FPG >250 to 500 mg/dL) or 4 (FPG >500 mg/dL) hyperglycemia were reported in 15.8%, 33.1% and 3.9% of patients, respectively, in phase III clinical study. Patients should be advised of the signs and symptoms of hyperglycemia (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, based on baseline FPG and HbA1c values, 56% of patients were considered pre-diabetic (FPG >100 to 126 mg/dL (5.6 to 6.9 mmol/L) and/or HbA1c 5.7 to 6.4%) and 4.2% of patients were considered diabetic (FPG ≥126 mg/dL (≥7.0 mmol/L) and/or HbA1c ≥6.5 %). There were no patients with type 1 diabetes mellitus based on reported medical history in the phase III clinical study. Among those pre-diabetic patients at baseline, 74.2% experienced hyperglycemia (any Grade) when treated with Trezilent. Among the patients who had Grade ≥2 (FPG 160 to 250 mg/dL) hyperglycemia, the median time to first occurrence of Grade ≥2 (FPG >160 to 250 mg/dL) hyperglycemia was 15 days (range: 5 days to 517 days) (based on laboratory findings). The median duration of Grade 2 (FPG >160 to 250 mg/dL) or higher hyperglycemia (based on laboratory findings) was 10 days (95% CI: 8 to 13 days).

In the phase III clinical study, in patients with hyperglycaemia, 163/187 (87.2%) were managed with anti-diabetic medication and 142/187 (75.9%) reported use of metformin as single agent or in combination with other anti-diabetic medication. The maximum dose of metformin recommended in phase III clinical study was 2,000 mg per day.

In patients with hyperglycemia of at least Grade 2 (FPG 160 to 250 mg/dL), median time to improvement by at least 1 Grade of the first event was 8 days (95% CI of 8 to 10 days). In all patients with elevated FPG, who continued fulvestrant treatment after discontinuing Trezilent, all FPG levels returned to baseline (normal).

In the phase III clinical study, patients with a history of diabetes mellitus intensified anti-diabetic medication(s) while on treatment with Trezilent; therefore these patients require monitoring and possibly intensified anti-diabetic treatment. Patients with poor glycemic control may be at a higher risk of developing severe hyperglycemia and associated complications.

The safety of Trezilent in patients with Type 1 and uncontrolled Type 2 diabetes has not been established as these patients were excluded from the Phase III clinical study.

Based on the severity of the hyperglycemia, Trezilent may require dose interruption, reduction, or discontinuation as described in Table 4-2 Dose modification and management for hyperglycemia. (see section 4 Dosage regimen and administration).

**Pneumonitis**

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

respiratory symptoms or are suspected to have developed pneumonitis, Trezilent 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, dyspnea, or interstitial infiltrates on radiologic exams and in whom infectious, neoplastic, and other causes have been excluded by means of appropriate investigations. Trezilent should be permanently discontinued in all patients with confirmed pneumonitis.

**Diarrhoea**

Severe diarrhoea, including dehydration and acute kidney injury, occurred in patients treated with Trezilent. Most patients (58%) experienced diarrhoea during treatment with Trezilent. 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).

Dose reductions of Trezilent were required in 6% of patients and 2.8% of patients permanently discontinued Trezilent due to diarrhoea. In the 164 patients that experienced diarrhoea, antidiarrhoeal medications (e.g., loperamide) were required to manage symptoms in 63% (104/164) of these patients.

Based on the severity of the diarrhoea, Trezilent may require dose interruption, reduction, or discontinuation as described in Table 4-4 (see section 4 Dosage regimen and administration). Advise patients to start antidiarrhoeal treatment, increase oral fluids, and notify their healthcare provider if diarrhoea occurs while taking Trezilent.

**Osteonecrosis of the jaw**

In the phase III clinical study, osteonecrosis of the jaw (ONJ) was reported in 4% of patients in the Trezilent plus fulvestrant arm, including 2% with a serious event. All patients experiencing ONJ were also exposed to prior or concomitant bisphosphonates or RANK-ligand inhibitors (e.g. denosumab).

Caution should be exercised when Trezilent and drugs known to cause ONJ are used either simultaneously, or sequentially. Trezilent treatment should not be initiated in patients with ongoing ONJ. 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 Trezilent. A dental examination with appropriate preventive dentistry is recommended prior to treatment with Trezilent in patients with risk factors for ONJ, such as invasive dental procedures, concomitant therapies, poor oral hygiene and comorbid disorders. In patients who develop ONJ, standard medical management should be initiated, including maintaining good oral hygiene, controlling pain and treating areas of infection with antibiotics and oral antibiotic mouth rinses. Patients should have appropriate nutrition and oral fluid intake.

# 6 Adverse drug reactions

## Summary of the safety profile

**SOLAR-1 safety information:**

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

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

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

On-treatment deaths, regardless of causality, were reported in 7 patients (2.5%) treated with Trezilent plus fulvestrant vs. 12 patients (4.2%) treated with placebo plus fulvestrant. In Trezilent plus fulvestrant treated patients, disease progression (5 patients, 1.8%) was the most frequent cause of death; the others were one each for cardio-respiratory arrest and second primary malignancy, neither of which were considered related to treatment with Trezilent.

The most common ADRs in Trezilent plus fulvestrant treated patients (reported at a frequency ≥20% and for which the frequency for Trezilent plus fulvestrant exceeds the frequency for placebo plus fulvestrant) were hyperglycaemia, diarrhoea, rash, nausea, fatigue and asthenia, decreased appetite, stomatitis, vomiting and weight decreased.

The most common Grade 3/4 ADRs (reported at a frequency ≥2% in the Trezilent plus fulvestrant arm and for which the frequency for Trezilent plus fulvestrant exceeds the frequency for placebo plus fulvestrant) were hyperglycaemia, rash and maculo-papular rash, fatigue, diarrhoea, lipase increased, hypertension, hypokalaemia, anaemia, weight decreased, gamma-glutamyltransferase increased, lymphopenia, nausea, stomatitis, alanine aminotransferase increased and mucosal inflammation.

**BYLieve safety information:**

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

In the alpelisib plus fulvestrant arm (127 patients), ADRs that were reported in ≥20% of patients were diarrhea (59.8%), hyperglycaemia (58.3%), nausea (45.7%), fatigue (29.1%), decreased appetite (28.3%), rash (28.3%) [plus maculo-papular rash (14.2%)], stomatitis (26.8%) and vomiting (23.6%). Grade 3 or grade 4 ADRs that were reported in ≥5% of patients were hyperglycaemia (28.3%), rash (9.4%), maculo-papular rash (9.4%), and diarrhea (5.5%).

The AEs observed in this study were consistent with the known safety profile of Trezilent in combination with fulvestrant. No new safety signals were observed.

## Tabulated summary of adverse drug reactions from clinical studies

ADRs from the phase III clinical study (Table 7-1) 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 ADR is based on the following convention (CIOMS III): 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).

**Table 7-1 Adverse drug reactions observed in the phase III clinical study**

| Adverse drug reactions | Trezilent + Fulvestrant N= 284 n (%) All Grades | Placebo + Fulvestrant N= 287 n (%) All Grades | Trezilent + Fulvestrant N= 284 n (%) Grades 3/4 | Placebo + Fulvestrant N=287 n (%) Grades 3/4 | Frequency category for Trezilent + Fulvestrant All Grades |
|---|---|---|---|---|---|
| **Blood and lymphatic system disorders** | | | | | |
| Anaemia | 29 (10.2) | 15 (5.2) | 11 (3.9) | 3 (1.0) | Very common |
| Lymphopenia | 14 (4.9) | 3 (1.0) | 7 (2.5) | 3 (1.0) | Common |
| Thrombocytopenia | 6 (2.1) | 0 | 2 (0.7) | 0 | Common |
| **Eye disorders** | | | | | |
| Vision blurred | 14 (4.9) | 2 (0.7) | 1 (0.4) | 0 | Common |
| Dry eye | 10 (3.5) | 1 (0.3) | 0 | 0 | Common |
| **Gastrointestinal disorders** | | | | | |
| Diarrhoea | 164 (57.7) | 45 (15.7) | 19 (6.7) | 1 (0.3) | Very common |
| Nausea | 127 (44.7) | 64 (22.3) | 7 (2.5) | 1 (0.3) | Very common |
| Stomatitis[1] | 85 (29.9) | 18 (6.3) | 7 (2.5) | 0 | Very common |
| Vomiting | 77 (27.1) | 28 (9.8) | 2 (0.7) | 1 (0.3) | Very common |
| Abdominal pain | 47 (16.5) | 32 (11.1) | 4 (1.4) | 3 (1.0) | Very common |
| Dyspepsia | 32 (11.3) | 16 (5.6) | 0 | 0 | Very common |
| Toothache | 12 (4.2) | 6 (2.1) | 1 (0.4) | 0 | Common |
| Gingivitis | 10 (3.5) | 2 (0.7) | 1 (0.4) | 0 | Common |
| Cheilitis | 8 (2.8) | 0 | 0 | 0 | Common |
| Gingival pain | 8 (2.8) | 0 | 0 | 0 | Common |
| Pancreatitis | 1 (0.4) | 0 | 1 (0.4) | 0 | Uncommon |
| **General disorders and administrative site conditions** | | | | | |
| Fatigue[2] | 120 (42.3) | 83 (28.9) | 15 (5.3) | 3 (1.0) | Very common |
| Mucosal inflammation | 54 (19.0) | 3 (1.0) | 6 (2.1) | 0 | Very common |

| Adverse drug reactions | Trezilent + Fulvestrant N= 284 n (%) All Grades | Placebo + Fulvestrant N= 287 n (%) All Grades | Trezilent + Fulvestrant N= 284 n (%) Grades 3/4 | Placebo + Fulvestrant N=287 n (%) Grades 3/4 | Frequency category for Trezilent + Fulvestrant All Grades |
|---|---|---|---|---|---|
| Peripheral oedema | 43 (15.1) | 15 (5.2) | 0 | 1 (0.3) | Very common |
| Pyrexia | 41 (14.4) | 14 (4.9) | 2 (0.7) | 1 (0.3) | Very common |
| Mucosal dryness [3] | 33 (11.6) | 12 (4.2) | 1 (0.4) | 0 | Very common |
| Oedema [4] | 17 (6.0) | 1 (0.3) | 0 | 0 | Common |
| **Immune system disorders** | | | | | |
| Hypersensitivity [5] | 10 (3.5) | 0 | 2 (0.7) | 0 | Common |
| **Infections and infestations** | | | | | |
| Urinary tract infection[6] | 29 (10.2) | 15 (5.2) | 2 (0.7) | 3 (1.0) | Very common |
| **Investigations** | | | | | |
| Weight decreased | 76 (26.8) | 6 (2.1) | 11 (3.9) | 0 | Very common |
| Blood creatinine increased | 29 (10.2) | 4 (1.4) | 5 (1.8) | 0 | Very common |
| Gamma-glutamyltransferase increased | 27 (9.5) | 20 (7.0) | 11 (3.9) | 14 (4.9) | Common |
| Alanine aminotransferase increased | 23 (8.1) | 16 (5.6) | 7 (2.5) | 6 (2.1) | Common |
| Lipase increased | 18 (6.3) | 11 (3.8) | 14 (4.9) | 10 (3.5) | Common |
| Glycosylated haemoglobin increased | 9 (3.2) | 0 | 0 | 0 | Common |
| **Metabolism and nutrition disorders** | | | | | |
| Hyperglycaemia | 184 (64.8) | 29 (10.1) | 105 (37.0) | 2 (0.7) | Very common |
| Decreased appetite | 101 (35.6) | 30 (10.5) | 2 (0.7) | 1 (0.3) | Very common |
| Hypokalaemia | 28 (9.9) | 5 (1.7) | 12 (4.2) | 1 (0.3) | Common |
| Hypocalcaemia | 12 (4.2) | 4 (1.4) | 3 (1.1) | 1 (0.3) | Common |
| Dehydration | 10 (3.5) | 4 (1.4) | 1 (0.4) | 3 (1.0) | Common |
| Ketoacidosis [7] | 2 (0.7) | 0 | 2 (0.7) | 0 | Uncommon |
| **Musculoskeletal and connective tissue disorders** | | | | | |
| Muscle spasms | 19 (6.7) | 11 (3.8) | 0 | 0 | Common |
| Myalgia | 19 (6.7) | 8 (2.8) | 1 (0.4) | 0 | Common |
| Osteonecrosis of jaw | 12 (4.2) | 4 (1.4) | 4 (1.4) | 2 (0.7) | Common |
| **Nervous system disorders** | | | | | |
| Headache | 51 (18.0) | 38 (13.2) | 2 (0.7) | 0 | Very common |
| Dysgeusia [8] | 51 (18.0) | 10 (3.5) | 1 (0.4) | 0 | Very common |

| Adverse drug reactions | Trezilent + Fulvestrant N= 284 n (%) All Grades | Placebo + Fulvestrant N= 287 n (%) All Grades | Trezilent + Fulvestrant N= 284 n (%) Grades 3/4 | Placebo + Fulvestrant N=287 n (%) Grades 3/4 | Frequency category for Trezilent + Fulvestrant All Grades |
|---|---|---|---|---|---|
| **Psychiatric disorders** | | | | | |
| Insomnia | 21 (7.4) | 12 (4.2) | 0 | 0 | Common |
| **Renal and Urinary disorders** | | | | | |
| Acute kidney injury | 15 (5.3) | 2 (0.7) | 5 (1.8) | 1 (0.3) | Common |
| **Respiratory, thoracic and mediastinal disorders** | | | | | |
| Pneumonitis [9] | 5 (1.8) | 1 (0.3) | 1 (0.4) | 1 (0.3) | Common |
| **Skin and subcutaneous tissue disorders** | | | | | |
| Rash [10] | 147 (51.8) | 21 (7.3) | 56 (19.7) | 1 (0.3) | Very common |
| Alopecia | 56 (19.7) | 7 (2.4) | 0 | 0 | Very common |
| Pruritus | 52 (18.3) | 17 (5.9) | 2 (0.7) | 0 | Very common |
| Dry skin [11] | 51 (18.0) | 11 (3.8) | 1 (0.4) | 0 | Very common |
| Erythema [12] | 17 (6.0) | 2 (0.7) | 2 (0.7) | 0 | Common |
| Dermatitis [13] | 10 (3.5) | 3 (1.0) | 2 (0.7) | 0 | Common |
| Palmar-plantar erythrodysaesthesia syndrome | 5 (1.8) | 1 (0.3) | 0 | 0 | Common |
| Erythema multiforme | 3 (1.1) | 0 | 2 (0.7) | 0 | Common |
| Stevens-Johnson syndrome | 1 (0.4) | 0 | 1 (0.4) | 0 | Uncommon |
| **Vascular disorders** | | | | | |
| Hypertension | 24 (8.5) | 15 (5.2) | 13 (4.6) | 9 (3.1) | Common |
| Lymphoedema | 15 (5.3) | 6 (2.1) | 0 | 0 | Common |

*[1] Stomatitis: also includes aphthous ulcer and mouth ulceration*
*[2] Fatigue: also includes asthenia*
*[3] Mucosal dryness: also includes dry mouth, vulvovaginal dryness*
*[4] Oedema: also includes face swelling, face oedema, eyelid oedema*
*[5] Hypersensitivity: also includes allergic dermatitis*
*[6] Urinary tract infection: also includes single case of urosepsis*
*[7] Ketoacidosis: also includes diabetic ketoacidosis (see section 6 Warnings and precautions)*
*[8] Dysgeusia : also includes ageusia, hypogeusia*
*[9] Pneumonitis: also includes interstitial lung disease*
*[10] Rash: also includes rash maculo-papular, rash macular, rash generalised, rash-papular, rash pruritic*
*[11] Dry skin: also includes skin fissures, xerosis, xeroderma*
*[12] Erythema: also includes erythema generalised*
*[13] Dermatitis: also includes dermatitis acneiform*

**Table 7-2 Laboratory abnormalities observed in the phase III study**

| Laboratory abnormalities | Trezilent + Fulvestrant N= 284 n (%) All Grades | Placebo + Fulvestrant N= 287 n (%) All Grades | Trezilent + Fulvestrant N= 284 n (%) Grades 3/4 | Placebo + Fulvestrant N=287 n (%) Grades 3/4 | Frequency category for Trezilent + Fulvestrant All Grades |
|---|---|---|---|---|---|
| **Haematological parameters** | | | | | |
| Lymphocyte count decreased | 147 (51.8) | 116 (40.4) | 23 (8.1) | 13 (4.5) | Very common |
| Haemoglobin decreased | 118 (41.5) | 83 (28.9) | 12 (4.2) | 3 (1.0) | Very common |
| Activated partial thromboplastin time increased | 60 (21.1) | 45 (15.7) | 2 (0.7) | 1 (0.3) | Very common |
| Platelet count decreased | 39 (13.7) | 17 (5.9) | 3 (1.1) | 0 | Very common |
| **Biochemical parameters** | | | | | |
| Glucose plasma increased | 223 (78.5) | 99 (34.5) | 110 (38.7) | 3 (1.0) | Very common |
| Creatinine increased | 190 (66.9) | 71 (24.7) | 8 (2.8) | 2 (0.7) | Very common |
| Gamma-glutamyl transferase increased | 148 (52.1) | 127 (44.3) | 30 (10.6) | 29 (10.1) | Very common |
| Alanine aminotransferase increased | 124 (43.7) | 99 (34.5) | 10 (3.5) | 7 (2.4) | Very common |
| Lipase increased | 119 (41.9) | 73 (25.4) | 19 (6.7) | 17 (5.9) | Very common |
| Calcium corrected decreased | 76 (26.8) | 57 (19.9) | 6 (2.1) | 4 (1.4) | Very common |
| Glucose plasma decreased | 73 (25.7) | 40 (13.9) | 1 (0.4) | 0 | Very common |
| Albumin decreased | 39 (13.7) | 22 (7.7) | 0 | 0 | Very common |
| Potassium decreased | 39 (13.7) | 8 (2.8) | 16 (5.6) | 2 (0.7) | Very common |
| Magnesium decreased | 31 (10.9) | 12 (4.2) | 1 (0.4) | 0 | Very common |

## Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

The following adverse drug reactions have been derived from post-marketing experience with Trezilent via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known.

**Table 7-3 Adverse drug reactions from spontaneous reports and literature (frequency not known)**

| |
|---|
| **Metabolism and nutrition disorders** |
| Hyperglycaemic hyperosmolar nonketotic syndrome (HHNKS) |
| **Skin and subcutaneous tissue disorders** |

## Description of selected ADRs and treatment recommendations, where applicable

### Hyperglycaemia

In the phase III clinical study, hyperglycaemia (FPG >160 mg/dL) was reported in 184 (64.8%) of patients. An event of hyperglycaemia resolved to ≤Grade 1 (FPG <160 mg/dL) in 166 (88.8%) of the 187 patients. Dose interruptions and adjustments due to hyperglycaemic events were reported in 26.8% and 28.9% of patients, respectively, in the Trezilent plus fulvestrant arm. Hyperglycaemic events leading to discontinuation of Trezilent and/or fulvestrant were reported in 19 (6.7 %) patients.

### Rash

In the phase III clinical study, rash events (including rash maculo-papular, rash macular, rash generalised, rash papular, rash pruritic, dermatitis and dermatitis acneiform) were reported in 153 (53.9%) patients. Rash may be accompanied by pruritus and dry skin in some cases. Rash was predominantly mild or moderate (Grade 1 or 2) and responsive to therapy. Maximum Grade 2 and 3 rash events were reported in 13.7% and 20.1% of patients, respectively. There were no Grade 4 cases of rash reported. Among the patients with Grade 2 or 3 rash, the median time to first onset of Grade 2 or 3 rash was 12 days (range: 2 days to 220 days). Dose interruptions and dose adjustments due to rash were reported in 21.8% and 9.2% of patients, respectively, in the Trezilent plus fulvestrant arm.

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

A subgroup of 86 patients received anti rash treatment, including anti-histamines, prior to onset of rash. In these patients, rash was reported less frequently than in the overall population, for all Grades rash (26.7% vs 53.9%), Grade 3 rash (11.6% vs 20.1%) and rash leading to permanent discontinuation of Trezilent (3.5% vs 4.2%). Accordingly, antihistamines may be initiated prophylactically, at the time of initiation of treatment with Trezilent. Based on the severity of rash, Trezilent may require dose interruption, reduction, or discontinuation as described in Table 4-3 Dose modification and management for rash (see section 4 Dosage regimen and administration).

### GI toxicity (nausea, diarrhoea, vomiting)

In the phase III study, diarrhoea, nausea and vomiting were (see Table 7-1 Adverse drug reactions) reported in 57.7%, 44.7% and 27.1% of the patients, respectively, and led to

discontinuation of Trezilent and/or fulvestrant in 8 (2.8%), 5 (1.8%) and 3 (1.1%) of the patients, respectively.

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

Severe diarrhoea and clinical consequences, such as dehydration and acute kidney injury have been reported during treatment with Trezilent and resolved with appropriate intervention (see Table 7-1 Adverse drug reactions). Patients should be managed according to local standard of care medical management, including electrolyte monitoring, administration of anti-emetics and antidiarrhoeal medications and/or fluid replacement and electrolyte supplements, as clinically indicated. In the phase III clinical study, anti-emetics (eg. ondansetron) and anti-diarrhoeal medications (eg: loperamide) were used in 27/149 (18.1%) and 104/164 (63.4%) of patients to manage symptoms.

**Osteonecrosis of the jaw (ONJ)**

In the phase III clinical study, ONJ was reported in 4.2% patients (12/284) in the Trezilent 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) or RANK-ligand inhibitors (e.g. denosumab). Therefore, in patients receiving Trezilent and bisphosphonates or RANK-ligand inhibitors, an increased risk of development of ONJ cannot be excluded.

# 7 Interactions

The elimination of alpelisib is majorly driven by non-hepatic hydrolysis (45%), mediated by multiple enzymes (esterases, amidases, choline esterase) and excretion by hepatobiliary export and intestinal secretion (40%). The overall contribution of CYP3A4 to the overall metabolism and clearance of alpelisib was shown to be low in humans (≤15%) and therefore Trezilent can be administered without any dose adjustments with drugs that are CYP3A4 inhibitors or inducers.

## Medicinal products that may increase alpelisib plasma concentrations

**BCRP inhibitors**

Alpelisib is a sensitive substrate for BCRP (breast cancer resistance protein) *in vitro*, predominantly expressed in the liver, intestine, and at blood-brain barrier. Absorption of alpelisib will not be affected by BCRP inhibition due to saturation of the transporter in the intestine. However, due to the involvement of BCRP in the hepatobiliary export and intestinal secretion of alpelisib, caution is advised when co-administering Trezilent with a BCRP inhibitor (e.g. eltrombopag, lapatininb, pantoprazole), as inhibition of BCRP in the liver and in the intestine after absorption may lead to an increase in systemic exposure of Trezilent.

## Medicinal products that may decrease alpelisib plasma concentrations

**Acid-reducing agents**

The co-administration of the H2 receptor antagonist ranitidine in combination with a single 300 mg oral dose of alpelisib slightly reduced the bioavailability of alpelisib and decreased overall exposure of alpelisib. In the presence of a low-fat low-calorie (LFLC) meal, AUCinf was decreased on average by 21% and Cmax by 36% with ranitidine. In the absence of food, the effect was more pronounced with a 30% decrease in AUCinf and a 51% decrease in Cmax with ranitidine compared to the fasted state without co-administration of ranitidine. Population pharmacokinetic analysis showed no significant effect of co-administration of acid-reducing agents, including proton pump inhibitors, H2 receptor antagonists and antacids, on the pharmacokinetics of alpelisib. Therefore, alpelisib can be co-administered with acidreducing agents, provided alpelisib is taken immediately after food.

## Medicinal products whose plasma concentrations may be altered by alpelisib

**CYP3A4 substrates**

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

Caution is recommended when Trezilent 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). Systemic exposures of such CYP3A4 auto-inhibitors and auto-inducers may be decreased and increased, respectively, when Trezilent is co-administered, based on PBPK (physiologically based pharmacokinetic) simulations.

**CYP2C9 substrates with narrow therapeutic index**

*In vitro* evaluations indicate that the pharmacological activity may be reduced by the CYP2C9 induction effects of alpelisib. Based on PBPK modeling data with sensitive CYP2C9 substrate warfarin, after co-administration of alpelisib (300 mg once daily for 20 days), AUC (area under curve) and Cmax (maximum concentration) ratios of warfarin were estimated to be 0.91 and 0.99, respectively, indicating no or weak induction potential of alpelisib on CYP2C9. No dose adjustment is required when Trezilent is co-administered with CYP2C9 substrates with narrow therapeutic index (e.g. warfarin). However, in the absence of clinical data, caution is recommended.

**CYP2B6 sensitive substrates with narrow therapeutic index**

Static mechanistic assessment with sensitive CYP2B6 substrates such as bupropion, a reduction of exposure by up to 3-fold can be expected when co-administered with alpelisib based on *in vitro* assessment, no clinical study was performed. Sensitive CYP2B6 substrates (eg bupropion) or CYP2B6 substrates with a narrow therapeutic window should be used with caution in combination with Trezilent, as Trezilent may reduce the clinical activity of such drugs.

### Drug-food interactions

In healthy subjects, co-administration of alpelisib with food resulted in an increased AUC of alpelisib by 77% (see section 4 Dosage regimen and administration and section 11 Clinical pharmacology). Therefore, Trezilent should be taken immediately after food, at approximately same time each day (see section 4 Dosage regimen and administration).

### Hormonal contraceptives

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

# 8 Pregnancy, lactation, females and males of reproductive potential

## 8.1 Pregnancy

### Risk summary

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

There are no adequate and well-controlled studies in pregnant women. Embryo-fetal development studies in rats and rabbits have demonstrated that oral administration of alpelisib during organogenesis induced embryo-toxicity, feto-toxicity, and teratogenicity. In rats and rabbits, following prenatal exposure to alpelisib, increased incidences of post-implantation loss, reduced fetal weights, and increased incidences of fetal abnormalities were observed starting at doses below (see animal data) the exposure in humans at the highest recommended dose of 300 mg.

Trezilent should not be used during pregnancy unless the benefits to the mother outweighs the risk to the fetus. If Trezilent is used during pregnancy, the patient should be advised of the potential risk to the fetus.

### Data

### Animal Data

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

In rats, oral administration of alpelisib was associated with maternal body weight loss or stagnation, low food consumption and embryonal death at 30 mg/kg/day, approximately 3.2 times (based on AUC) the exposure in humans at the highest recommended dose of 300 mg. Low maternal body weight gain, increased incidences of enlarged brain ventricle in the fetuses, reduced fetal weight, decreased bone ossification and skeletal malformations were seen at 10 mg/kg/day, that is equal to approximately 0.9 times below the exposure in humans at the highest recommended dose.

In rabbits, at doses of ≥25 mg/kg/day, maternal body weight loss with reduced food intake was observed. At 15 mg/kg/day, slight transient body weight loss was observed. At ≥15 mg/kg/day increased embryo-fetal deaths and malformations were observed, mostly related to the tail and head, and were associated with increased serum glucose levels in dams. At 25 mg/kg/day, reduced mean fetal weight was observed. The dose of 15 mg/kg/day dose in rabbits is equivalent to approximately 5.5 times (based on AUC) the exposure achieved at the highest recommended human dose.

In rats and rabbits, no fetal effects were observed at 3 mg/kg/day, and considered to be the no-observable-adverse-effect-level (NOAEL) for fetal abnormalities. The maternal systemic exposures (AUC) at the NOAEL were 0.12 (rats) or 0.86 (rabbits) times the exposure in humans at the highest recommended dose of 300 mg.

## 8.2 Lactation

### Risk summary

It is not known if alpelisib is transferred into human or animal milk after administration of Trezilent. There are no data on the effects of alpelisib on the breastfed child or the effects of alpelisib on milk production.

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

## 8.3 Females and males of reproductive potential

### Pregnancy testing

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

### Contraception

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 fetus. Sexually-active females of reproductive potential should use effective contraception (methods that result in less than 1% pregnancy rates) when using Trezilent during treatment and for at least 1 week after stopping treatment with alpelisib. It is currently unknown whether alpelisib may reduce the effectiveness of systemically acting hormonal contraceptives.

### Infertility

There is no data on the effect of alpelisib on fertility. Based on repeat dose toxicity studies on animals, Trezilent may impair fertility in males and females of reproductive potential, at doses approximately 2.8 times the exposure in humans, at the highest recommended dose of 300 mg/day (based on AUC) (see section 13 Non-clinical safety data).

# 9 Overdosage

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

In cases where accidental over-dosage of Trezilent was reported in the clinical studies, the adverse events associated with the overdose were consistent with the known safety profile of Trezilent and included hyperglycemia, nausea, asthenia and rash.

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

# 10 Clinical pharmacology

## Pharmacotherapeutic group, ATC

Antineoplastic agents, other antineoplastic agents L01EM03.

## Mechanism of action (MOA)

Alpelisib is an α specific class I phosphatidylinositol3kinase (PI3Kalpha) inhibitor.

Class I PI3K lipid kinases are key components of the PI3K/AKT/mTOR (mammalian target of rapamycin) signaling pathway.

Gain-of-function mutations in the gene encoding the catalytic alpha-subunit of PI3K (PIK3CA) lead to activation of PI3Kalpha manifested by increased lipid kinase activity, growth-factor independent activation of Akt-signaling, cellular transformation and the generation of tumors in a diverse array of preclinical models.

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

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

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

## Pharmacodynamics (PD)

In biochemical assays, alpelisib inhibited wild type PIK3alpha ($IC_{50}$=4.6 nmol/L) and its 2 most common somatic mutations (H1047R, E545K) ($IC_{50}$~4 nmol/L) more potently than the PI3Kdelta ($IC_{50}$=290 nmol/L) and PI3Kgamma ($IC_{50}$=250 nmol/L) isoforms and showed significantly reduced activity against PI3Kbeta ($IC_{50}$=1,156 nmol/L).

The potency and selectivity of alpelisib was confirmed at the cellular level in mechanistic and relevant tumor cell lines.

## Cardiac electrophysiology

Serial, triplicate ECGs (electrocardiogram) 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. A pharmacokinetic-pharmacodynamic analysis included a total of 134 patients treated with alpelisib at doses ranging from 30 to 450 mg.

The analysis demonstrates the absence of a clinically significant QTcF prolongation at the recommended 300 mg dose with or without fulvestrant. The estimated mean change from baseline in QTcF was <10 msecs (7.2 ms; 90% CI: 5.62, 8.83) at the observed geometric-mean Cmax at steady-state (2,900 ng/mL) following single agent administration at the recommended 300 mg dose.

## Pharmacokinetics (PK)

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 mg to 400 mg. The PK was mostly comparable in both oncology patients and healthy subjects.

## Absorption

Following oral administration of alpelisib, median time to reach peak plasma concentration (Tmax) ranged between 2.0 to 4.0 hours, independent of dose, time or regimen. Based on absorption modelling bioavailability was estimated to be very high (>99%) under fed conditions but lower under fasted conditions (~68.7% at a 300 mg dose). Steady-state plasma levels of alpelisib after daily dosing can be expected to be reached on day 3, following onset of therapy in most patients.

### Food effect

Alpelisib absorption is affected by food. In healthy volunteers after a single 300 mg oral dose of alpelisib, compared to the fasted state, a high-fat high-calorie (HFHC) meal (985 calories with 58.1 g of fat) increased AUCinf by 73% and Cmax by 84%, and a low-fat low-calorie (LFLC) meal (334 calories with 8.7 g of fat) increased AUCinf by 77% and Cmax by 145%. No significant difference was found for AUCinf between LFLC and HFHC with a geometric mean ratio of 0.978 [CI: 0.876, 1.09] showing that neither fat content nor overall caloric intake has a considerable impact on absorption. The increase in gastrointestinal solubility by bile, secreted in response to food intake, is considered to be the driver of the food effect. Hence, Trezilent should be taken immediately after food, at approximately the same time each day.

### Acid reducing agents

The co-administration of the H2 receptor antagonist ranitidine in combination with a single 300 mg oral dose of alpelisib slightly reduced the bioavailability of alpelisib and decreased overall exposure of alpelisib. In the presence of a LFLC meal, AUCinf was decreased on average by 21% and Cmax by 36% with ranitidine. In the absence of food, the effect was more pronounced with a 30% decrease in AUCinf and a 51% decrease in Cmax with ranitidine compared to the

fasted state without co-administration of ranitidine. Trezilent can be co-administered with drugs that are acid-reducing agents, if Trezilent is taken immediately after food. Population pharmacokinetic analysis showed no significant effect on the PK of Trezilent by co-administration of acid reducing agents including proton pump inhibitors, H2 receptor antagonists and antacids.

### 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. There was no evidence for distribution into red blood cells caused by metabolites. Alpelisib did not penetrate the blood-brain-barrier in rats. As Trezilent is a substrate of human efflux transporters, penetration of the blood-brain-barrier is not expected to occur in human. The volume of distribution of alpelisib at steady-state (Vss/F) is estimated at 114 L (intersubject CV% 46%).

### Biotransformation/metabolism

*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 to 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/hr (CV% 21%) based on population PK analysis under fed conditions. The population derived half-life, independent of dose and time, was 8 to 9 hours at steady state of 300 mg, once daily.

In human mass-balance study, after oral administration, alpelisib and its metabolites are excreted in the feces (81.0%), mainly through hepatobiliary export and/or intestinal secretion of alpelisib or metabolized to BZG791. Excretion in the urine is minor (13.5%), with unchanged alpelisib (2%). Following 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

Based on the results of metabolic *in vitro* induction and inhibition studies, alpelisib may induce the metabolic clearance of co-medications metabolized by CYP2B6, CYP2C9 and CYP3A4

and may inhibit the metabolic clearance of co-medications metabolized CYP3A4 (time-dependent inhibition) if sufficiently high concentrations are achieved *in vivo*.

In a drug-drug interaction study, co-administration of alpelisib with everolimus, a sensitive CYP3A4 substrate, confirmed that there are no clinically significant pharmacokinetic interactions (increase 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, also confirmed by PBPK modeling with everolimus and midazolam (≤15% increase in AUC). Due to the concurrent induction and time-dependent inhibition by alpelisib, PBPK simulations with substrates of CYP3A4 that also possess an additional time-dependent inhibition and induction potential on CYP3A4 that affects their own metabolism predict changes in exposure (decrease or increase) less than 2-fold, depending on the substrate.

**CYP2C9 substrates**

In lieu of a clinical study, PBPK modeling showed that AUC and Cmax ratios of warfarin (10 mg single dose) were estimated to be 0.91 and 0.99, respectively, after repeated co-administration of alpelisib (300 mg), indicating no or weak induction potential of alpelisib on CYP2C9.

**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, OAT3, OCT2, MATE1, MATE2K). As unbound systemic steady state concentrations (or concentrations at the liver inlet) at both the therapeutic dose and maximum tolerated dose are significantly lower than the experimentally determined unbound inhibition constants or IC50, the inhibition 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.

**Fulvestrant:** Data from a clinical study in patients with breast cancer indicated no effect of fulvestrant on alpelisib exposure (and vice versa) following co-administration of the drugs.

## Special populations

**Effect of age, weight and gender**

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

### Pediatric patients (below 18 years)

The pharmacokinetics of Trezilent in pediatric patients have not been established.

### Geriatric patients (65 years or above)

Of 284 patients who received Trezilent in the phase III study (in Trezilent plus fulvestrant arm), 117 patients were ≥65 years of age and 34 patients were ≥75 years of age. No overall differences

in safety or effectiveness of Trezilent were observed between these patients and younger patients (see section 4 Dosage regimen and administration).

### Race/Ethnicity

Population PK analyses and PK analysis from a single agent study in Japanese cancer patients showed that there are no clinically relevant effects of ethnicity on the systemic exposure of Trezilent.

Non-compartmental PK parameters after single and multiple daily doses of Trezilent 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. Patients with severe renal impairment have not been studied and caution should be used. Based on a population pharmacokinetic analysis that included 117 patients with normal renal function (eGFR [estimated glomerular filtration rate] ≥90 mL/min/1.73 $m^2$) / (CLcr ≥90 mL/min), 108 patients with mild renal impairment (eGFR 60 to <90 mL/min/1.73$m_2$)/ (CLcr 60 to <90 mL/min), and 45 patients with moderate renal impairment (eGFR 30 to <60 mL/min/1.73 $m_2$), mild and moderate renal impairment had no effect on the exposure of alpelisib (see section 4 Dosage regimen and administration).

### 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 trial in patients with hepatic impairment, moderate and severe hepatic impairment had negligible effect on the exposure of alpelisib (see section 4 Dosage regimen and administration). The mean exposure for alpelisib was increased by 1.26-fold in patients with severe (GMR [geometric mean ratio]: 1.00 for Cmax; 1.26 for AUClast /AUCinf) hepatic impairment.

Based on a population pharmacokinetic analysis that included 230 patients with normal hepatic function, 45 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 Dosage regimen and administration).

## 11 Clinical studies

### SOLAR-1

Trezilent was evaluated in a pivotal phase III, randomized, double-blind, placebo controlled study of Trezilent in combination with fulvestrant in men and postmenopausal women with HR+, HER2- locally advanced breast cancer whose disease had progressed or recurred on or after an aromatase inhibitor based treatment (with or without CDK4/6 combination).

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

Within the cohort with a PIK3CA mutation, 169 patients were randomized to receive Trezilent in combination with fulvestrant and 172 patients were randomized to placebo in combination with fulvestrant. Within this cohort, 170 (49.9%) patients had liver/lung metastases and 20 (5.9%) patients had received prior CDK4/6 inhibitor treatment.

Within the cohort without PIK3CA mutation, 115 patients were randomized to receive Trezilent in combination with fulvestrant and 116 were randomized to receive placebo in combination with fulvestrant. 112 (48.5%) patients had liver/lung metastases and 15 (6.5%) patients had prior CDK4/6 inhibitor treatment.

In the cohort with PIK3CA mutation, 97.7% of patients received prior hormonal therapy and 47.8% of patients had the last setting as metastatic and 51.9% of patients whose last setting was adjuvant therapy. Overall, 85.6% of the patients were considered to have endocrine resistant disease; primary endocrine resistance was observed in 13.2% and secondary endocrine resistance in 72.4% of patients.

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

During the randomized treatment phase, Trezilent 300 mg or Trezilent matching placebo was administered orally once daily on a continuous basis. Fulvestrant 500 mg was administered intramuscularly on Cycle 1 Day 1 and 15 and then at Day 1 of a 28-day cycle during treatment phase (administration +/- 3 days).

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

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

Other secondary endpoints included PFS for patients without PIK3CA mutation, OS for patients without a PIK3CA mutation, as well as overall response rate (ORR) and clinical benefit rate (CBR) by PIK3CA mutation cohort.

**Cohort with PIK3CA mutation**

Patients enrolled with a PIK3CA mutation had a median age of 63 years (range 25 to 92). 44.9% patients were 65 years of age or older and <85 years. The patients included were White (66.3%), Asian (21.7%), Black or African American (1.2%).

**Primary analysis**

The study met its primary objective at the final PFS analysis (data cut-off date 12-Jun-2018) demonstrating a statistically significant improvement in PFS by investigator assessment in the PIK3CA mutant cohort for patients receiving Trezilent plus fulvestrant, compared to patients receiving placebo plus fulvestrant (HR = 0.65 with 95% CI: 0.50, 0.85, one sided stratified log-rank test p= 0.00065), with an estimated 35% risk reduction of disease progression or death in favor of treatment with Trezilent plus fulvestrant. The median PFS was prolonged by 5.3 months, from 5.7 months (95% CI: 3.7, 7.4) in the placebo plus fulvestrant arm to 11 months (95% CI: 7.5, 14.5) in the Trezilent plus fulvestrant arm.

Primary PFS results were supported by consistent results from a blinded independent review committee (BIRC) assessment in this cohort, which included a randomly selected subset of 50% of randomized patients (HR = 0.48 with 95% CI: 0.32, 0.71).

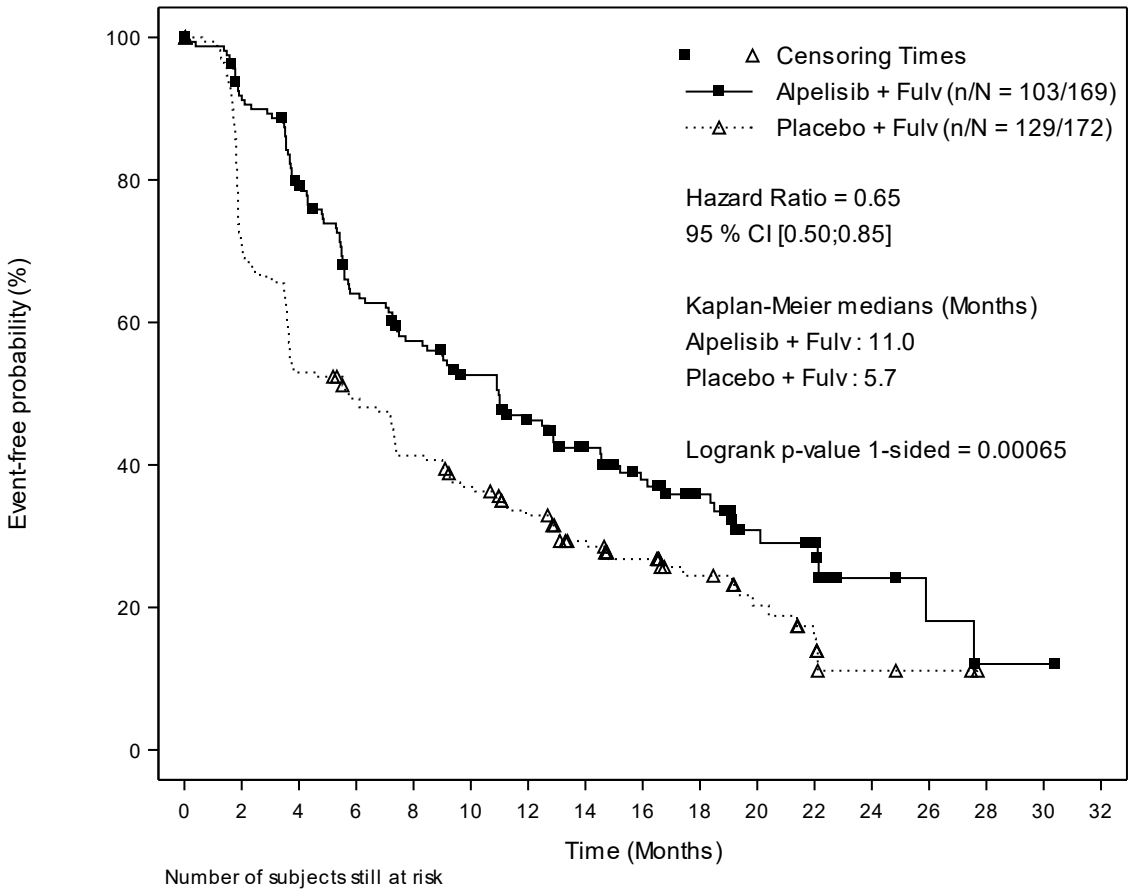
PFS results are summarized in Table 12-1,Figure 12-1 and 12-2.

**Table 12-1 Study C2301- Primary efficacy analysis - Summary of results based on RECIST (FAS, cohort with PIK3CA mutation)**

| | **Trezilent + Fulvestrant (n=169)** | **Placebo + Fulvestrant (n=172)** | **Hazard ratio (HR)** | **p-value[a]** |
|---|---|---|---|---|
| **Median progression-free survival (PFS[a]) (months, 95% CI)** | | | | |
| *Investigator radiological assessment* | | | | |
| PIK3CA mutant cohort (N=341) | 11.0 (7.5 to 14.5) | 5.7 (3.7 to 7.4) | 0.65 (0.50 to 0.85) | 0.00065 |
| *Blinded independent review committee assessment** | | | | |
| PIK3CA mutant cohort (N=173) | 11.1 7.3 to 16.8 | 3.7 2.1 to 5.6 | 0.48 (0.32 to 0.71) | N/A |

*Data cut-off date: 12JUN2018*
*CI=confidence interval; N=number of patients; N/A = is not applicable*
*[a]p-value is obtained from the one-sided stratified log-rank test.*
**Sample-based audit approach of 50% randomized patients*

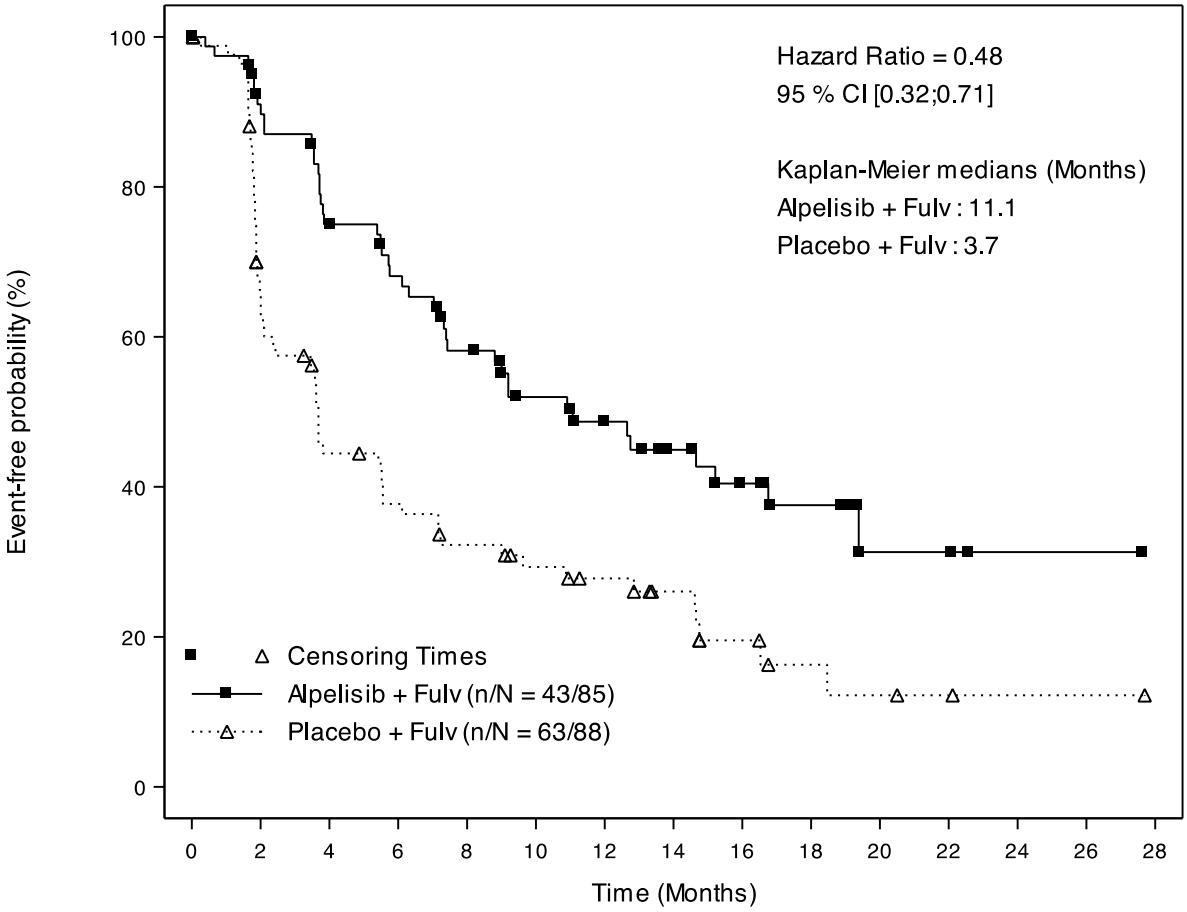
**Figure 12-1** **Study C2301 primary efficacy analysis - Kaplan-Meier plot of PFS per investigator assessment (FAS, PIK3CA mutation cohort). Data cut-off date: 12-Jun-2018**




Number of subjects still at risk

| Time (Months) | 0 | 2 | 4 | 6 | 8 | 10 | 12 | 14 | 16 | 18 | 20 | 22 | 24 | 26 | 28 | 30 | 32 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Alpelisib + Fulv | 169 | 145 | 123 | 97 | 85 | 75 | 62 | 50 | 39 | 30 | 17 | 14 | 5 | 3 | 1 | 1 | 0 |
| Placebo + Fulv | 172 | 120 | 89 | 80 | 67 | 58 | 48 | 37 | 29 | 20 | 14 | 9 | 3 | 2 | 0 | 0 | 0 |

**Figure 12-2** **Study C2301 Kaplan-Meier plot of PFS per BIRC assessment (FAS, PIK3CA mutant cohort). Data cut-off date: 12-Jun-2018.**




Number of subjects still at risk

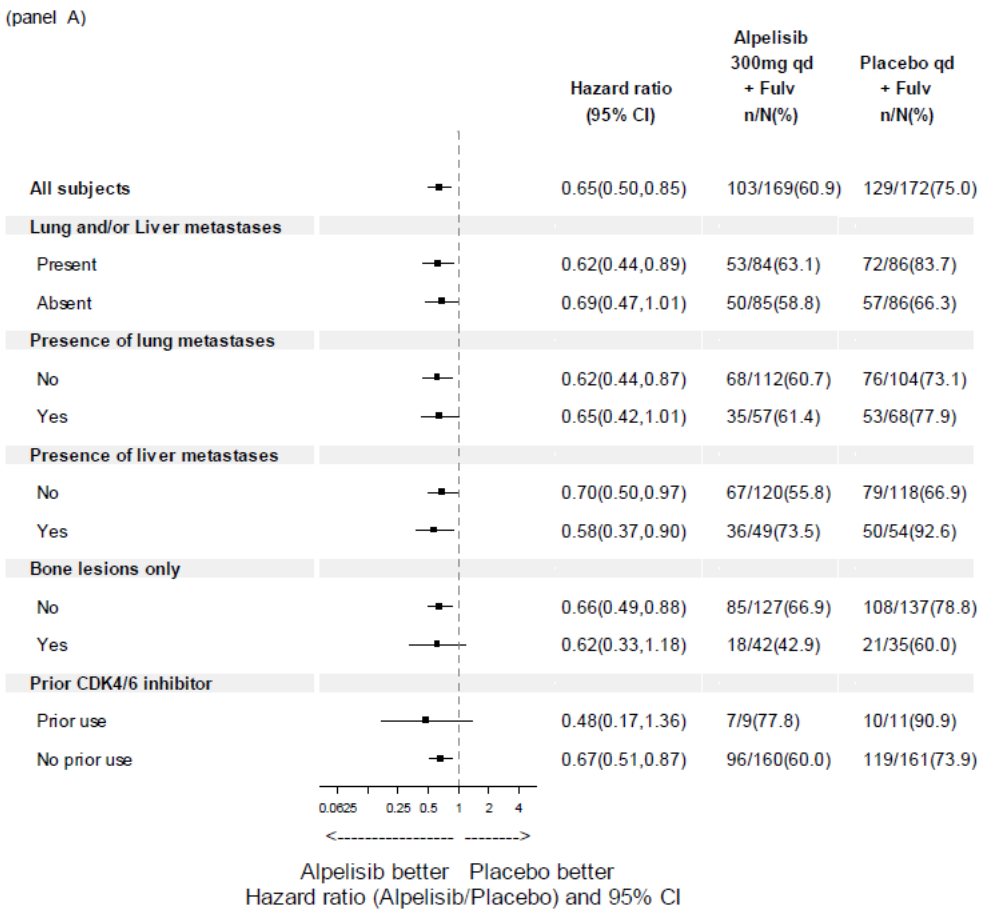
| Time (Months) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Alpelisib + Fulv | 85 | 77 | 69 | 66 | 56 | 55 | 49 | 47 | 40 | 37 | 32 | 31 | 26 | 24 | 21 | 19 | 16 | 12 | 12 | 11 | 3 | 3 | 3 | 1 | 1 | 1 | 1 | 1 | 0 |
| Placebo + Fulv | 88 | 83 | 53 | 46 | 34 | 33 | 28 | 27 | 23 | 23 | 19 | 17 | 16 | 14 | 12 | 7 | 7 | 4 | 4 | 3 | 3 | 2 | 2 | 1 | 1 | 1 | 1 | 1 | 0 |

PFS subgroup analyses by randomization stratification factors demonstrated a homogeneous and generally consistent treatment effect per investigator assessment across major demographic and prognostic subgroups irrespective of CDK4/6i prior treatment and presence or absence of lung/liver metastases.

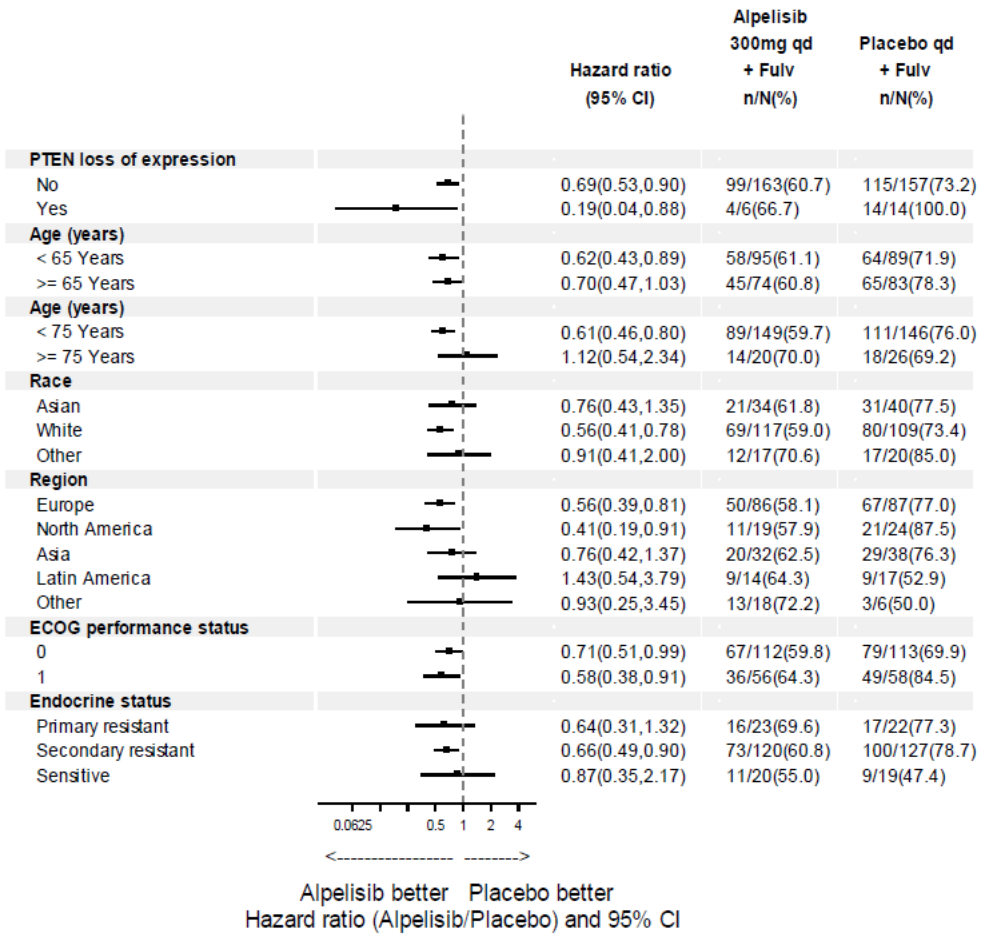
Although limited in patient numbers, for the analysis of prior CDK4/6i treatment sub-group, the HR (95% CI) for PFS was 0.48 (0.17, 1.36). In the subgroup of patients with presence of lung/liver metastases, the HR (95% CI) was 0.62 (0.44, 0.89). See Figure 12-3 and 12-4 for details.

**Figure 12-3** **Study C2301 - PFS per investigator assessment in major demographic and prognostic subgroups (FAS, PIK3CA mutant cohort). Data cut-off date: 12-Jun-2018.**

(panel A)



(panel B)



(panel C)

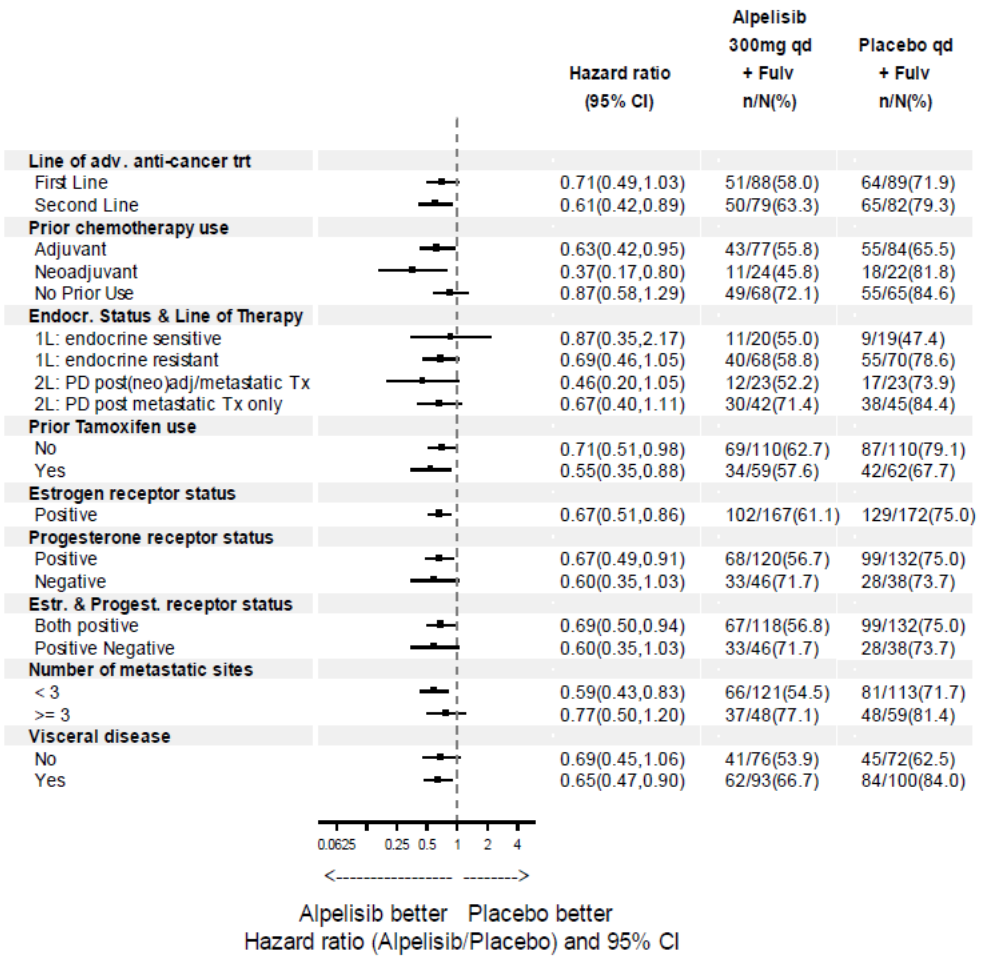
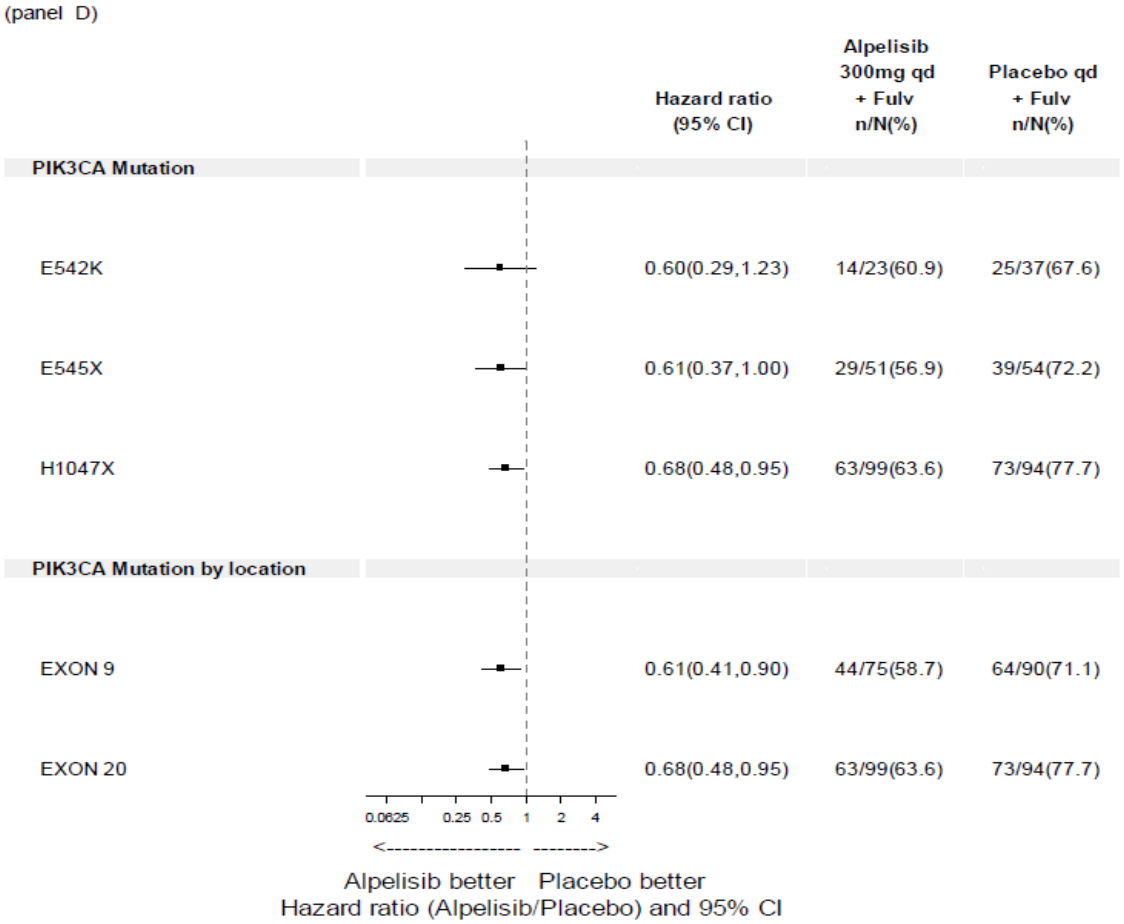


**Figure 12-4 Study C2301 - PFS per investigator assessment by PIK3CA mutations (FAS, PIK3CA mutant cohort). Data cut-off date: 12-Jun-2018.**




Treatment with the combination of Trezilent plus fulvestrant was associated with marked improvements in ORR and CBR relative to placebo + fulvestrant. See Table 12-2 for details.

**Table 12-2 Study C2301 - Overall response rate and clinical benefit rate per investigator assessment (FAS, PIK3CA mutant cohort). Data cut-off date: 12-Jun-2018.**

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

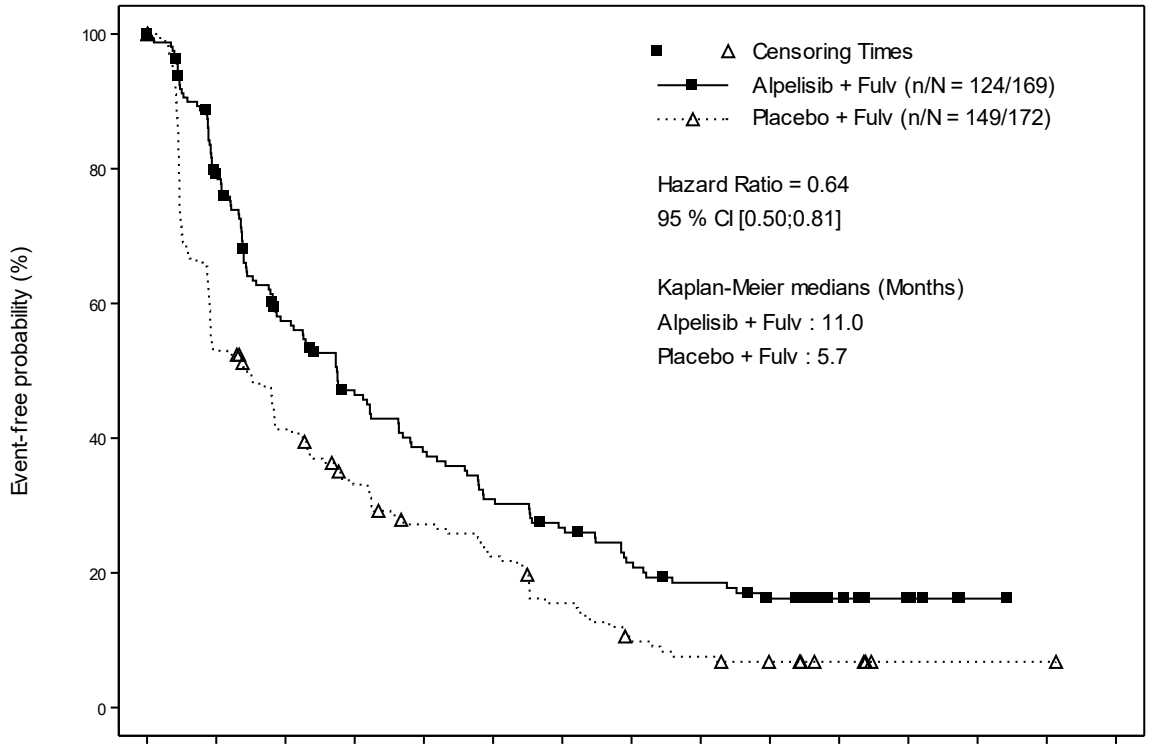
*[a] ORR= proportion of patients with confirmed Complete Response or Partial Response*
*[b] CBR: proportion of patients with confirmed Complete Response or Partial Response, or (Stable Disease or Non-Complete Response/Non-Progression Disease >=24 weeks)*
*[c] p-value is obtained from the Cochran-Mantel Haenszel test.*

The global health status/Quality of Life (QoL) outcomes were similar between the Trezilent plus fulvestrant arm and the placebo plus fulvestrant arm. Time-to-Deterioration (TTD) in global health status EORTC QLQ-C30 (European Organization for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30) was defined as time between baseline and first occurrence of ≥10 point worsening of global health status (EORTC QLQ-C30 global health scale score) compared to baseline with no later improvement above this threshold observed during the treatment period or death due to any cause. The addition of Trezilent to fulvestrant showed no relevant difference in TTD in EORTC QLQ-C30 global health scale score compared with placebo plus fulvestrant, (HR=1.03 ; 95% CI: 0.72, 1.48)

**Final OS Analysis**

The final OS analysis was conducted using a data cut-off date of 23-Apr-2020 and PFS was re-run using this data cut. With a median duration from randomization to data cut-off of approximately 42 months, the PFS benefit was sustained and consistent with results from the final PFS analysis. There was an estimated 36% risk reduction of progression or death in favor of treatment with Trezilent plus fulvestrant (HR = 0.64; 95% CI: 0.50, 0.81). See Figure 12-5 for details.

**Figure 12-5** **Study C2301 - Kaplan-Meier plot of PFS per investigator assessment (FAS, PIK3CA mutant cohort): descriptive update with data cut-off date of 23-Apr-2020**

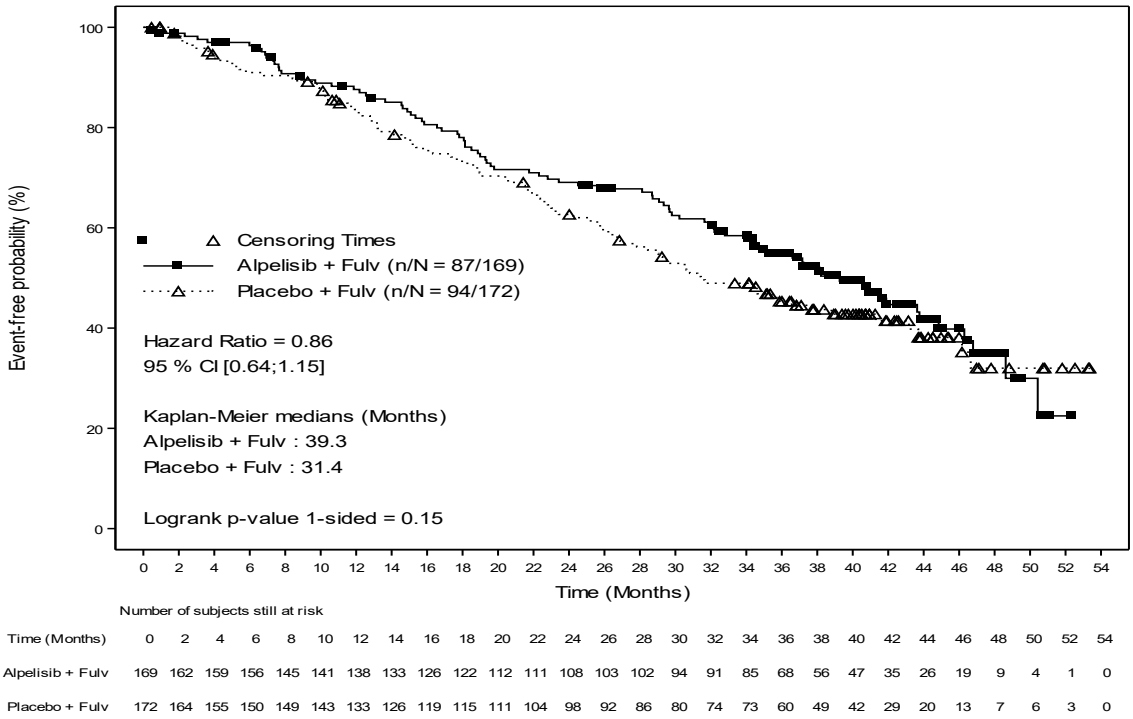



Number of subjects still at risk

| Time (Months) | 0 | 4 | 8 | 12 | 16 | 20 | 24 | 28 | 32 | 36 | 40 | 44 | 48 | 52 | 56 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Alpelisib + Fulv | 169 | 123 | 85 | 66 | 54 | 44 | 37 | 29 | 24 | 18 | 12 | 6 | 1 | 0 | 0 |
| Placebo + Fulv | 172 | 89 | 67 | 51 | 40 | 33 | 22 | 13 | 10 | 7 | 4 | 1 | 1 | 1 | 0 |

At the final OS analysis, the study did not meet its key secondary objective. As of the data cut-off date of 23-Apr-2020, a total of 87 (51.5%) deaths were reported in the Trezilent plus fulvestrant arm and 94 (54.7%) in the placebo plus fulvestrant arm. The HR was 0.86 (95% CI: 0.64, 1.15; p = 0.15, one-sided) and the pre-specified O'Brien-Fleming efficacy boundary of $p \leq 0.0161$ was not crossed. Median OS was prolonged by a clinically relevant 7.9 months, from 31.4 months (95% CI: 26.8, 41.3) in the placebo plus fulvestrant arm to 39.3 months (95% CI: 34.1, 44.9) in the Trezilent plus fulvestrant arm. See Figure 12-6 for details.

**Figure 12-6 Study C2301 key secondary analysis - Kaplan-Meier plot of OS (FAS, PIK3CA mutant cohort) with cut-off date of 23-Apr-2020.**




Number of subjects still at risk

| Time (Months) | 0 | 2 | 4 | 6 | 8 | 10 | 12 | 14 | 16 | 18 | 20 | 22 | 24 | 26 | 28 | 30 | 32 | 34 | 36 | 38 | 40 | 42 | 44 | 46 | 48 | 50 | 52 | 54 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Alpelisib + Fulv | 169 | 162 | 159 | 156 | 145 | 141 | 138 | 133 | 126 | 122 | 112 | 111 | 108 | 103 | 102 | 94 | 91 | 85 | 68 | 56 | 47 | 35 | 26 | 19 | 9 | 4 | 1 | 0 |
| Placebo + Fulv | 172 | 164 | 155 | 150 | 149 | 143 | 133 | 126 | 119 | 115 | 111 | 104 | 98 | 92 | 86 | 80 | 74 | 73 | 60 | 49 | 42 | 29 | 20 | 13 | 7 | 6 | 3 | 0 |

OS subgroup analyses by randomization stratification factors demonstrated a homogeneous and generally consistent treatment effect per investigator assessment. Although limited in patient numbers, for the analysis of prior CDK4/6i treatment subgroup, median OS in the Trezilent plus fulvestrant arm was 29.8 months (95% CI: 6.7, 38.2) compared to 12.9 months (95% CI: 2.5, 34.6) in the placebo plus fulvestrant arm. In the subgroup of patients with presence of lung/liver metastases, median OS in the Trezilent plus fulvestrant arm was 37.2 months (95% CI: 28.7, 43.6) compared to 22.8 months (95% CI: 19, 26.8) in the placebo plus fulvestrant arm.

### Cohort without PIK3CA mutation

The proof of concept criteria to conclude a treatment benefit with Trezilent and fulvestrant with respect to PFS in patients in the PIK3CA non-mutant cohort were not met (HR = 0.85; 95% CI: 0.58, 1.25) (see section 4 Dosage regimen and administration).

### BYLieve

Trezilent was evaluated in a Phase II, multicenter, open-label, three-cohort, non-comparative study of Trezilent plus endocrine therapy (either fulvestrant or letrozole) in patients (pre- and post-menopausal women and men), 18 years or older, with HR-positive, HER2-negative advanced (locoregionally recurrent or metastatic) breast cancer, not amenable to curative

therapy harboring PIK3CA mutation(s) in the tumor tissue, whose disease has progressed on or after prior treatments.

A total of 380 patients, with HR-positive, HER2-negative advance breast cancer harboring a PIK3CA mutation in tumor tissue, were enrolled.

Patients were assigned to cohort A (alpelisib 300 mg plus fulvestrant 500 mg; patients whose last prior treatment was a CDK4/6i plus any AI), cohort B (alpelisib 300 mg plus letrozole 2.5 mg; patients whose last prior treatment was a CDK4/6i plus fulvestrant), or cohort C (Trezilent 300 mg plus fulvestrant 500 mg; patients who failed prior AI based therapy and received systemic chemotherapy or endocrine therapy as last prior treatment ) based on their most recent prior therapy. Patients were treated until disease progression, intolerable toxicity, or until 18 months after last subject first treatment. Treatment crossover between cohorts was not permitted in this study.

The primary objective of the study was to assess the proportion of patients who were alive without disease progression at 6-months based on local Investigator assessment per RECIST v1.1 separately in cohorts A and C (alpelisib in combination with fulvestrant) and cohort B (alpelisib in combination with letrozole) among patients with HR-positive, HER2- negative advance breast cancer harboring a PIK3CA mutation who have progressed on or after prior treatments.

The analysis of the primary endpoint was to be performed for each cohort 6 months after the last patient had started treatment or discontinued early.

Results are available for Cohort A. With a median duration of follow-up of 11.7 months (calculated from the start of treatment to the data cut-off date of 17-Dec-2019 ) 61/121 patients (50.4%, 95% CI: 41.2, 59.6) were alive without disease progression at 6-months. The study met the primary objective for cohort A (lower bound of 95% CI was >30%).

One of the key secondary endpoints was progression-free survival (PFS).

Based on Investigator assessment, 72 PFS events were observed and the median PFS was 7.3 months (95% CI: 5.6, 8.3).

## 12 Non-clinical safety data

Alpelisib was evaluated in safety pharmacology, single- and repeated dose toxicity, genotoxicity and photo-toxicity studies.

**Safety pharmacology and repeat dose toxicity**

The majority of the observed alpelisib effects were related to the pharmacological activity of alpelisib as a p110alpha specific inhibitor of the PI3K pathway, such as the influence on the glucose homeostasis resulting in hyperglycemia 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 effects. Effects on bone marrow and lymphoid tissue were generally reversible on cessation of treatment. Effects on the pancreas and reproductive organs did not fully reverse but showed a tendency towards reversion.

**Cardiovascular safety pharmacology:** In an *in vitro* hERG (human Ether-à-go-go-Related Gene) test, (where functionality of the human cardiac hERG channel heterologously expressed in HEK293 cells *in vitro* is assessed), an IC50 of 9.4 microM (4.2 microgram/mL) was found. No relevant electrophysiological effect was seen in dogs in several studies, up to single doses of 180 mg/kg *in-vivo*. An *in vivo* telemetry study in dogs showed an elevated blood pressure, starting at exposure lower than the exposure in humans, at the highest recommended dose of 300 mg/day.

**Carcinogenicity and mutagenicity**

No carcinogenicity studies have been conducted.

Alpelisib was not mutagenic in an in vitro bacterial reverse mutation (Ames) assay, or aneugenic or clastogenic in human cell micronucleaus and chromosome aberration tests in vitro. Alpelisib was not genotoxic in an in vivo rat micronucleus test.

**Reproductive toxicity**

Please see section 9 Pregnancy, lactation, females and males of reproductive potential.

**Infertility**

A fertility study in rats has not been performed. However, in repeated-dose toxicity studies up to 13 weeks duration, adverse effects were observed in reproductive organs of males and females, such as vaginal atrophy and oestrus cycle variations in rats (at or above 6 mg/kg/day, a dose that provides plasma exposure levels below the exposure in humans, at the highest recommended dose of 300 mg/day based on AUC), or prostate atrophy in dogs (at 15 mg/kg/day, at plasma exposure levels about 2.8 times the exposure in humans, at the highest recommended dose of 300 mg/day based on AUC) (see section 9 Pregnancy, lactation, females and males of reproductive potential).

**Phototoxicity**

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

**Juvenile animal studies**

Juvenile animal studies are not available.

# 13 Pharmaceutical information

## Incompatibilities

Not applicable.

## Special precautions for storage

Do not store above 30°C.

Trezilent must be kept out of the reach and sight of children.

The expiry date is indicated in the packaging.

**Pack Size**

Box 300 mg daily dose, 2 wallets @ 2 blisters @ 7 film-coated tablets 150 mg, Reg.No. xxxxxxxxxxxxxx

Box 250 mg daily dose, 2 wallets @ 1 blister @ 7 film-coated tablets 200 mg and 1 blister @ 7 film-coated tablets 50 mg, Reg.No. xxxxxxxxxxxxxx

Box 200 mg daily dose, 1 wallet @ 2 blisters @ 7 film-coated tablets 200 mg, Reg.No. xxxxxxxxxxxxxx

**HARUS DENGAN RESEP DOKTER**

Manufactured by Novartis Pharma Stein AG, Stein, Switzerland

Packed by Lek Pharmaceutical d.d., Ljubljana, Slovenia

For Novartis Pharma AG, Basel, Switzerland

Imported by PT Novartis Indonesia, Jakarta, Indonesia

*Based on CDS v2.1 10-May-2021*

# **TREZILENT**™ (alpelisib)
Tablet salut selaput 50 mg, 150 mg, dan200 mg

## Informasi Produk Untuk Pasien

DISETUJUI OLEH BPOM: 19/12/2022

EREG10000512000255
EREG10000512000256
EREG10000512000257

**Peringatan dan Perhatian untuk Efek Samping Serius**

Pengobatan dengan Trezilent harus diberikan oleh dokter yang berpengalaman dengan penggunaan obat-obatan anti kanker.

Beberapa efek samping serius dibawah ini telah dilaporkan pada pasien yang diobati dengan Trezilent.

- Hipersensitivitas, termasuk reaksi anafilaksis
- *Severe cutaneous reactions* termasuk *Stevens-Johnson Syndrome*, *Drug Reaction with Eosinophilia and Systemic Symptoms* dan *Erythema Multiforme*
- Hiperglikemia, termasuk *hyperglycaemic hyperosmolar non-ketocic syndrome* dan pada beberapa kasus *diabetic ketoacidosis*
- Pneumonia

Bacalah brosur ini dengan saksama sebelum Anda mengonsumsi Trezilent.

Mohon simpan brosur ini. Anda mungkin akan membutuhkan brosur ini untuk dibaca kembali

Obat ini diresepkan hanya untuk Anda. Jangan gunakan obat ini untuk penyakit lain; jangan berikan obat ini kepada orang lain karena dapat membahayakan meskipun gejala penyakitnya serupa dengan gejala penyakit Anda.

Jika terjadi efek samping yang parah atau Anda mengalami efek samping lain yang tidak tertera pada brosur ini, mohon hubungi doter, apoteker atau tenaga kesehatan.

Apabila Anda memiliki pertanyaan lebih lanjut, mohon hubungi dokter, apoteker atau tenaga kesehatan.

## Apa isi brosur ini




DISETUJUI OLEH BPOM: 19/12/2022

EREG10000512000255
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EREG10000512000257

# 1 Apakah Trezilent itu dan apa kegunaannya.

## Apakah Trezilent itu

Trezilent tablet salut selaput mengandung zat aktif alpelisib yang termasuk ke dalam golongan obat yang disebut sebagai *phosphatidylinositol-3-kinase (PIK3CA) inhibitors* dan berguna untuk mengobati kanker payudara jenis tertentu.

## Apakah kegunaan Trezilent

Trezilent merupakan obat yang memerlukan resep dokter yang digunakan oleh wanita yang sudah menopause untuk pengobatan kanker payudara stadium lanjut dengan *hormone receptor (HR)-positive*, *human epidermal growth factor receptor 2 (HER2)-negative*, dan dengan mutasi gen spesifik (PIK3CA) yang penyakitnya mengalami progresi setelah pemberian obat berbasis terapi hormonal. Trezilent digunakan secara kombinasi dengan fulvestrant, salah satu terapi hormonal untuk pengobatan kanker payudara.

Sampel darah atau jaringan tumor yang diambil dari tubuh akan diuji terlebih dahulu untuk melihat ada tidaknya mutasi atau perubahan pada gen yang dikenal dengan PIK3CA. Jika hasilnya positif, besar kemungkinan kanker tersebut memberikan respons terhadap pengobatan dengan Trezilent.

## Cara kerja Trezilent

Trezilent bekerja dengan menghambat efek enzim *phosphatidylinositol-3-kinases (PI3K*), yaitu enzim yang berperan dalam memberikan sinyal ke sel kanker untuk tumbuh dan berkembang menjadi sel-sel kanker baru. Dengan menghambat kinerja enzim ini, Trezilent dapat menekan pertumbuhan dan menurunkan kemampuan sel kanker untuk membentuk sel-sel kanker baru serta mampu membunuh sel kanker.

Trezilent harus digunakan secara kombinasi dengan obat lain, yaitu fulvestrant.

Tanyakan kepada dokter, apoteker atau tenaga kesehatan, jika Anda memiliki pertanyaan terkait cara kerja Trezilent atau mengapa Anda diresepkan obat ini.

# 2 Apa yang harus Anda ketahui sebelum dan selama mengonsumsi Trezilent

Ikuti petunjuk dari dokter Anda secara saksama. Informasi yang Anda dapatkan dari dokter mungkin berbeda dengan informasi umum yang tertera pada brosur ini.

## Jangan mengonsumsi Trezilent

Jika Anda alergi (hipersensitif) terhadap alpelisib atau kandungan lain yang terdapat pada obat ini.

Jika Anda merasa akan bisa mengalami alergi, mintalah anjuran dari dokter Anda.

DISETUJUI OLEH BPOM: 19/12/2022

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EREG10000512000256
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## Peringatan dan Perhatian

**Jika salah satu kondisi berikut ini terjadi pada Anda, beritahukan kepada dokter atau apoteker sebelum Anda mengonsumsi Trezilent:**

- Jika Anda sedang mengalami atau pernah mengalami kondisi kadar gula darah tinggi (atau gejala yang ditimbulkan oleh kadar gula yang tinggi seperti rasa haus berlebih dan mulut kering, buang air kecil lebih sering dari biasanya atau peningkatan jumlah urin, kelelahan atau merasa tidak enak badan, peningkatan nafsu makan yang disertai dengan penurunan berat badan).
- Jika Anda pernah mengalami ruam, kulit kemerahan, lepuh pada bibir, mata, atau mulut, pengelupasan kulit dengan atau tanpa demam, yang boleh jadi merupakan tanda-tanda penyakit *Stevens-Johnson syndrome (SJS), erythema multiforme (EM), toxic epidermal necrolysis (TEN),* atau *drug reaction with eosinophilia and systemic symptoms (DRESS).*
- Jika Anda memiliki penyakit tulang yang parah, yang mempengaruhi rahang (*osteonecrosis* pada rahang/*osteonecrosis of the jaw*).

**Segera beritahukan dokter atau apoteker jika Anda mengalami gejala ini pada saat pengobatan dengan Trezilent:**

- Jika Anda mengalami ruam atau gatal, atau biduran, sesak napas, mengi atau batuk, perasaan seperti melayang, pusing, perubahan tingkat kesadaran, tekanan darah rendah, kulit kemerahan, bengkak pada muka atau tenggorokan, kebiruan pada bibir, lidah, atau kulit (boleh jadi merupakan tanda-tanda reaksi hipersensitivitas berat).
- Jika Anda mengalami masalah pernapasan yang baru atau berubah-ubah, meliputi sesak napas, batuk, napas tersengal-sengal, nyeri pada dada saat bernapas, kebiruan pada bibir, lidah, atau kulit, cegukan, yang boleh jadi merupakan tanda-tanda pneumonitis non-infeksius dan pneumonia.
- Jika Anda mengalami peningkatan kadar gula darah, seperti rasa haus, mulut kering, perasaan sering ingin buang air kecil, kelelahan, peningkatan nafsu makan dengan penurunan berat badan, kebingungan, mual, muntah, napas beraroma buah, sesak napas, dan kulit kering atau kemerahan, yang boleh jadi merupakan tanda-tanda hiperglikemia atau komplikasinya.
- Jika Anda mengalami ruam, kulit kemerahan, lepuh pada bibir, mata, atau mulut, pengelupasan kulit dengan atau tanpa demam, yang boleh jadi merupakan tanda-tanda penyakit *Stevens-Johnson syndrome (SJS), erythema multiforme (EM), toxic epidermal necrolysis (TEN),* atau *drug reaction with eosinophilia and systemic symptoms (DRESS).*
- Jika muncul gejala baru atau perburukan gejala yang mempengaruhi mulut Anda (seperti gigi goyang, nyeri atau bengkak, sariawan yang tidak kunjung sembuh, atau keluar cairan)
- Jika mengalami diare.

Dokter Anda mungkin akan menghentikan sementara atau mengurangi dosis atau menghentikan secara permanen pengobatan Anda dengan Trezilent.

## Pemantauan selama pengobatan dengan Trezilent

Anda akan di tes darah secara rutin sebelum dan selama pengobatan dengan Trezilent untuk memantau kadar gula darah di tubuh Anda. Kadar gula darah dapat dipengaruhi oleh Trezilent.

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Jika diperlukan, dokter dapat menghentikan sementara atau mengurangi dosis Trezilent sampai terjadi perbaikan pada kadar gula darah Anda. Dokter Anda juga dapat memutuskan untuk menghentikan secara permanen pengobatan Anda dengan Treezilent. Anda juga mungkin akan mendapatkan tes darah lainnya, seperti untuk pemantauan elektrolit (kalium, kalsium) selama pengobatan dengan Trezilent.

### Pasien usia lanjut (usia 65 tahun ke atas)

Anda dapat menggunakan Trezilent dengan dosis yang sama seperti pada pasien dewasa umumnya jika Anda berusia 65 tahun ke atas.

### Anak dan remaja (di bawah usia 18 tahun)

Trezilent tidak diperuntukan bagi anak dan remaja di bawah usia 18 tahun.

### Mengonsumsi obat-obat lain (interaksi dengan obat lain)

Sebelum mengonsumsi Trezilent, beri tahukan dokter atau apoteker jika Anda sedang atau pernah mengonsumsi obat-obat lain, termasuk obat dan suplemen yang didapatkan tanpa resep dokter, untuk memastikan tidak terjadi interaksi dengan Trezilent. Obat-obat yang dimaksud umumnya sebagai berikut:

- eltrombopag, obat yang digunakan untuk pengobatan trombosit yang rendah
- obat-obat yang digunakan untuk pengobatan kanker payudara tipe tertentu lainnya, seperti lapatinib, ribociclib
- everolimus, obat yang digunakan untuk pengobatan beberapa jenis kanker
- pantoprazole, obat yang digunakan untuk mengurangi asam lambung atau mengobati ‘panas dalam’
- midazolam, obat yang digunakan untuk membuat Anda mengantuk atau membuat tidur
- rifampicin, obat yang digunakan untuk membunuh bakteri yang menyebabkan infeksi
- encorafenib, obat yang digunakan untuk pengobatan kanker kulit tipe tertentu
- warfarin, obat yang digunakan untuk mengurangi penggumpalandarah

Trezilent dapat meningkatkan atau menurunkan kadar obat-obat lain dalam darah, termasuk obat dan suplemen yang tidak memerlukan resep dokter dan/atau obat-obat herbal. Pastikan Anda menginformasikan kepada dokter Anda riwayat pengobatan Anda sebelumnya dan yang sedang berlangsung, termasuk pengobatan herbal yang Anda lakukan sebelum dan selama mengonsumsi Trezilent.

Anda juga perlu memberitahukan dokter Anda jika Anda sedang mengonsumsi Trezilent dan jika Anda diresepkan obat baru yang belum pernah Anda konsumsi sebelumnya selama pengobatan dengan Trezilent.

Tanyakan kepada dokter atau apoteker jika Anda tidak yakin apakah obat-obat yang Anda konsumsi termasuk obat-obat yang tertera di atas.

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### Mengonsumsi Trezilent bersamaan dengan makanan dan minuman (interaksi dengan makanan dan minuman)

Anda harus mengonsumsi Trezilent pada waktu yang sama setiap hari, segera setelah makan.

### Pasien wanita usia subur

Trezilent dapat membahayakan janin. Trezilent tidak boleh digunakan selama kehamilan, kecuali benar-benar diperlukan. Jika Anda wanita usia subur, dokter akan memeriksa apakah Anda sedang hamil dan jika diperlukan, tes kehamilan akan dilakukan sebelum memulai pengobatan dengan Trezilent.

Jika Anda berpotensi hamil, Anda harus menggunakan metode kontrasepsi yang efektif selama pengobatan dengan Trezilent sampai dengan setidaknya 1 minggu setelah pengobatan dengan Trezilent dihentikan. Tanyakan kepada dokter Anda terkait pilihan metode kontrasepsi yang efektif.

Trezilent dapat mengurangi kesuburan pada pasien.

### Kehamilan dan menyusui

Trezilent tidak boleh digunakan selama menyusui. Jika Anda sedang hamil atau menyusui, tanyakan kepada dokter Anda sebelum memulai pengobatan.

Dokter Anda akan mendiskusikan dengan Anda terkait risiko yang bisa timbul jika Anda mengonsumsi Trezilent selama kehamilan atau masa menyusui.

## 3 Cara mengonsumsi Trezilent

Anda harus mengonsumsi Trezilent sesuai petunjuk dokter atau apoteker. Dokter atau apoteker akan memberitahukan berapa tablet yang harus Anda konsumsi dan pada hari apa saja Anda harus mengonsumsi obat tersebut. Tanyakan kembali kepada dokter atau apoteker jika Anda tidak yakin. Anda tidak boleh mengubah dosis atau jadwal pengobatan tanpa berkonsultasi terlebih dahulu dengan dokter Anda.

Jangan melebihi dosis yang direkomendasikan oleh dokter Anda.

### Berapa dosis Trezilent yang harus Anda konsumsi

- Dosis awal Trezilent adalah 300 mg (2 tablet 150 mg) sekali sehari. Dokter Anda akan memberitahukan berapa banyak tepatnya jumlah tablet Trezilent yang harus Anda konsumsi. Dokter Anda dapat menurunkan dosisnya menjadi 250 mg atau 200 mg per hari.
- Anda harus mengonsumsi Trezilent pada waktu yang sama setiap hari, segera setelah makan.
- Jika Anda muntah setelah menelan tablet Trezilent, jangan mengonsumsi tablet Trezilent baru untuk menggantikan, Anda harus menunggu sampai jadwal minum obat selanjutnya.
- Dokter Anda juga akan menginformasikan berapa dosis fulvestrant yang harus Anda konsumsi dan kapan Anda harus mengonsumsinya.

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Tergantung dari respons tubuh Anda terhadap pengobatan dengan Trezilent, dokter Anda dapat menyesuaikan dosis pengobatan Anda. Anda harus mengikuti rekomendasi dari dokter Anda. Jika Anda mengalami efek samping, dokter boleh jadi akan menganjurkan dosis yang lebih rendah, melewatkan dosis, atau menghentikan pengobatan.

## Kapan Anda mengonsumsi Trezilent

Trezilent sebaiknya dikonsumsi pada waktu yang sama setiap harinya untuk memudahkan Anda mengingat kapan Anda harus meminum obat.

## Bagaimana cara mengonsumsi Trezilent

Trezilent harus ditelan utuh (tablet tidak boleh dikunyah, digerus, atau dipotek sebelum ditelan). Anda tidak boleh mengonsumsi tablet jika rusak, retak,atau tidak utuh.

## Berapa lama Anda harus mengonsumsi Trezilent

Anda harus mengonsumsi Trezilent selama masih dianjurkan oleh dokter Anda.

Pengobatan dengan Trezilent merupakan pengobatan jangka panjang, yang dapat berlangsung selama berbulan-bulan atau bertahun-tahun. Dokter Anda akan memonitor kondisi Anda secara rutin untuk melihat apakah pengobatan tersebut memberikan efek yang diharapkan.

Jika Anda memiliki pertanyaan terkait durasi pengobatan dengan Trezilent, tanyakan kepada dokter atau apoteker.

## Apabila Anda mengonsumsi Trezilent lebih dari yang seharusnya

Apabila Anda secara tidak sengaja mengonsumsi terlalu banyak tablet Trezilent, atau ada orang lain yang tidak sengaja mengonsumsi obat Anda, segera hubungi dokter atau rumah sakit terdekat. Tunjukan kemasan Trezilent. Tindakan medis bisa jadi diperlukan.

## Jika Anda lupa mengonsumsi Trezilent

Jika Anda lupa mengonsumsi Trezilent, Anda masih dapat meminum obat tersebut, segera setelah makan,tetapi tidak lebih dari 9 jam dari jadwal minum obat Anda seharusnya. Jika Anda baru ingat setelah lewat 9 jam dari jadwal minum obat seharusnya, lewatkan dosis untuk hari itu. Hari berikutnya, minumlah obat sesuai dengan dosis Anda untuk hari itu. Jangan mengonsumsi dosis ganda untuk menggantikan dosis yang telah Anda lewatkan.

## Apabila Anda berhenti mengonsumsi Trezilent

Menghentikan pengobatan dengan Trezilent dapat menyebabkan perburukan kondisi Anda. Jangan menghentikan pengobatan kecuali atas anjuran dokter Anda.

Jika Anda memiliki pertanyaan lebih lanjut terkait penggunaan Trezilent, tanyakan kepada dokter atau apoteker.

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## 4 Efek samping yang mungkin terjadi

Seperti halnya semua obat, pasien yang diobati dengan Trezilent mungkin mengalami efek samping, meskipun tidak terjadi pada semua pasien.

### Beberapa efek samping dapat tergolong serius

Jika Anda mengalami efek samping serius, **hentikan pengobatan dan segera beri tahukan dokter Anda.**

**Sangat umum:** *dapat memengaruhi lebih dari 1 per 10 orang*

- Jika Anda mengalami rasa haus berlebih, buang air kecil lebih sering atau jumlah urin yang lebih banyak, dan/atau mengalami peningkatan nafsu makan dengan penurunan berat badan (boleh jadi gejala peningkatan kadar gula darah atau hiperglikemia, peningkatan *glycosilated haemoglobin*).

**Umum:** *dapat memengaruhi hingga pada 1 per 10 orang*

- Ruam, gatal, biduran, kulit kemerahan, kebiruan pada bibir, lidah, atau kulit, mengi atau batuk, perasaan seperti melayang, pusing, perubahan tingkat kesadaran, tekanan darah rendah, kulit kemerahan, bengkak pada muka atau tenggorokan (boleh jadi gejala hipersensitivitas).
- Gangguan pernapasan, meliputi sesak napas, batuk, napas tersengal-sengal, nyeri dada saat bernapas, kebiruan pada bibir, lidah, atau kulit, atau cegukan (boleh jadi gejala pneumonitis).
- Demam ;batuk; hidung meler; pembesaran kelenjar getah bening; nyeri sendi; ruam; berkeringat malam hari; penurunan berat badan (boleh jadi gejala menurunnya kadar limfosit, salah satu jenis sel darah putih).
- Buang air kecil lebih jarang dan jumlah urin yang lebih sedikit dari biasanya, bengkak di kaki, pergelangan kaki, dan di sekitar mata, kelelahan, bingung, mual, kejang, nyeri dada (boleh jadi gejala gangguan ginjal akut).
- Nyeri, pembengkakan, atau mati rasa pada rahang, rahang terasa berat, atau gigi terasa goyang (boleh jadi gejala osteonekrosis pada rahang).
- Ruam, kulit kemerahan, lepuh pada bibir, mata, atau mulut, kulit mengelupas (kemungkinan gejala *erythema multiforme*).

**Tidak umum:** *dapat memengaruhi hingga pada 1 per 100 orang*

- Sesak napas, sakit kepala, mual, muntah (boleh jadi gejala peningkatan kadar asam dalam darah, ketoasidosis).
- Nyeri hebat pada daerah perut di atas lambung (boleh jadi gejala pankreatitis).
- Ruam, kulit kemerahan, lepuh pada bibir, mata, atau mulut, kulit mengelupas, demam (boleh jadi gejala *Stevens-Johnson syndrome* [SJS]).

**Frekuensi tidak diketahui:** *frekuensi tidak dapat diestimasi dari data yang tersedia*

- Kebingungan, mulut kering, kulit kering atau kemerahan, mual, muntah, kelelahan, sering ‘kebelet’ buang air kecil, haus (boleh jadi gejala *hyperglycaemic hyperosmolar nonketotic syndrome [HHNKS]*).

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- Ruam, demam (boleh jadi gejala *drug reaction with eosinophilia and systemic symptoms [DRESS]*).

## Efek samping lain yang dapat terjadi

Efek samping lain yang dapat terjadi termasuk daftar di bawah ini. Jika salah satu dari efek samping ini terjadi pada Anda dan menjadi parah, segera beritahukan kepada dokter, apoteker atau tenaga kesehatan.

**Sangat umum:** *dapat memengaruhi lebih dari 1 per 10 orang*

- Buang air kecil sering dan terasa nyeri (boleh jadi gejala infeksi saluran kemih)
- Lemah, lesu, kulit pucat (boleh jadi gejala rendahnya kadar sel darah merah[anemia])
- Kehilangan nafsu makan
- Sakit kepala
- Sensasi kecap tidak normal (*dysgeusia*)
- Diare
- Mual
- Muntah
- Luka atau sariawan pada mulut disertai pembengkakan pada gusi (stomatitis)
- Nyeri perut
- Rasa tidak nyaman di lambung, gangguan pencernaan (dispepsia)
- Ruam
- Kebotakan atau kerontokan rambut (*alopecia*)
- Gatal (*pruritus*)
- Kulit kering
- Kelelahan (*fatigue*)
- Nyeri, kemerahan atau pembengkakan pada selaput lendir (mukosa) saluran napas, saluran cerna, atau saluran reproduksi (peradangan mukosa)
- Pembengkakan pada tangan, pergelangan kaki, atau kaki (edema perifer)
- Demam (*pyrexia*)
- Selaput lendir menjadi kering
- Penurunan berat badan
- Gangguan fungsi ginjal (ditandai dengan peningkatan kadar kreatinin dalam darah)

**Umum:** *dapat memengaruhi hingga pada 1 per 10 orang*

- Gusi berdarah, bengkak, atau terasa nyeri saat ditekan (tanda-tanda peradangan gusi)
- Perdarahan spontan atau memar (tanda kadar trombosit yang rendah)
- Penglihatan kabur
- Pembengkakan pada seluruh tubuh *(generalised edema)*
- Mata kering

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- Penurunan kadar kalsium dalam darah, yang kadang-kadang dapat menyebabkan kram (hipokalsemia)
- Penurunan kadar kalium dalam darah disertai tanda-tanda lainnya, seperti kelemahan otot, kejang otot, irama jantung abnormal (hipokalemia)
- Kemerahan dan/atau pembengkakan dan, bisa juga,pengelupasan kulit pada telapak tangan dan telapak kaki yang dapat disertai kesemutan dan rasa sakit seperti terbakar (tanda-tanda *hand-foot syndrome*)
- Dehidrasi
- Sakit kepala, pusing (boleh jadi gejala tekanan darah tinggi)
- Pembengkakan pada sebagian atau seluruh lengan (termasuk jari tangan) atau kaki (termasuk jari kaki), badan terasa berat, pergerakan terbatas, rasa tidak nyaman, penebalan kulit, dan infeksi berulang (boleh jadi gejala limfedema)
- Kejang otot
- Nyeri otot (mialgia)
- Sakit gigi
- Bibir pecah-pecah (*cheilitis*)
- Nyeri gusi
- Eritema
- Peradangan kulit dengan ruam (dermatitis)
- Susah tidur (insomnia)

Selama pengobatan dengan Trezilent, Anda dapat pula mengalami efek samping yang terdeteksi melalui hasil tes darah abnormal, yang memberikan dokter Anda informasi terkait fungsi bagian tubuh tertentu

**Sangat umum:**

- Peningkatan kadar enzim berikut: *gamma glutamyl transferase, alanine aminotransferase, lipase*
- Peningkatan kadar kreatinin dan gula darah
- Penurunan kadar limfosit dan trombosit
- Penurunan kadar gula, kalsium, kalium, magnesium, hemoglobin, albumin dalam darah
- Pemanjangan aPTT (*activated partial thromboplastin time*)

## 5 Cara penyimpanan Trezilent

- Jauhkan obat dari jangkauan anak-anak.
- Jangan mengonsumsi obat setelah tanggal kedaluarsa yang tercantum pada kemasan obat.
- Simpan dengan menggunakan kemasan aslinya.
- Simpan pada suhu dibawah 30°C.

Jangan mengonsumsi obat ini jika Anda melihat kerusakan atau tanda perusakan pada kemasan.

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Tanyakan kepada apoteker terkait cara pembuangan obat-obatan yang sudah tidak Anda gunakan lagi.

# 6 Informasi lebih lanjut

## Apakah kandungan Trezilent

**Zat aktif** dari Trezilent adalah alpelisib.

**Kandungan lain** dari Trezilent adalah:

Tablet inti: *Microcrystalline cellulose, mannitol, sodium starch glycolate, hypromellose,* dan *magnesium stearate.*

Bahan penyalut: *Hypromellose, titanium dioxide, macrogol / polyethylene glycol (PEG), talc, iron oxide red,* dan *iron oxide black.*

## Bagaimana bentuk dan isi Trezilent

Trezilent dipasarkan dalam bentuk tablet salut selaput dalam blister aluminium.
Tablet salut selaput: 50 mg, 150 mg dan 200 mg alpelisib.

- 50 mg: Merah muda cerah, tidak berbelah, bulat dan melengkung dengan tepi lebih tipis, dan memiliki cetakan “L7” dan “NVR” pada masing-masing sisi. Setiap tablet salut selaput mengandung 50 mg alpelisib.
- 150 mg: Merah pucat, tidak berbelah, oval dan melengkung dengan tepi lebih tipis dan memiliki cetakan “UL7” dan “NVR” pada masing-masing sisi. Setiap tablet salut selaput mengandung 150 mg alpelisib.
- 200 mg: Merah terang, tidak berbelah, oval dan melengkung dengan tepi lebih tipis dan memiliki cetakan “YL7” dan “NVR” pada masing-masing sisi. Setiap tablet salut selaput mengandung 200 mg alpelisib.

## Kemasan

Dus (dosis harian 300 mg), 2 amplop @ 2 blister @ 7 tablet salut selaput 150 mg, No. Reg. xxxxxxxxxxxxxx
Dus (dosis harian 250 mg), 2 amplop @ 1 blister @ 7 tablet salut selaput 200 mg dan 1 blister @ 7 tablet salut selaput 50 mg, No. Reg. xxxxxxxxxxxxxx
Dus (dosis harian 200 mg), 1 amplop @ 2 blister @ 7 tablet salut selaput 200 mg, No. Reg. xxxxxxxxxxxxxx

**HARUS DENGAN RESEP DOKTER**

## Produsen obat

Diproduksi oleh Novartis Pharma Stein AG, Stein, Swiss

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Dikemas oleh Lek Pharmaceutical d.d., Ljubljana, Slovenia
Untuk Novartis Pharma AG, Basel, Swiss
Diimpor oleh PT Novartis Indonesia, Jakarta, Indonesia

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