▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION - PIQRAY® (alpelisib) tablets

1. NAME OF THE MEDICINE

Alpelisib

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance

All PIQRAY tablets contain alpelisib.

PIQRAY 50 mg tablet
Each tablet contains 50 mg of alpelisib.

PIQRAY 150 mg tablet
Each tablet contains 150 mg of alpelisib.

PIQRAY 200 mg tablet
Each tablet contains 200 mg of alpelisib.

Excipients

For the list of excipients, see section 6.1 List of Excipients.

3. PHARMACEUTICAL FORM

Film coated tablets

PIQRAY 50 mg tablet

Light pink, unscored, round and curved with bevelled edges, imprinted with “L7” on one side and “NVR” on the other side.

PIQRAY 150 mg tablet

Pale red, unscored, ovaloid and curved with bevelled edges, imprinted with “UL7” on one side and “NVR” on the other side.

PIQRAY 200 mg tablet

Light red, unscored, ovaloid and curved with bevelled edges, imprinted with “YL7” on one side and “NVR” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PIQRAY in combination with fulvestrant, is indicated for the treatment of postmenopausal women, and men, with hormone receptor positive, HER2-negative, advanced or metastatic breast cancer with a PIK3CA mutation as detected by a validated test following progression on or after an endocrine-based regimen.

4.2 Dose and method of administration

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

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

The safety and efficacy of alpelisib in combination with a GnRH agonist in pre- or peri-menopausal women has not been established.

There was no treatment benefit demonstrated in patients without PIK3CA mutations, in the phase III clinical study (see section 5.1 Pharmacodynamic properties).

Adult Dose

Recommended Dosage

The recommended dose of PIQRAY is 300 mg (two 150 mg film-coated tablets) taken orally, once daily. PIQRAY should be taken immediately following food, at approximately the same time each day (see section 5.1 Pharmacodynamic properties and section 4.5 Interactions). The maximum recommended daily dose of PIQRAY is 300 mg. If patient vomits after taking the PIQRAY 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 PIQRAY, 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 product 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.

Missed dose

If a dose of PIQRAY 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 missed dose should be skipped for that day. On the next day, PIQRAY should be taken at its usual time.

Dose modifications

The recommended daily dose of PIQRAY is 300 mg. Management of severe or intolerable adverse drug reactions may require temporary dosing interruption, reduction, and/or discontinuation of PIQRAY. If dosing reduction is required, the dosing reduction guidelines for adverse drug reactions (ADRs) are listed in Table 1. A maximum of 2 dosing reductions are recommended, after which the patient should be discontinued from treatment with PIQRAY. Dosing reduction should be based on worst preceding toxicity.

Table 1 Recommended Dosing reduction guidelines for adverse drug reactions for PIQRAY[1]

PIQRAY 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 2, 3, 4 and 5 summarize recommendations for dosing interruption, reduction or discontinuation of PIQRAY 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 PIQRAY.

Hyperglycaemia

Consultation with a Healthcare Professional (HCP) with experience in the management of hyperglycemia should be considered and lifestyle changes as per local guidelines, 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 PIQRAY. Glucose levels should be corrected in patients with abnormal glucose levels which are in the range of pre-diabetic or diabetic before initiating PIQRAY, and should be closely monitored to enable early detection and early treatment of hyperglycemia.

After initiating treatment with PIQRAY, 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 PIQRAY, FG should be monitored as clinically indicated, and at least twice weekly until FG decreases to ≤8.9 mmol/L. 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. Dosing modifications and management guidelines for hyperglycaemia are described in Table 2.

Rash

Oral antihistamine administration may be considered prophylactically, at the time of initiation of treatment with PIQRAY. Based on the severity of rash, PIQRAY may require dose interruption, reduction, or discontinuation as described in Table 3 (see section 4.8 Adverse effects).

Diarrhoea

Please refer to Table 4 for dosing modifications and management guidelines.

Other toxicities

Please refer to Table 5 for the dosing modification and management for other toxicities (excluding hyperglycaemia and rash).

Fulvestrant

For dose modification guidelines in the event of toxicity or for any other relevant safety information, refer to the fulvestrant product information.

Table 2 Dosing Modification and Management for Hyperglycaemia[1]

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

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

[2] Applicable anti-diabetic medications, like metformin, SGLT2 inhibitors or insulin sensitisers (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 1000 mg with dinner, followed by further increase to 1000 mg bid if needed (see section 4.4 Special warnings and precautions for use).

[3]As recommended in the phase III clinical study, insulin may be used for 1-2 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 normalising after interruption of PIQRAY

Table 3 Dosing Modification and Management for Rash[1]

Grade	Recommendation
All Grades	Consultation with dermatologist should always be considered
Grade 1 (<10% body surface area (BSA) with active skin toxicity)	No PIQRAY dose adjustment required. Initiate topical corticosteroid treatment. Consider adding oral antihistamine treatment to manage symptoms. If active rash is not improved within 28 days of appropriate treatment, add a low dose systemic corticosteroid.
Grade 2 (10-30% BSA with active skin toxicity)	No PIQRAY dose adjustment required. Initiate or intensify topical corticosteroid and oral antihistamine treatment. Consider low dose systemic corticosteroid treatment. If rash improves to Grade ≤1 within 10 days, systemic corticosteroid may be discontinued.
Grade 3 (e.g.: severe rash not responsive to medical management). (>30% BSA with active skin toxicity)	Interrupt PIQRAY until rash improves to Grade ≤ 1. Initiate or intensify topical/systemic corticosteroid and anti-histamine treatment. Once rash improves to Grade ≤ 1, resume PIQRAY at next lower dose level
Grade 4 (e.g.: severe bullous, blistering or exfoliating skin conditions). (any % BSA associated with extensive superinfection, with IV antibiotics indicated; life-threatening consequences)	Permanently discontinue PIQRAY.

[1]*Grading according to CTCAE Version 5.0*

Table 4 Dosing Modification and Management for Diarrhoea

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

Grade	Recommendation

[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.

Table 5 Dosing Modification and Management for other toxicities (excluding hyperglycaemia, rash and diarrhoea)[1]

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

[1] *Grading according to CTCAE Version 5.0*

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

[3]For Grade 2 total bilirubin elevation, interrupt Piqray dose until 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.

Special populations

Renal impairment

Based on population pharmacokinetic analysis, no dose adjustment is necessary in patients with mild or moderate renal impairment (see section 5.1). Caution should be used in patients with severe renal impairment as there is no experience with PIQRAY in this population (see section 5.1).

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 5.1).

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

Paediatric use

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

Use in the elderly

No dosage regimen adjustment is required in patients 65 years or above (see section 5.1).

Administration

PIQRAY 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.

4.3 Contraindications

PIQRAY is contraindicated in patients with hypersensitivity to the active substance or any of the excipients (see Section 6.1 List of excipients).

4.4 Special warnings and precautions for use

Hypersensitivity (including anaphylactic reaction)

Serious hypersensitivity reactions (including anaphylactic reaction and anaphylactic shock), manifested by symptoms including, but not limited to, dyspnoea, flushing, rash, fever or tachycardia were reported in patients treated with PIQRAY in clinical studies (see section 4.8 Adverse drug reactions). PIQRAY should be permanently discontinued and should not be re-introduced in patients with serious hypersensitivity reactions. Appropriate treatment should be promptly initiated.

Severe cutaneous reactions

Severe cutaneous reactions have been reported with PIQRAY. In the Phase III clinical study, Stevens-Johnson syndrome (SJS) and erythema multiforme (EM) were reported in 1 (0.4%) and 3 (1.1%) patients, respectively. Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported in the post marketing setting (see section 4.8 Adverse effects). PIQRAY 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, PIQRAY should be interrupted until the etiology of the reaction has been determined. A consultation with dermatologist is recommended. If a severe cutaneous reaction is confirmed, PIQRAY should be permanently discontinued. PIQRAY should not be reintroduced in patients who have experienced previous severe cutaneous reactions. If a severe cutaneous reaction is not confirmed, PIQRAY may require treatment interruption, dose reduction, or treatment discontinuation as described in Table 3 Dose modification and management for rash (see section 4.2 Dosage and method of administration).

Hyperglycaemia

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

Hyperglycaemia was reported in 64.8% of patients treated with PIQRAY in the phase III clinical study. Grade 2 (FPG 160 – 250 mg/dL), 3 (FPG >250 – 500 mg/dL) or 4 (FPG > 500 mg/dL) hyperglycaemia were reported in 15.8%, 33.1% and 3.9% of patients, respectively, in phase III clinical study. Patients should be advised of the signs and symptoms of hyperglycaemia (e.g. excessive thirst, urinating more often than usual or higher amount of urine than usual, and 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 > 100-126 mg/dL (5.6 to 6.9 mmol/L) and/or HbA1c 5.7-6.4%) and 4.2% of patients were considered diabetic (FPG ≥ 126 mg/dL (≥7.0 mmol/L) and/or HbA1c ≥ 6.5 %). 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 hyperglycaemia (any Grade) when treated with PIQRAY. Among the patients who had Grade ≥ 2 (FPG 160 – 250 mg/dL) hyperglycaemia , the median time to first occurrence of Grade ≥ 2 (FPG > 160 – 250 mg/dL) hyperglycaemia was 15 days (range: 5 days to 517 days) (based on laboratory findings). The median duration of Grade 2 (FPG > 160 – 250 mg/dL) or higher hyperglycaemia (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 2000 mg per day.

In patients with hyperglycaemia of at least Grade 2 (FPG 160 – 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 PIQRAY, 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 PIQRAY; therefore these patients require monitoring and possibly intensified anti-diabetic treatment. Patients with poor glycaemic control may be at a higher risk of developing severe hyperglycaemia and associated complications.

The safety of PIQRAY in patients with Type 1 and uncontrolled Type 2 diabetes has not been established as these patients were excluded from the Phase III clinical study. Based on the severity of the hyperglycaemia, PIQRAY may require dose interruption, reduction, or discontinuation as described in Table 2 Dose Modification and Management for hyperglycaemia (see section 4.2 Dosage regimen and administration).

Pneumonitis

Pneumonitis including serious cases of pneumonitis/acute interstitial lung disease have been reported in PIQRAY treated patients in clinical studies. Patients should be advised to promptly report any new or worsening respiratory symptoms. In patients who have new or worsening respiratory symptoms or are suspected to have developed pneumonitis, PIQRAY treatment should be interrupted immediately and the patient should be evaluated for pneumonitis. A diagnosis of non-infectious pneumonitis should be considered in patients presenting with non-specific respiratory signs and symptoms such as hypoxia, cough, dyspnoea, or interstitial infiltrates on radiologic exams and in whom infectious, neoplastic, and other causes have been excluded by means of appropriate investigations. PIQRAY should be permanently discontinued in all patients with confirmed pneumonitis.

Diarrhoea

Severe diarrhoea, including dehydration and acute kidney injury, occurred in patients treated with PIQRAY. Most patients (58%) experienced diarrhoea during treatment with PIQRAY. 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 PIQRAY were required in 6% of patients and 2.8% of patients permanently discontinued PIQRAY due to diarrhoea. In the 164 patients that experienced diarrhoea, anti-diarrhoeal medications (e.g., loperamide) were required to manage symptoms in 63% (104/164) of these patients.

Based on the severity of the diarrhoea, PIQRAY may require dose interruption, reduction, or discontinuation as described in Table 4 (see section 4.2 Dose and method of administration). Advise patients to start antidiarrhoeal treatment, increase oral fluids, and notify their healthcare provider if diarrhoea occurs while taking PIQRAY.

Use in hepatic impairment

See Section 4.2 (Dose and method of administration – special populations) and Section 5.2 (Pharmacokinetic properties)

Use in renal impairment

See Section 4.2 (Dose and method of administration – special populations) and Section 5.2 (Pharmacokinetic properties)

Use in the elderly

See Section 4.2 (Dose and method of administration – special populations) and Section 5.2 (Pharmacokinetic properties)

Paediatric use

See Section 4.2 (Dose and method of administration – special populations) and Section 5.2 (Pharmacokinetic properties)

Effects on laboratory tests

Refer to Table 7.

4.5 Interactions with other medicines and other forms of 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 PIQRAY 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 *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 PIQRAY with a BCRP inhibitor (e.g. eltrombopag, lapatinib, pantoprazole), as inhibition of BCRP in the liver and in the intestine after absorption may lead to an increase in systemic exposure of PIQRAY.

Medicinal products whose plasma concentrations may be altered by alpelisib

CYP3A4 substrates

In vitro, alpelisib is a time-dependent inhibitor and an inducer of CYP3A4. No dose adjustment is required when co-administering PIQRAY with CYP3A4 substrates (e.g. everolimus, midazolam).

Caution is recommended when PIQRAY 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 PIQRAY is co-administered, based on PBPK simulations.

CYP2C9 substrates with narrow therapeutic index

In vitro, alpelisib is an inducer of CYP2C9. 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 and Cmax 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 PIQRAY 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

Alpelisib is an inducer of CYP2B6 *in vitro.* 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 (e.g. bupropion) or CYP2B6 substrates with a narrow therapeutic window should be used with caution in combination with PIQRAY, as PIQRAY 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 4.2 Dosage and administration and section 5.1). Therefore, PIQRAY should be taken immediately after food, at approximately same time each day (see section 4.2 Dosage and administration).

Hormonal contraceptives

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

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 weak *in vitro* inhibition towards the efflux transporters P-gp, BCRP, and BSEP, solute carrier transporters at the liver inlet (OATP1B1, OATP1B3, and OCT1) and solute carrier transporters in the kidney (OCT2, MATE1, and MATE2K). As unbound systemic steady state concentrations at the therapeutic dose are significantly lower than the experimentally determined unbound inhibition constants or IC_{50}, the inhibition will not translate into clinical significance. However, given the relatively high intestinal and hepatic inlet concentrations of alpelisib, clinically relevant inhibition of oral absorption of P-gp substrates and hepatic uptake of OCT1, OATP1B1 and OAT1B3 substrates may occur. Both alpelisib and the major metabolite, BZG791 inhibited the renal uptake transporter OAT3 (Ki 29.4 and 1.38 μM, respectively) *in vitro*, and thus alpelisib might increase plasma concentrations of drugs that are predominantly excreted by this transporter. As an *in vitro* inhibitor of OATP1B1 (IC50 20.9 μM) alpelisib might also increase plasma concentrations of drugs that are OATP1B1 substrates and predominantly cleared by hepatic metabolism.

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.

4.6 Fertility, pregnancy, and lactation

Fertility

There is no data on the effect of alpelisib on fertility. Based on repeat dose toxicity studies in animals, PIQRAY may impair fertility in males and females of reproductive potential.

Dedicated fertility studies were not conducted with alpelisib. In repeated-dose toxicity studies up to 13-weeks duration, adverse effects were observed in reproductive organs including vaginal epithelial atrophy, vaginal atrophy and oestrous cycle variations in rats at doses ≥ 2 mg/kg/day (0.1 times the exposure in humans at the recommended dose of 300 mg/day based on AUC), and decreased secretion in prostate and seminal vesicle in rats at ≥ 10 mg/kg/day (0.8 times the exposure in humans) and prostate glandular atrophy in dogs at 15 mg/kg/day (2.3 times the exposure in humans) and tubular degeneration/atrophy in the pilot study in dogs at ≥ 10 mg/kg/day (~1 times the exposure in humans).

Use in Pregnancy (Category D)

Based on animal data and its mechanism of action, PIQRAY 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-lethality, feto-toxicity, and teratogenicity. Increased incidences of post-implantation loss, reduced fetal weights, and increased incidences of fetal abnormalities were observed at 10 mg/kg/day in rats and 15 mg/kg/day in rabbits with systemic exposures 0.8 (rat) and 5 times (rabbit) the exposure in humans at the highest recommended dose of 300 mg/day based on AUC.

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

Contraception

A negative pregnancy status for females of reproductive potential should be verified prior to starting treatment with PIQRAY.

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 PIQRAY during treatment and for at least 4 days after stopping treatment with alpelisib. It is currently unknown whether alpelisib may reduce the effectiveness of systemically acting hormonal contraceptives.

Male patients with sexual partners who are pregnant, possibly pregnant, or who could become pregnant should use condoms during sexual intercourse while taking PIQRAY and for at least 4 days after stopping treatment with PIQRAY.

Use in Lactation

It is not known if alpelisib is transferred into human or animal milk after administration of PIQRAY. 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 PIQRAY, it is recommended that women should not breastfeed during treatment and for at least 4 days after the last dose of PIQRAY.

4.7 Effects on ability to drive and use machines

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

4.8 Adverse effects (undesirable effects)

Summary of the safety profile

The overall safety evaluation of PIQRAY 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 PIQRAY plus fulvestrant or placebo plus fulvestrant; 284 of whom received PIQRAY at the recommended starting dose of 300 mg dose in combination with fulvestrant, using the proposed treatment regimen.

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

PIQRAY dose reductions due to adverse events (AEs), regardless of causality occurred in 57.7 % of patients receiving PIQRAY plus fulvestrant and in 4.5 % of patients receiving placebo plus fulvestrant. Permanent discontinuations of PIQRAY and/or fulvestrant due to adverse events were reported in 25 % of patients compared to and 4.5 % with placebo and/or fulvestrant. The most common AEs leading to treatment discontinuation of both PIQRAY 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 PIQRAY plus fulvestrant vs. 12 patients (4.2 %) treated with placebo plus fulvestrant. In PIQRAY 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 PIQRAY.

The most common adverse drug reactions (ADRs) in PIQRAY plus fulvestrant treated patients (reported at a frequency > 20 % and for which the frequency for PIQRAY 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 PIQRAY plus fulvestrant arm and for which the frequency for PIQRAY plus fulvestrant exceeds the frequency for placebo plus fulvestrant) were hyperglycaemia, rash and rash maculo-papular, fatigue, diarrhoea, lipase increased, hypertension, hypokalaemia, anaemia, weight decreased, gamma-glutamyltransferase increased, lymphopenia, nausea, stomatitis, alanine aminotransferase increased and mucosal inflammation.

Tabulated summary of adverse drug reactions from clinical studies

ADRs from the phase III clinical study (Table 6) 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 6 Adverse drug reactions observed in the phase III clinical study

Adverse drug reactions	PIQRAY + Fulvestrant N= 284 n (%) All Grades	Placebo + Fulvestrant N= 287 n (%) All Grades	PIQRAY + Fulvestrant N= 284 n (%) Grades 3/4	Placebo + Fulvestrant N=287 n (%) Grades 3/4	Frequency category for PIQRAY + 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
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

Adverse drug reactions	PIQRAY + Fulvestrant N= 284 n (%) All Grades	Placebo + Fulvestrant N= 287 n (%) All Grades	PIQRAY + Fulvestrant N= 284 n (%) Grades 3/4	Placebo + Fulvestrant N=287 n (%) Grades 3/4	Frequency category for PIQRAY + Fulvestrant All Grades
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
Hypokalemia	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
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					

Adverse drug reactions	PIQRAY + Fulvestrant N= 284 n (%) All Grades	Placebo + Fulvestrant N= 287 n (%) All Grades	PIQRAY + Fulvestrant N= 284 n (%) Grades 3/4	Placebo + Fulvestrant N=287 n (%) Grades 3/4	Frequency category for PIQRAY + Fulvestrant All Grades
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 4.4, Special warnings and precautions for use)*

[8] *Dysgeusia : also includes ageusia, hypogeusia*

[9] *Pneumonitis: also includes interstitial lung disease*

[10] *Rash: also includes rash maculo-papular, rash macular, rash generalized, 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 Laboratory abnormalities observed in the phase III study

Laboratory abnormalities	PIQRAY + Fulvestrant N= 284 n (%) All Grades	Placebo + Fulvestrant N= 287 n (%) All Grades	PIQRAY + Fulvestrant N= 284 n (%) Grades 3/4	Placebo + Fulvestrant N=287 n (%) Grades 3/4	Frequency category for PIQRAY + Fulvestrant All Grades
Hematological parameters					
Lymphocyte count decreased	147 (51.8)	116 (40.4)	23 (8.1)	13 (4.5)	Very common
Hemoglobin 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 PIQRAY 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 8 Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

Metabolism and nutrition disorders
Hyperglycaemic hyperosmolar nonketotic syndrome (HHNKS)
Skin and subcutaneous tissue disorders
Drug reaction with eosinophilia and systemic symptoms (DRESS)

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 PIQRAY plus fulvestrant arm. Hyperglycaemic events leading to discontinuation of PIQRAY 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 generalized, 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 (Graded 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 PIQRAY plus fulvestrant arm.

Topical corticosteroid treatment should be initiated at the first signs of rash and systemic 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 PIQRAY 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 PIQRAY (3.5 % vs 4.2 %). Accordingly, antihistamines may be initiated prophylactically, at the time of initiation of treatment with PIQRAY. Based on the severity of rash, PIQRAY may require dose interruption, reduction, or discontinuation as described in Table 3 Dose Modification and Management for rash (see section 4.2 Dosage and administration).

GI toxicity (nausea, diarrhoea, vomiting)
In the phase III study, diarrhoea, nausea and vomiting were reported in 57.7 %, 44.7 % and 27.1 % of the patients, respectively, and led to discontinuation of PIQRAY and/or fulvestrant in 8 (2.8 %), 5 (1.8 %) and 3 (1.1 %) of the patients, respectively (see Table 6).

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 PIQRAY and resolved with appropriate intervention (see Table 5). 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 (e.g. ondansetron) and anti-diarrhoeal medications (e.g. 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 PIQRAY 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 PIQRAY and bisphosphonates or RANK-ligand inhibitors, an increased risk of development of ONJ cannot be excluded.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

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

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

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

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antineoplastic agents, other antineoplastic agents

Anatomical Therapeutic Chemical (ATC Code): L01XX65

5.1 Pharmacodynamic properties

Mechanism of action

Alpelisib is a class I phosphatidylinositol3kinase (PI3K) inhibitor with higher activity against PI3Kα than other members of class I PI3K. 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 α-subunit of PI3K (PIK3CA) lead to activation of PI3Kα manifested by increased lipid kinase activity, growth-factor independent activation of Akt-signaling, cellular transformation and the generation of tumours in preclinical models.

In vitro, alpelisib treatment inhibited the phosphorylation of PI3K downstream targets Akt as well as its various downstream effectors in breast cancer cells and showed activity 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 tumour growth inhibition in relevant tumour 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-tumour activity than either treatment alone in xenograft models derived from ER+, PIK3CA mutated breast cancer cell lines (MCF-7 and KPL1).

Pharmacodynamic effects

In biochemical assays, alpelisib inhibited wild type PIK3α and its 2 most common somatic mutations (H1047R, E545K) (IC_{50}~5 nmol/L) more potently than the PI3Kδ (IC_{50} = 60 nmol/L) and PI3Kγ (IC_{50} = 560 nmol/L) isoforms and showed significantly reduced activity against PI3Kβ (IC_{50} = 1156 nmol/L).

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

Cardiac electrophysiology

Serial, triplicate ECGs were collected following a single dose and at steady-state to evaluate the effect of alpelisib on the QTcF interval in patients with advanced cancer. 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 ms (7.2 ms; 90% CI: 5.62, 8.83) at the observed geometric-mean Cmax at steady-state (2900 ng/mL) following single agent administration at the recommended 300 mg dose.

Clinical Trials

Placebo-controlled study C2301

PIQRAY was evaluated in this pivotal phase III, randomized, double-blind study of PIQRAY 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. There were 341 patients enrolled by tumor tissue in the cohort with a PIK3CA mutation and 231 enrolled in the cohort without a PIK3CA mutation. Of the 341 patients in the cohort with a PIK3CA mutation, 336 (99%) patients had one or more PIK3CA mutations confirmed in tumor tissue using the QIAGEN therascreen® PIK3CA RGQ PCR Kit. Out of the 336 patients with PIK3CA mutations confirmed in tumor tissue, 19 patients had no plasma specimen available for testing with the QIAGEN therascreen® PIK3CA RGQ PCR Kit. Of the remaining 317 patients with PIK3CA mutations confirmed in tumor tissue, 177 patients (56%) had PIK3CA mutations identified in plasma specimen, and 140 patients (44%) did not have PIK3CA mutations identified in plasma specimen.

Patients were randomized to receive either PIQRAY 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 PIQRAY 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 PIQRAY 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 performance status, tumour burden, and prior antineoplastic therapy were well balanced between the study arms.

During the randomized treatment phase, PIQRAY 300 mg or PIQRAY 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 PIQRAY 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 Tumours (RECIST v1.1), based on the investigator assessment in patients with PIK3CA mutation advanced breast cancer. The key secondary end point was overall survival (OS) for patients with PIK3CA mutation status.

Other secondary endpoints included PFS for patients without PIK3CA mutation, OS for patients without PIK3CA mutation, as well as overall response rate (ORR) by PIK3CA 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 %).

The median duration of follow-up in the cohort with PIK3CA mutation was 20 months.

The efficacy results in the cohort with PIK3CA mutation demonstrated a statistically significant improvement in PFS in patients receiving PIQRAY plus fulvestrant, compared to patients receiving placebo plus fulvestrant (hazard ratio [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. Efficacy results from the study are summarized in Table 9 and Figure 1.

Primary PFS results for cohort with PIK3CA mutation were supported by consistent results from a blinded independent review committee (BIRC) assessment in this cohort.

At the time of final PFS analysis, 27% (92/341) of patients had died, and overall survival follow-up was immature. The pre-specified O'Brien-Fleming stopping boundary was not crossed at the first interim OS analysis.

Treatment with the combination of PIQRAY plus fulvestrant was associated with improvements in ORR relative to placebo + fulvestrant. The ORR was 26.6 % (95% CI: 20.1, 34.0) in the PIQRAY plus fulvestrant arm and 12.8% (95% CI: 8.2, 18.7) in the placebo plus fulvestrant arm. See Table 10 for details.

For patients with measurable disease at baseline, the ORR was 35.7 % (95% CI: 27.4, 44.7) in the PIQRAY plus fulvestrant arm and 16.2 % (95% CI: 10.4, 23.5) in the placebo plus fulvestrant arm.

Cohort without PIK3CA mutation

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

Table 9 C2301- Summary of efficacy results based on RECIST criteria (cohort with PIK3CA mutation)

	PIQRAY + 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 7.5-14.5	5.7 3.7-7.4	0.65 0.50-0.85	0.00065

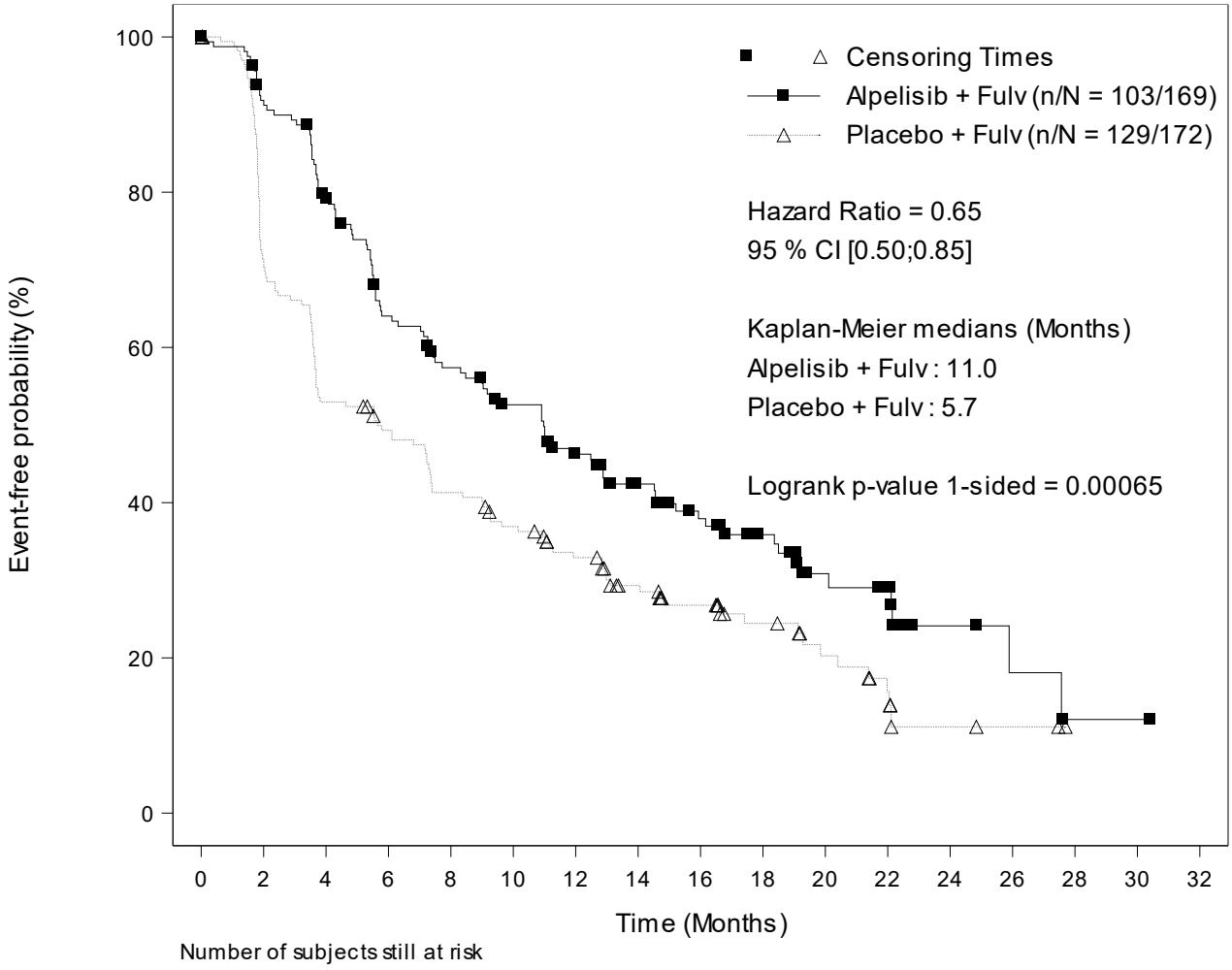
CI=confidence interval; N=number of patients;
[a]p-value is obtained from the one-sided stratified log-rank test.

Table 10 C2301 Efficacy results (ORR) based on Investigator assessment (cohort with PIK3CA mutation)

Analysis	**alpelisib plus fulvestrant (%, 95% CI)**	**Placebo plus fulvestrant (%, 95% CI)**
Full analysis set	N=169	N=172
Objective Response Rate[a]	26.6 (20.1, 34.0)	12.8 (8.2, 18.7)
Patients with measurable disease	**N=126**	**N=136**
Objective Response Rate[a]	35.7 (27.4, 44.7)	16.2 (10.4, 23.5)

[a] ORR= proportion of subjects with confirmed Complete Response or Partial Response

Figure 1 Kaplan-Meier plot of Progression Free Survival in cohort with PIK3CA mutation per local investigator assessment



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

5.2 Pharmacokinetic properties

The pharmacokinetics (PK) 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, PIQRAY should be taken immediately after food, at approximately 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 AUC_{inf} and a 51 % decrease in C_{max} with ranitidine compared to the fasted state without co-administration of ranitidine. PIQRAY can be co-administered with drugs that are acid-reducing agents, if PIQRAY is taken immediately after food. Population pharmacokinetic analysis showed no significant effect on the PK of PIQRAY 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. The volume of distribution of alpelisib at steady-state (Vss/F) is estimated at 114 L (intersubject CV % 46 %).

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, and choline esterase) not limited to the liver. CYP3A4-mediated metabolites and glucuronides amounted to ~15% of the dose and BZG791 accounted for ~40-45% of the dose. The rest of the absorbed fraction of the dose was excreted as alpelisib.

Excretion

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 300mg, 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 [14C] alpelisib, 94.5% of the total administered radioactive dose was recovered within 8 days.

Linearity/non-linearity

The pharmacokinetics were found to be linear with respect to dose and time under fed conditions between 30 and 450 mg. After multiple doses, Alpelisib exposure (AUC) at steady-state is only slightly higher than that of a single dose with an average accumulation of 1.3 to 1.5 with a daily dosing regimen.

Special Patient Populations

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 ≥90 mL/min/1.73 m^2) / (CLcr ≥90 mL/min), 108 patients with mild renal impairment (eGFR 60 to <90 mL/min/1.73m^2)/ (CLcr 60 to <90 mL/min), and 45 patients with moderate renal impairment (eGFR 30 to <60 mL/min/1.73 m^2), mild and moderate renal impairment had no effect on the exposure of alpelisib (see section 4.2 Dosage 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 4.2 Dosage and administration). The mean exposure for alpelisib was increased by 1.26-fold in patients with severe (GMR: 1.00 for C_{max}; 1.26 for AUC_{last} /AUC_{inf}) hepatic impairment.

Based on a population pharmacokinetic analysis that included 230 patients with normal hepatic function, 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 4.2 Dosage and administration).

Paediatric use

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

Use in the elderly

Of 284 patients who received PIQRAY in the phase III study (in PIQRAY 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 PIQRAY were observed between these patients and younger patients (see section 4.2 Dosage and administration).

Age, body 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 PIQRAY dose adjustment.

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 PIQRAY.

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

5.3 Preclinical Safety Data

Cardiovascular safety pharmacology

In an *in vitro* hERG test, (where functionality of the human cardiac hERG channel heterologously expressed in HEK293 cells *in vitro* is assessed), an IC50 of 9.4 µM (4.2 µg/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.

Genotoxicity

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

Carcinogenicity

Carcinogenicity studies have not been conducted with alpelisib

6. PHARMACEUTICAL PARTICULARS

6.1 List Of Excipients

PIQRAY tablets contain the following inactive ingredients: microcrystalline cellulose, mannitol, sodium starch glycollate, hypromellose, magnesium stearate (vegetable source), macrogol, iron oxide red CI77491, iron oxide black CI77499, titanium dioxide (E171), and purified talc.

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for Storage

Store in the original package in order to protect from moisture. Keep out of reach of children.

6.5 Nature and contents of the container

PIQRAY tablets are supplied in PVC/PCTFE (polyvinylchloride/polychlorotrifluoroethylene) or PA/Al/PVC (polyamide/aluminium/polyvinylchloride)/aluminium laminate blister packs.

PIQRAY 50 mg and PIQRAY 200 mg film-coated tablets

14 day* or 28 day calendar packs containing 28 film-coated tablets (fourteen 50 mg and fourteen 200 mg) or 56 film-coated tablets (twenty-eight 50 mg and twenty-eight 200 mg).

PIQRAY 150 mg film-coated tablets

14 day* or 28 day calendar packs containing 28 or 56 film-coated tablets.

PIQRAY 200 mg film-coated tablets

14 day* or 28 day calendar packs containing 14 or 28 film-coated tablets.

*Not all pack sizes are supplied.

6.6 Special precautions for disposal

Any unused product should not be disposed of in household waste or wastewater. Return it to a pharmacist for safe disposal.

6.7 Physicochemical properties

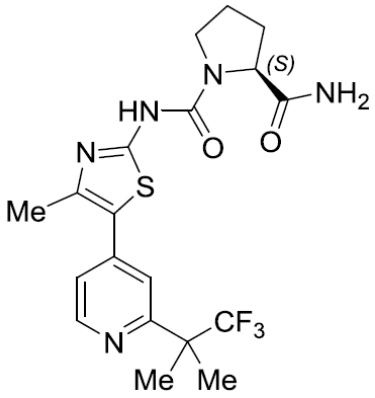
Chemical name (IUPAC): (2*S*)-N^1-{4-Methyl-5-[2-(1,1,1-triflu ro-2-methylpropan-2-yl)pyridin-4-yl]-1,3-thiazol-2-yl}pyrrolidine-1,2-dicarboxamide

Molecular formula: $C_{19}H_{22}F_3N_5O_2S$

Relative molecular mass: 441.47

Alpelisib is a white to almost white powder at room temperature. It is sparingly soluble in methanol, acetone, and absolute ethanol; it is insoluble/practically insoluble in water, and demonstrates pH-dependent aqueous solubility. Alpelisib is most soluble at pH 1 and has two experimentally determined dissociation constants with pKa values of 3.3 and 9.4. The pH of a 1.0 % (m/v) solution of alpelisib in water/ethanol (50:50 v/v) is approximately 6.2. In an n-octanol/pH 6.8 buffer system, alpelisib has a log D of 2.8. Alpelisib is optically active.

Chemical structure



Chemical Abstracts Service (CAS) number

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7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8. SPONSOR

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9. DATE OF FIRST APPROVAL

20 March 2020

10 DATE OF REVISION

09 February 2021

Summary table of changes

Section changed	Summary of new information
4.2	Dosing recommendations updated for hyperglycaemia, rash, diarrhea and other toxicities (excluding hyperglycaemia, rash and diarrhea)
4.4	Hyperglycaemia precaution amended to include ketoacidosis and hyperglycaemic hyperosmolar nonketotic syndrome (HHNKS) cases from post-market

	Addition of optional sub-headings “Use in hepatic impairment” and Use in renal impairment” and mandatory sub-headings “use in the elderly”, “paediatric use”
4.8	Add hyperglycaemic hyperosmolar non-ketotic syndrome (HHNKS) to the list of ADRs from spontaneous reports and literature cases Description of selected ADRs: add text to indicate that some patients with ONJ were exposed to prior or concomitant RANK-ligand inhibitors
4.9	Addition of mandatory ‘overdose’ text from TGA template for providing product information
5	Revised ATC code
5.2	pH reducing agents amended to Acid reducing agents
6.3	Hyphen removed from “shelf-life” heading
6.5	Converted brand name from lower case to upper case

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