▼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 – ITOVEBI® (INAVOLISIB) FILM-COATED TABLET

1 NAME OF THE MEDICINE

Inavolisib

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 3 mg film-coated tablet contains 3 mg inavolisib.

Each 9 mg film-coated tablet contains 9 mg inavolisib.

Excipients with known effect: Lactose.

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

3 PHARMACEUTICAL FORM

Film-coated tablets.

Inavolisib 3 mg film-coated tablet is red and round convex-shaped with an “INA 3” debossing on one side.

Inavolisib 9 mg film-coated tablet is pink and oval-shaped with an “INA 9” debossing on one side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Itovebi, in combination with palbociclib and fulvestrant, is indicated for the treatment of adult patients with *PIK3CA*-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer, following recurrence on or within 12 months of completing adjuvant endocrine therapy.

4.2 DOSE AND METHOD OF ADMINISTRATION

General

Patients with HR-positive, HER2-negative, locally advanced or metastatic breast cancer should be selected for treatment with Itovebi based on the presence of one or more *PIK3CA* mutations using a validated assay. *PIK3CA* mutation status should be established prior to initiation of Itovebi therapy.

Dose

The recommended dose of Itovebi is 9 mg taken orally once daily with or without food.

Itovebi should be administered in combination with palbociclib and fulvestrant. The recommended dose of palbociclib is 125 mg taken orally once daily for 21 consecutive days followed by 7 days off treatment to comprise a complete cycle of 28 days. Refer to the product information for palbociclib and fulvestrant for dosing information.

Treatment of pre/perimenopausal women with Itovebi should also include a luteinizing hormone-releasing hormone (LHRH) agonist in accordance with local clinical practice.

For male patients, consider treatment with an LHRH agonist according to local clinical practice.

Duration of Treatment

It is recommended that patients are treated with Itovebi until disease progression or unacceptable toxicity.

Delayed or Missed Doses

Patients should be encouraged to take their dose at approximately the same time each day. If a dose of Itovebi is missed, it can be taken within 9 hours after the time it is usually taken. After more than 9 hours, the dose should be skipped for that day. On the next day, Itovebi should be taken at the usual time. If the patient vomits after taking the Itovebi 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.

Dose Modification

Management of adverse reactions may require temporary interruption, dose reduction, or discontinuation of treatment with Itovebi.

The recommended dose reduction guidelines for adverse reactions are listed in Table 1.

Table 1 Dose Reduction Guidelines for Adverse Reactions

Dose Reduction Schedule	Dose Modified
Starting dose	9 mg daily
First dose reduction	6 mg daily
Second dose reduction	3 mg daily[a]
[a]Itovebi treatment should be permanently discontinued if patients are unable to tolerate the 3 mg daily dose.	

The dose of Itovebi may be re-escalated to a maximum daily dose of 9 mg based on clinical evaluation of the patient by the treating physician.

Hyperglycaemia

Before initiating treatment with Itovebi, fasting plasma glucose (FPG)/blood glucose (FBG) and HbA_{1C} levels should be tested, and plasma/blood glucose levels should be optimised in all patients. Evaluate patients for renal impairment prior to treatment with Itovebi (see section 4.2 Dose and Method of Administration-Renal impairment and section 5.2 Pharmacokinetic Properties). After initiating treatment with Itovebi, patient fasting glucose (FPG or FBG) levels should be monitored or self-monitored based on the recommended schedule (see section 4.4 Special Warnings and Precautions For Use - General).

A patient card is available for dissemination by the treating physician.

Table 2 Dose Modification and Management for Hyperglycaemia

Fasting Glucose Levels[a]	**Recommendation[b]**
> ULN to 8.9 mmol/L	● No adjustment of Itovebi required. ● Consider dietary modifications (e.g., low carbohydrate diet) and ensure adequate hydration. ● Consider initiating or intensifying oral anti-hyperglycaemic medications[c] for patients with risk factors for hyperglycaemia[d].
> 8.9 – 13.9 mmol/L	● Interrupt Itovebi until fasting glucose level decreases to ≤ 8.9 mmol/L. ● Initiate or intensify anti-hyperglycaemic medication[c,e]. ● Resume Itovebi at the same dose level. ● If fasting glucose level persists > 11.1 – 13.9 mmol/L for 7 days under appropriate anti-hyperglycaemic treatment, consultation with a healthcare professional experienced in the treatment of hyperglycaemia is recommended.
> 13.9 – 27.8 mmol/L	● Interrupt Itovebi. ● Initiate or intensify anti-hyperglycaemic medication[c,e]. ● Administer appropriate hydration if required. ● If fasting glucose level decreases to ≤ 8.9 mmol/L within 7 days, resume Itovebi at the same dose level. ● If fasting glucose level decreases to ≤ 8.9 mmol/L in ≥ 8 days, resume Itovebi at one lower dose level (see Table 1). ● If fasting glucose level > 13.9 – 27.8 mmol/L recurs within 30 days, interrupt Itovebi until fasting glucose level decreases to ≤ 8.9 mmol/L. Resume Itovebi at one lower dose level (see Table 1).
> 27.8 mmol/L	● Interrupt Itovebi. ● Initiate or intensify anti-hyperglycaemic medication[c,e]. ● Assess for volume depletion and ketosis and administer appropriate hydration. ● If fasting glucose level decreases to ≤ 8.9 mmol/L, resume Itovebi at one lower dose level (see Table 1). ● If fasting glucose level > 27.8 mmol/L recurs within 30 days, permanently discontinue Itovebi.

ULN = upper limit of normal

[a] Fasting glucose levels (FPG or FBG) should be checked prior to dosing. Fasting glucose levels referenced in this table reflect hyperglycaemia grading according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

[b] Metformin prophylaxis was recommended for patients with risk factors in the INAVO120 study (see section 4.4 Special Warnings and Precautions For Use - General).

[c] Initiate applicable anti-hyperglycaemic medications, such as metformin, sodium-glucose cotransporter-2 (SGLT2) inhibitors, dipeptidyl peptidase-4 [DPP-4] inhibitors), or insulin sensitisers (such as thiazolidinediones), and review the respective prescribing information for dosing and dose titration recommendations, including local hyperglycaemia treatment guidelines. Metformin was recommended in the INAVO120 study as the preferred initial agent. See section 4.8 Adverse Effects (Undesirable Effects) **-**Description of selected adverse drug reactions.

[d] Risk factors for hyperglycaemia include, but are not limited to, (pre)diabetes, HbA_{1C} ≥ 5.7% to < 6.5%, BMI ≥ 30 kg/m^2, ≥ 45 years of age, history of gestational diabetes, and family history of diabetes mellitus (see section 4.4 Special Warnings and Precautions For Use - General).

Fasting Glucose Levels[a]	Recommendation[b]
[e] In the INAVO120 study, short-term insulin was allowed to control blood glucose levels with a goal of maintaining blood glucose levels on oral agents only once the acute episode resolves.	

Other adverse reactions

Table 3 Dose Modification and Management for Other Adverse Reactions

Adverse Reaction	Grade[a]	Recommendation
Stomatitis (see section 4.4 Special Warnings and Precautions For Use)	Grade 1[a]	• No adjustment of Itovebi required. • Initiate or intensify appropriate medical therapy (e.g., corticosteroid-containing mouthwash) as clinically indicated.
	Grade 2[a]	• Withhold Itovebi until recovery to Grade ≤ 1. • Initiate or intensify appropriate medical therapy. Resume Itovebi at the same dose level. • For recurrent Grade 2 stomatitis, withhold Itovebi until recovery to Grade ≤ 1, then resume Itovebi at one lower dose level.
	Grade 3[a]	• Withhold Itovebi until recovery to Grade ≤ 1. • Initiate or intensify appropriate medical therapy. Resume Itovebi at one lower dose level.
	Grade 4[a]	• Permanently discontinue Itovebi.
Diarrhoea (see section 4.4 Special Warnings and Precautions For Use)	Grade 1[a]	• No adjustment of Itovebi required. • Initiate appropriate medical therapy and monitor as clinically indicated.
	Grade 2[a]	• Withhold Itovebi until recovery to Grade ≤ 1, then resume Itovebi at the same dose level. • Initiate or intensify appropriate medical therapy and monitor as clinically indicated. • For recurrent Grade 2 diarrhoea, withhold Itovebi until recovery to Grade ≤ 1, then resume Itovebi at one lower dose level.
	Grade 3[a]	• Withhold Itovebi until recovery to Grade ≤ 1, then resume Itovebi at one lower dose level. • Initiate or intensify appropriate medical therapy and monitor as clinically indicated.
	Grade 4[a]	• Permanently discontinue Itovebi.
Haematologic Toxicities (see 4.8 Adverse Effects (Undesirable Effects))	Grade 1, 2 or 3[a]	• No adjustment of Itovebi required. • Monitor complete blood count and for signs or symptoms of haematologic toxicities as clinically indicated.
	Grade 4[a]	• Withhold Itovebi until recovery to Grade ≤ 2. • Resume Itovebi at the same dose level or reduce to one lower dose level as clinically indicated.
For all grades: Initiate supportive therapy and monitor as clinically indicated.		
	Grade 1	• No adjustment of Itovebi required.

Adverse Reaction	Grade[a]	Recommendation
Other Adverse Reactions (see 4.8 Adverse Effects (Undesirable Effects))	Grade 2	● Consider interruption of Itovebi, if clinically indicated, until recovery to Grade ≤ 1. ● Resume Itovebi at the same dose level.
	Grade 3, first event	● Interrupt Itovebi until recovery to Grade ≤ 1. ● Resume Itovebi at the same dose level or at one lower dose level based on clinical evaluation (see Table 1).
	Grade 3, recurrent OR Grade 4, non-life-threatening	● Interrupt Itovebi until recovery to Grade ≤ 1. ● Resume Itovebi at one lower dose level (see Table 1).
	Grade 4, life-threatening	● Permanently discontinue Itovebi.
[a] Based on CTCAE version 5.0.		

Special Populations

Paediatric use

The safety and efficacy of Itovebi has not been established in children and adolescents (< 18 years).

Elderly

No dose adjustment of Itovebi is required in patients ≥ 65 years of age. For details on geriatric data, see section 4.4 Special Warnings and Precautions For Use - Use in the elderly.

Renal impairment

No dose adjustment is required in patients with mild renal impairment (eGFR ≥ 60 to < 90 mL/min). The recommended starting dosage of Itovebi for patients with moderate renal impairment (eGFR 30 to < 60 mL/min) is 6 mg orally once daily. The safety and efficacy of Itovebi have not been established in patients with severe renal impairment. For details on renal impairment data, see section 4.4 Special Warnings and Precautions For Use-Use in renal impairment and section 5.2 Pharmacokinetic Properties-Pharmacokinetics in Special Populations.

Hepatic impairment

No dose adjustment is required in patients with mild hepatic impairment (total bilirubin > ULN to ≤ 1.5 x ULN or AST > ULN and total bilirubin ≤ ULN). The safety and efficacy of Itovebi have not been studied in patients with moderate to severe hepatic impairment. For details on hepatic impairment data, see section 4.4 Special Warnings and Precautions For Use - Use in hepatic impairment.

4.3 CONTRAINDICATIONS

Itovebi is contraindicated in patients with a known hypersensitivity to inavolisib or any of the excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

Hyperglycaemia

Severe hyperglycaemia, including complications such as life-threatening ketoacidosis, can occur in patients treated with Itovebi.

In the INAVO120 pivotal clinical trial, 46% of patients who received Itovebi were treated with oral anti-hyperglycaemic medications and 7% were treated with insulin to manage increased fasting glucose.

The safety of Itovebi in patients with Type 1 diabetes mellitus, or Type 2 diabetes mellitus requiring ongoing anti-hyperglycaemic treatment have not been studied. Patients with a history of well-controlled Type 2 diabetes mellitus may require intensified anti-hyperglycaemic treatment and close monitoring of fasting glucose levels as clinically indicated. Itovebi should not be administered until fasting glucose levels are optimised. Consultation with a healthcare professional experienced in the treatment of hyperglycaemia should be considered before initiating Itovebi.

Before initiating treatment with Itovebi, fasting glucose levels (FPG or FBG) and HbA_{1C} levels should be tested, and fasting glucose levels should be optimised in all patients. Patients should also be advised of the signs and symptoms of hyperglycaemia (e.g., excessive thirst, urinating more often, blurred vision, mental confusion, difficulty breathing, or increased appetite with weight loss) and to immediately contact a healthcare professional if these symptoms occur. Optimal hydration should be maintained prior to and during treatment.

After initiating treatment with Itovebi, fasting glucose levels should be monitored or self-monitored once every 3 days for the first week (Day 1 to 7), then once every week for the next 3 weeks (Day 8 to 28), then once every 2 weeks for the next 8 weeks, then once every 4 weeks thereafter, and as clinically indicated. HbA_{1C} should be monitored every 3 months and as clinically indicated, according to the instructions of a healthcare professional.

In patients with risk factors for hyperglycaemia including, but not limited to, (pre)diabetes, $HbA_{1C} \geq 5.7\%$, BMI ≥ 30 kg/m^2, ≥ 45 years of age, history of gestational diabetes, and family history of diabetes mellitus, fasting glucose levels should be monitored or self-monitored more frequently as clinically indicated. Anti-hyperglycaemic treatment should be initiated or adjusted as required (see section 4.2 Dose and Method of Administration – Dose Modification). Metformin prophylaxis was recommended for patients with risk factors for hyperglycaemia in the INAVO120 study.

If a patient experiences hyperglycaemia after initiating treatment with Itovebi, fasting glucose levels should be monitored more closely as clinically indicated. During treatment with anti-hyperglycaemic medication, fasting glucose levels should continue to be monitored at least once a week for 8 weeks, followed by once every 2 weeks, and as clinically indicated. Fasting glucose

monitoring at home should be considered for patients who have risk factors for hyperglycaemia or who experience hyperglycaemia.

Based on the severity of the hyperglycaemia, Itovebi may require dose interruption, reduction, or discontinuation as described in Table 2 (see section 4.2 Dose and Method of Administration – Dose Modification). All patients should be instructed on lifestyle changes (e.g., dietary modifications, physical activity).

Stomatitis

Severe stomatitis can occur in patients treated with Itovebi.

Stomatitis occurred in 51% of patients treated with Itovebi in combination with palbociclib and fulvestrant, including Grade 3 events in 6% of patients. The median time to first onset was 13 days (range: 1 to 610 days).

Stomatitis led to interruption of Itovebi in 10%, to dose reduction in 3.7%, and to discontinuation of Itovebi in 0.6% of patients.

Corticosteroid mouthwash was recommended for prophylaxis of stomatitis for all patients in clinical studies. In patients who received Itovebi in combination with palbociclib and fulvestrant, 38% used a mouthwash containing corticosteroid for management or prophylaxis of stomatitis.

Patients should be advised to start alcohol-free corticosteroid mouthwash at the first sign of stomatitis and to avoid alcohol- or peroxide-containing mouthwashes as they may exacerbate the condition (see section 4.8 Adverse Effects (Undesirable Effects) - Description of selected adverse drug reactions). Dietary modifications (e.g., avoiding spicy foods) should be considered.

Monitor patients for signs and symptoms of stomatitis. Withhold, reduce dose, or permanently discontinue Itovebi based on severity (see section 4.2 Dose and Method of Administration – Dose Modification).

Diarrhoea

Severe diarrhoea, including dehydration and acute kidney injury, can occur in patients treated with Itovebi.

Diarrhoea occurred in 48% of patients treated with Itovebi in combination with palbociclib and fulvestrant, including Grade 3 events in 3.7% of patients. The median time to first onset was 15 days (range: 2 to 602 days). Anti-diarrhoeal medicines were used in 28% (46/162) of patients who received Itovebi in combination with palbociclib and fulvestrant to manage symptoms. Dose interruptions were required in 7% of patients, and dose reductions occurred in 1.2% of patients.

Monitor patients for signs and symptoms of diarrhoea. Advise patients to increase oral fluids and start anti-diarrhoeal treatment at the first sign of diarrhoea while taking Itovebi. Withhold,

reduce dose, or permanently discontinue Itovebi based on severity (see section 4.2 Dose and Method of Administration – Dose Modification).

Embryofetal Toxicity

Based on the animal studies and pharmacological activity of inavolisib, Itovebi is expected to cause fetal harm when administered to pregnant women (see section 4.6 Use in pregnancy). Pregnant women should be advised of potential risk to the fetus. Females of reproductive potential and male patients should be advised to use effective contraception during treatment with Itovebi and for 2 weeks after the last dose of Itovebi (see section 4.4 Special Warnings and Precautions For Use - Females and males of reproductive potential).

Drug Abuse and Dependence

There is no evidence that Itovebi has the potential for drug abuse or dependence.

Females and Males of Reproductive Potential

Fertility
There are no clinical studies conducted to evaluate the effect of Itovebi on fertility. Based on animal studies, inavolisib may impact fertility in females and males of reproductive potential (see section 4.6 Effects on fertility).

Pregnancy testing
The pregnancy status of females of reproductive potential should be verified prior to initiating Itovebi therapy. Pregnant women should be clearly advised of the potential risk to the fetus.

Contraception
Female
Patients should be advised to use effective non-hormonal contraception during treatment with Itovebi and for 2 weeks after the last dose of Itovebi (see section 4.4 Special Warnings and Precautions For Use - General).

Male
It is not known if Itovebi is present in semen. To avoid potential fetal exposure during pregnancy, male patients with female partners of childbearing potential or pregnant female partners should use a condom during treatment with Itovebi and for 2 weeks after the last dose of Itovebi (see section 4.4 Special Warnings and Precautions For Use - General).

Use in hepatic impairment

No dose adjustment is required in patients with mild hepatic impairment (total bilirubin > ULN to ≤ 1.5 x ULN or AST > ULN and total bilirubin ≤ ULN). The safety and efficacy of Itovebi in patients with moderate to severe hepatic impairment have not been studied. See section 4.2 Dose and Method of Administration - Special Populations and section 5.2 Pharmacokinetic Properties - Pharmacokinetics in Special Populations.

Use in renal impairment

No dose adjustment is required in patients with mild renal impairment (eGFR 60 to < 90 mL/min) based on population pharmacokinetic analysis. Reduce the dosage in patients with moderate renal impairment (eGFR 30 to < 60 mL/min based on CKD-EPI) – see section 4.2 Dose and Method of Administration – Dose modification). The safety and efficacy of Itovebi have not

been established in patients with severe renal impairment. See section 4.2 Dose and Method of Administration - Special Populations and section 5.2 Pharmacokinetic Properties - Pharmacokinetics in Special Populations.

Itovebi is known to be excreted by the kidney, and the risk of adverse reactions may be greater in patients with impaired renal function.

Use in the elderly

The safety and efficacy of Itovebi have been studied in geriatric patients up to 79 years of age. Of the 162 patients who received Itovebi in INAVO120, 14.8% were ≥ 65 years of age and 3% were ≥ 75 years of age.

The available data on the efficacy of Itovebi in patients 65 years and older do not suggest overall differences compared to younger patients. Analysis of the safety of Itovebi comparing patients ≥ 65 years of age to younger patients suggests a higher incidence of Itovebi dosage modifications/interruptions (79.2% versus 68.1%). There are an insufficient number of patients ≥ 75 years of age to assess whether there are differences in safety or efficacy.

Paediatric use

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

Effects on laboratory tests

See section 4.8 Adverse Effects (Undesirable Effects) - Clinical Trials.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No pharmacokinetic drug-drug interaction studies have been conducted with Itovebi.

Effects of inavolisib on other drugs

CYP Substrates

In vitro, inavolisib induced CYP2B6, CYP3A4, CYP2C8, CYP2C9 and CYP2C19, and was a time-dependent inhibitor of CYP3A. Inavolisib was not an inducer of CYP1A2 and no clinically relevant inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 was seen.

Transporters

In vitro studies have shown that inavolisib does not appear to have the potential to inhibit any of the transporters tested (P-glycoprotein [P-gp], breast cancer resistance protein [BCRP], OATP1B1, OATP1B3, OCT1, OCT2, MATE1, MATE2K, OAT1, or OAT3) at clinically relevant concentrations.

Effects of other drugs on inavolisib

CYP Inhibitors/Inducers

Inavolisib is not a substrate for CYP450 enzymes, suggesting a low likelihood of interaction between inavolisib and CYP inhibitors or inducers.

Transporters

In vitro studies have shown that inavolisib is not a substrate of OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT2, MATE1, or MATE2K, but is a substrate of P-gp and BCRP. However, based on the pharmacokinetic profile of inavolisib, inhibitors or inducers of P-gp and/or BCRP are not expected to have a clinically relevant drug-drug interaction with inavolisib.

Acid-reducing Agents

In clinical studies, concomitant use of proton pump inhibitors did not have a clinically meaningful effect on inavolisib exposure.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No clinical studies have been conducted to evaluate the effect of Itovebi on fertility. Based on animal studies, inavolisib may impact fertility in females and males of reproductive potential.

In male rats, dose-dependent atrophy of the prostate and seminal vesicle and decreased organ weights without microscopic correlate in the epididymis and testis were observed at doses ≥ 1.5 mg/kg/day (≥ 0.4 times the exposure at a clinical dose of 9 mg PO based on AUC). In male dogs, focal inspissation of seminiferous tubule contents and multinucleated spermatids in the testis and epithelial degeneration/necrosis in the epididymis were observed following 4 weeks of dosing at 3 mg/kg/day (5 times the exposure at a clinical dose of 9 mg PO based on AUC) and decreased sperm count was observed following 3 months of dosing at 1 mg/kg/day (similar to the human exposure at the recommended dose of 9 mg PO based on AUC). The findings in dogs were reversible.

In female rats, atrophy in the uterus and vagina, decreased ovarian follicles, and/or findings suggestive of an interruption/alteration of the oestrous cycle were observed following 4 weeks or 3 months of dosing at doses ≥ 3 mg/kg/day (≥ 1.2 times the human exposure at the recommended dose of 9 mg/day based on AUC). Findings in the uterus, vagina, and oestrous cycle observed in the 4-week toxicity study were not observed following 4 weeks of recovery. Recovery was not assessed in the 3-month study in rats..

Use in pregnancy – Pregnancy Category D

Itovebi is not recommended during pregnancy.

No clinical studies of Itovebi in pregnant women have been performed. Based on animal studies and the pharmacological activity of inavolisib, Itovebi is expected to cause fetal harm when administered to pregnant women, including teratogenicity and miscarriage (see section 4.4 Special Warnings and Precautions For Use - Females and males of reproductive potential).

Oral administration of doses ≥ 2 mg/kg/day to pregnant rats during the period of organogenesis resulted in lower fetal body weights and placental weights, embryofetal death, fetal malformations (including kyphosis of vertebral column, fused thoracic arch, microphthalmia) and variations (including dilated renal pelvis, short supernumerary rib, wavy rib). At a dose of 2 mg/kg/day, maternal exposures were 0.8 times the human exposure at the recommended dose of 9 mg/day based on AUC.

Labour and Delivery

The use of Itovebi during labour and delivery has not been established.

Use in lactation.
It is not known whether inavolisib is excreted in human breast milk.

No studies have been conducted to assess the impact of inavolisib on milk production or its presence in breast milk. Because of the potential for serious adverse reactions in the breastfed infant, it is recommended that women should not breastfeed during Itovebi treatment and for 1 week after the last dose of Itovebi.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Itovebi has no or negligible influence on the ability to drive or use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trials
Summary of Safety Profile

The overall safety profile of Itovebi is based on data from 162 patients with locally advanced or metastatic breast cancer who received Itovebi in combination with palbociclib and fulvestrant in the INAVO120 Phase 3, randomised study. The median duration of Itovebi treatment at the time of the analysis was 9.2 months (range: 0 to 38.8 months).

Fatal adverse reactions occurred in 3.7% of patients who received Itovebi with palbociclib and fulvestrant, including (0.6% each) acute coronary syndrome, cerebral haemorrhage, cerebrovascular accident, COVID-19 infection, and gastrointestinal haemorrhage.

Permanent discontinuation of Itovebi due to an adverse reaction occurred in 6% of patients. Adverse reactions which resulted in permanent discontinuation of Itovebi included hyperglycaemia (1.2%), and (0.6% each) stomatitis, gastric ulcer, intestinal perforation, anal abscess, increased ALT, decreased weight, bone pain, musculoskeletal pain, transitional cell carcinoma, and acute kidney injury.

The safety of Itovebi was also evaluated in the GO39374 Phase 1, dose-escalation study in patients with *PIK3CA*-mutated, HR-positive, HER2-negative, locally advanced or metastatic breast cancer who were enrolled to receive Itovebi in combination with palbociclib and fulvestrant (n=20); in combination with palbociclib, fulvestrant, and metformin (n=20); and in combination with palbociclib and letrozole (n=33). The safety profile of Itovebi in Study GO39374 was generally consistent with that observed in INAVO120.

Tabulated summary of adverse drug reactions from clinical trials
Adverse drug reactions from the INAVO120 study are listed by MedDRA system organ class in Table 4. The corresponding frequency category for each adverse drug reaction is based on the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000).

Table 4 Adverse Drug Reactions with ≥ 5% (All Grades) or ≥ 2% (Grade 3-4) Higher Incidence in the Itovebi Arm in INAVO120

System Organ Class Adverse Reaction	Itovebi + Palbociclib + Fulvestrant N=162			Placebo + Palbociclib + Fulvestrant N=162	
	Frequency Category (All Grades)	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Infections and Infestations					
Urinary Tract Infection	Very Common	13	1.2*	7.4	0
Blood and Lymphatic System Disorders					
Thrombocytopenia[a]	Very Common	48.1	14.2	45.1	4.3
Anaemia[b]	Very Common	37	6.2*	36.4	1.9*
Metabolism and Nutrition Disorders					
Hyperglycaemia[c]	Very Common	59.9	5.6*	9.9	0
Decreased appetite	Very Common	23.5	0	8.6	0
Hypokalaemia	Very Common	16	2.5	6.2	0
Hypocalcaemia	Common	8.6	1.2*	2.5	0.6*
Nervous System Disorders					
Headache	Very Common	21	0	13.6	0
Eye Disorders					
Dry eye	Common	8.6	0	3.1	0
Gastrointestinal Disorders					
Stomatitis[d]	Very Common	51.2	5.6*	26.5	0
Diarrhoea	Very Common	48.1	3.7*	16	0
Nausea	Very Common	27.8	0.6*	16.7	0
Vomiting	Very Common	14.8	0.6*	4.9	1.2*
Dyspepsia	Common	8	0	2.5	0
Skin and Subcutaneous Tissue Disorders					
Rash[e]	Very Common	25.3	0	17.3	0
Alopecia	Very Common	18.5	0	5.6	0
Dry skin[f]	Very Common	13	0	4.3	0
General Disorders and Administration Site Conditions					
Fatigue	Very Common	37.7	1.9*	25.3	1.2*
Investigations					
Alanine aminotransferase increased	Very Common	17.3	3.7*	13	1.2*
Weight decreased	Very Common	17.3	3.7*	0.6	0
Blood insulin increased	Common	6.2	0	0.6	0

Grading according to CTCAE version 5.0.

* No Grade 4 events were observed.

[a] Includes platelet count decreased and thrombocytopenia.

System Organ Class Adverse Reaction	Itovebi + Palbociclib + Fulvestrant N=162			Placebo + Palbociclib + Fulvestrant N=162	
	Frequency Category (All Grades)	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
[b] Includes anaemia and hemoglobin decreased.					
[c] Includes hyperglycaemia, blood glucose increased, hyperglycaemic crisis, glycated serum protein increased, glucose tolerance impaired, diabetes mellitus, Type 2 diabetes mellitus, and glycosylated hemoglobin increased.					
[d] Includes aphthous ulcer, glossitis, glossodynia, lip ulceration, mouth ulceration, mucosal inflammation, and stomatitis.					
[e] Includes dermatitis, dermatitis acneiform, dermatitis bullous, erythema, folliculitis, rash, rash erythematous, rash maculo-papular, rash popular, rash pruritic, and rash pustular.					
[f] Includes dry skin, skin fissures, xerosis, and xeroderma.					

Other adverse reactions with < 5% (all grades) or < 2% (Grade 3-4) greater incidence reported in patients in the Itovebi arm than the placebo arm are presented below:
Gastrointestinal Disorders: Abdominal pain, including abdominal pain, abdominal pain upper, abdominal pain lower (all grades: 15.4%; Grade 3: 0.6%; no Grade 4 events); dysgeusia, including dysgeusia, ageusia, and hypogeusia (all grades: 8.6%; Grade 3-4: 0%)

Description of selected adverse drug reactions
Hyperglycaemia
In the INAVO120 study, increased fasting glucose occurred in 85% of patients treated with Itovebi, including 22% of patients with Grade 2 (FPG > 8.9 to 13.9 mmol/L), 12% with Grade 3 (FPG > 13.9 to 27.8 mmol/L), and 0.6% with Grade 4 (FPG > 27.8 mmol/L) events. Among the patients who experienced hyperglycaemia, the rate of new onset of hyperglycaemia events was highest during the first two months of treatment (range: 1 to 32 months) with a median time to first onset of 7 days (range: 2 to 955 days).

In patients who received Itovebi in combination with palbociclib and fulvestrant, 43.8% were managed with anti-hyperglycaemic medication including metformin as a single agent or in combination with other anti-hyperglycaemic medication (i.e., insulin, DPP-4 inhibitors, and sulfonylureas), SGLT2 inhibitors, thiazolidinediones, and DPP-4 inhibitors. In patients with fasting glucose levels > 8.9 mmol/L with at least one level (see Table 2) improvement in fasting glucose levels (n=52), the median time to improvement was 8 days (range: 2 to 43 days).

Hyperglycaemia led to interruption of Itovebi in 27.8%, to dose reduction of Itovebi in 2.5%, and to discontinuation of Itovebi in 1.2% of patients.

Stomatitis
Severe stomatitis can occur in patients treated with Itovebi. Stomatitis was reported in 51.2% of patients treated with Itovebi in combination with palbociclib and fulvestrant; Grade 1 events were reported in 32.1% of patients, Grade 2 events in 13.6% of patients, and Grade 3 events in 5.6% of patients. No Grade 4 stomatitis events were reported. The median time to first onset was 13 days (range: 1 to 610 days).

Stomatitis led to interruption of Itovebi in 9.9%, to dose reduction of Itovebi in 3.7%, and to discontinuation of Itovebi in 0.6% of patients.

In patients who received Itovebi in combination with palbociclib and fulvestrant, 24.1% used a mouthwash containing dexamethasone for management of stomatitis.

Corticosteroid mouthwash was recommended for prophylaxis of stomatitis in the INAVO120 study. Among patients who received Itovebi in combination with palbociclib and fulvestrant, prophylaxis containing dexamethasone or triamcinolone was used in 19.1% and 1.2% of patients, respectively.

Diarrhoea
Severe diarrhoea, including dehydration and acute kidney injury, can occur in patients treated with Itovebi. Diarrhoea was reported in 48.1% of patients treated with Itovebi in combination with palbociclib and fulvestrant; Grade 1 events were reported in 27.8% of patients, Grade 2 events in 16.7% of patients, and Grade 3 events in 3.7% of patients. No Grade 4 diarrhoea events were reported. The median time to first onset was 15 days (range: 2 to 602 days).

Diarrhoea led to interruption of Itovebi in 6.8%, to dose reduction of Itovebi in 1.2%, and did not lead to discontinuation of Itovebi in any patients.

Anti-diarrhoeal medicines (e.g., loperamide) were used in 28.4% of patients who received Itovebi in combination with palbociclib and fulvestrant to manage symptoms.

Laboratory Abnormalities

Table 5 summarises treatment-emergent shifts from baseline in laboratory abnormalities in the INAVO120 study.

Table 5 Laboratory Abnormalities with a ≥ 2% (All Grades or Grade 3-4) Higher Incidence in the Itovebi Arm in INAVO120

Laboratory Abnormality	Itovebi + Palbociclib + Fulvestrant[a]		Placebo + Palbociclib + Fulvestrant[b]	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Haematology				
Neutrophils (total, absolute) decreased	95.1	82	97	78.8
Haemoglobin decreased	87.5	7.5*	85.1	2.5*
Glucose (fasting) increased[c]	85.4	12.1	42.9	0
Platelets decreased	83.8	15.6	71.4	3.7
Lymphocytes (absolute) decreased	72.1	9	68.2	14.4
Chemistry				
Calcium decreased	41.9	3.1	31.7	3.7
Potassium decreased	37.5	6.2	20.5	0.6*
Creatinine increased	37.5	1.9*	29.8	1.2*
ALT increased	34.4	3.1*	28.6	1.2*
Sodium decreased	27.5	2.5*	18.6	2.5

Laboratory Abnormality	Itovebi + Palbociclib + Fulvestrant[a]		Placebo + Palbociclib + Fulvestrant[b]	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Magnesium decreased	26.9	0.6	20.5	0
Albumin decreased	25	0.6*	18.1	0
Lipase (fasting) increased	16	1.4*	6.9	0
Glucose (fasting) decreased[c]	6.4	0	3.2	0

ALT = alanine aminotransferase

Grading according to CTCAE version 5.0

* No Grade 4 events were observed.

[a] The denominator used to calculate the rate varied from 122 to 160 based on the number of patients with a baseline value and at least one post-treatment value.

[b] The denominator used to calculate the rate varied from 131 to 161 based on the number of patients with a baseline value and at least one post-treatment value.

[c] Grading according to CTCAE version 4.03.

Post-marketing experience

The following adverse drug reactions have been identified from post-marketing experience with Itovebi (Table 6) based on spontaneous case reports and literature cases. Adverse drug reactions are listed according to system organ classes in MedDRA and the corresponding frequency category estimation for each adverse drug reaction is based on the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000).

Table 6 Adverse Drug Reactions Reported From Post-Marketing Experience

System Organ Class Adverse Reaction	Frequency category	CDS reference
Metabolism and Nutrition Disorders		
Ketoacidosis	Uncommon[a]	[##]

[a]This adverse reaction was from postmarketing experience outside the clinical trial dataset. The frequency category was estimated as the upper limit of the 95% confidence interval calculated on the basis of the total number of patients exposed to inavolisib in clinical trials.

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

There is limited experience of overdose with Itovebi in clinical trials. In clinical studies, Itovebi was administered at doses up to 12 mg once daily.

The highest dose administered in the INAVO120 study was 18 mg in one patient. The event of accidental overdosage was resolved in one day and did not require treatment or lead to dose modification of any study drugs.

Patients who experience overdose should be closely supervised and supportive care instituted. There are no known antidotes for Itovebi.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Inavolisib is a potent (low picomolar K_i) inhibitor of the phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) catalytic subunit alpha isoform protein (p110α; encoded by the *PIK3CA* gene). In addition, inavolisib promotes the degradation of mutated p110α (mutant degrader). The PI3K signaling pathway is commonly dysregulated in HR-positive breast cancer, often due to activating *PIK3CA* mutations. With its dual mechanism of action, inavolisib inhibits the activity of downstream PI3K pathway targets, including AKT, resulting in reduced cellular proliferation and induction of apoptosis in *PIK3CA*-mutated breast cancer cell lines. In *PIK3CA*-mutated breast cancer xenograft models, inavolisib reduced tumour growth, which was more pronounced in combination with a CDK4/6 inhibitor (palbociclib) and endocrine therapy.

Clinical trials

Locally Advanced or Metastatic Breast Cancer

INAVO120

The efficacy of Itovebi in combination with palbociclib and fulvestrant was evaluated in a Phase 3, randomised, double-blind, placebo-controlled study in adult patients with *PIK3CA*-mutated, HR-positive, HER2-negative, locally advanced or metastatic breast cancer whose disease progressed during or within 12 months of completing adjuvant endocrine therapy and who have not received prior systemic therapy for locally advanced or metastatic disease. The study excluded patients with Type 1 diabetes mellitus or Type 2 diabetes mellitus requiring ongoing systemic therapy at the start of study treatment.

PIK3CA mutation status was prospectively determined through testing of plasma-derived circulating tumour DNA (ctDNA) using a next-generation sequencing (NGS) assay at a central laboratory, or in local laboratories using various validated polymerase chain reaction (PCR) or NGS assays on tumour tissue or plasma.

A total of 325 patients were randomised 1:1 to receive either Itovebi 9 mg (n=161) or placebo (n=164) orally once daily, in combination with palbociclib and fulvestrant, until disease progression or unacceptable toxicity. In addition, pre/perimenopausal women and men

received an LHRH agonist throughout therapy. Randomization was stratified by presence of visceral disease (yes or no), endocrine resistance (primary or secondary), and geographic region (North America/Western Europe, Asia, other).

The baseline demographic and disease characteristics were: median age 54 years (range: 27 to 79 years); 98.2% female; 38.2% were pre/perimenopausal; 58.8% White, 38.2% Asian, 2.5% unknown, 0.6% Black or African American; 6.2% Hispanic or Latino; and Eastern Cooperative Oncology Group (ECOG) performance status of 0 (63.4%) or 1 (36.3%). Tamoxifen (56.9%) and aromatase inhibitors (50.2%) were the most commonly used adjuvant endocrine therapies. The demographics and baseline disease characteristics were balanced and comparable between study arms.

The primary efficacy outcome measure was investigator (INV)-assessed progression-free survival (PFS) per Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1. The secondary efficacy outcome measures included overall survival (OS), objective response rate (ORR), best overall response (BOR), clinical benefit rate (CBR), duration of response (DOR), and time to confirmed deterioration (TTCD) in pain, physical function, role function, and global health status/health-related quality of life (HRQoL).

Efficacy results are summarized in Table 7 and Figure 1. INV-assessed PFS results were supported by consistent results from blinded independent central review (BICR) assessment. At the time of the PFS analysis, OS data were not mature with 30% deaths in the overall population.

Table 7 Efficacy Results in Patients with Locally Advanced or Metastatic Breast Cancer in INAVO120

Efficacy Endpoint	**Itovebi + Palbociclib + Fulvestrant N=161**	**Placebo + Palbociclib + Fulvestrant N=164**
Primary Endpoint		
INV-Assessed Progression-Free Survival[a]		
Patients with event, n (%)	82 (50.9)	113 (68.9)
Median, months (95% CI)	15 (11.3, 20.5)	7.3 (5.6, 9.3)
Hazard ratio (95% CI)	0.43 (0.32, 0.59)	
p-value	< 0.0001	
Secondary Endpoints		
Overall Survival[b]		
Patients with event, n (%)	42 (26.1)	55 (33.5)
Median, months (95% CI)	NE (27.3, NE)	31.1 (22.3, NE)
Hazard ratio (95% CI)	0.64 (0.43, 0.97)	
p-value	0.0338	
Objective Response Rate[a,c]		
Patients with CR or PR, n (%)	94 (58.4)	41 (25)
95% CI	(50.4, 66.1)	(18.6, 32.3)
Best Overall Response[a,d]		

Efficacy Endpoint	Itovebi + Palbociclib + Fulvestrant N=161	Placebo + Palbociclib + Fulvestrant N=164
Patients with CR or PR, n (%)	103 (64)	49 (29.9)
95% CI	(56, 71.4)	(23, 37.5)
Duration of Response		
Median DOR, months (95% CI)	18.4 (10.4, 22.2)	9.6 (7.4, 16.6)
Clinical Benefit Rate		
Patients, n (%)	121 (75.2)	77 (47)
95% CI	(67.7, 81.6)	(39.1, 54.9)

CI = confidence interval; CR = complete response; NE = not evaluable; PR = partial response

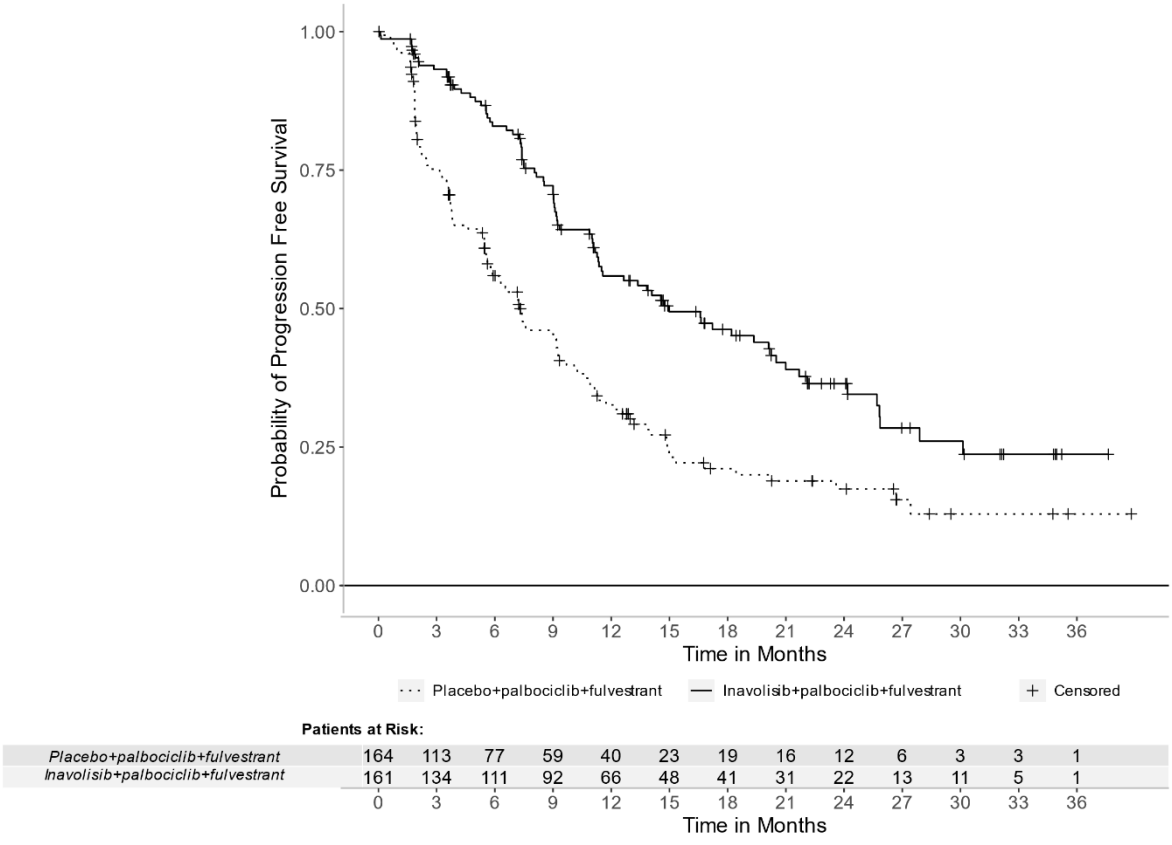
[a] Per RECIST version 1.1.

[b] Based on interim analysis. Under the interim analysis stopping boundary ($p \leq 0.0098$), statistical significance was not reached.

[c] ORR is defined as the proportion of patients with a CR or PR on two consecutive occasions ≥ 4 weeks apart, as determined by the investigator.

[d] BOR is defined as the proportion of patients with a CR or PR, as determined by the investigator.

Figure 1: INV-Assessed Progression-Free Survival in Patients with Locally Advanced or Metastatic Breast Cancer in INAVO120



Prespecified PFS analyses per investigator assessment showed a generally consistent treatment effect in favor of the Itovebi arm in patient subgroups including age, sex, ethnicity, race, ECOG

performance status, menopausal status, presence of visceral disease (yes or no), presence of liver metastases (yes or no), number of metastatic organ sites, and endocrine resistance (primary or secondary).

Patient-Reported Outcomes

PFS results were supported by a longer time to clinically meaningful deterioration in patient-reported worst pain severity, defined as an increase of 2 or more points from baseline on the Brief Pain Inventory worst pain item score, favoring the Itovebi arm (median 30.9 months [95% CI: 16.6, NE] versus 18.1 months [95% CI: 13.1, NE]).

Other patient-reported endpoints measured by the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30) suggest that patients maintained their baseline levels of HRQoL, physical functioning, and role functioning while on treatment. Mean scores at baseline for HRQoL (65.5 and 66.3), physical function (80.4 and 80.1), and role function (80.2 and 79) in the Itovebi and placebo arms, respectively, were comparable with no changes of 10 points or greater from baseline mean score observed during the course of treatment. Additionally, no differences in the median time to a confirmed ≥ 10-point, clinically meaningful deterioration in HRQoL (29 [95% CI: 15.8, NE] and 27.4 [95% CI: 15, NE] months), physical function (23.7 [95% CI: 18.4, 28.4] and 22.7 [95% CI: 13.3, 27.4] months), or role function (25.7 [95% CI: 18.4, NE] and 24.2 [95% CI: 7.4, NE] months) were observed between the Itovebi and placebo arms, respectively, indicating that patients in both arms maintained their day-to-day functioning and HRQoL for a similar duration of time.

Patients also reported on seven selected symptomatic toxicities (diarrhoea, nausea, vomiting, fatigue, mouth sores, decreased appetite, and rash) via the Patient-Reported Outcomes – Common Terminology Criteria for Adverse Events (PRO-CTCAE) corresponding to the known, reportable side effects of Itovebi, palbociclib, and fulvestrant, as well as their overall level of bother due to treatment side effects via a single item/question.

Completion rates in both arms were > 90% at baseline and > 80% at subsequent time points where > 50% of randomised patients were on treatment.

In both arms, worst post-baseline levels of ‘moderate’/‘somewhat’ or less were reported by > 70% of patients for decreased appetite, nausea, and vomiting, and by > 60% of patients for mouth sores, diarrhoea, and fatigue. Greater proportions of patients in the Itovebi arm reported post-baseline symptomatic toxicities at ‘severe’/‘frequently’ or ‘very severe’/‘almost constantly’ levels; these differences were greatest for mouth sores, decreased appetite, and diarrhoea (Table 8). Rash was reported in 53.9% and 40.5% of patients in the Itovebi and placebo arms, respectively, post-baseline.

Table 8: Proportion of Patients Reporting Worst Post-baseline Levels of PRO-CTCAE Symptoms Items in INAVO120

Symptom (Attribute)[a]	Baseline Score ≤ 1[a]		Post-baseline Score ≤ 2[a]		Post-baseline Score ≥ 3[a]	
	Inavo+P+F (N=148)	Pbo+P+F (N=152)	Inavo+P+F (N=152)	Pbo+P+F (N=158)	Inavo+P+F (N=152)	Pbo+P+F (N=158)
Mouth sores (severity), %	97.3	97.4	69.7	91.1	30.2	8.9
Decreased appetite (severity), %	89.9	91.5	73	87.4	27	12.7
Nausea (frequency), %	89.2	91.4	80.3	86.7	19.7	13.3
Vomiting (frequency), %	95.9	98	94.1	96.8	5.9	3.2
Diarrhoea (frequency), %	91.2	93.5	67.1	89.9	32.9	10.1
Fatigue (severity), %	73.6	73	63.2	72.8	36.8	27.2

Symptom (Attribute)	Baseline Presence		Post-baseline Presence	
	Inavo+P+F (N=148)	Pbo+P+F (N=152)	Inavo+P+F (N=152)	Pbo+P+F (N=158)
Rash (yes/no), %	94.6 (No)	95.4 (No)	53.9 (Yes)	40.5 (Yes)

Inavo+P+F = Itovebi plus palbociclib and fulvestrant arm; N/A = not applicable; Pbo+P+F = placebo plus palbociclib and fulvestrant arm

[a] The symptom attribute scoring is defined by amount/frequency/severity with a score of 0 = 'not at all'/'never'/'none'; 1 = 'a little bit'/'rarely'/'mild'; 2 = 'somewhat'/'occasionally'/'moderate'; 3 = 'quite a bit'/'frequently'/'severe'; 4 = 'very much'/'almost constantly'/'very severe'.

Patients reported low levels of overall bother from treatment side effects (i.e., 'not at all' or 'a little bit') at baseline in both the Itovebi arm (91.2%) and placebo arm (94.1%). During the course of treatment, a similar proportion of patients in both arms (≥ 90% in each arm) reported increased levels of bother, mostly at levels 'moderate'/'somewhat' or less, suggesting that Itovebi did not increase treatment burden when added to palbociclib and fulvestrant.

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetics of inavolisib were characterized in patients with locally advanced or metastatic *PIK3CA*-mutated solid tumours, including breast cancer, under an oral dosing regimen ranging from 6 mg to 12 mg daily and in healthy subjects at 9 mg single dose.

Inavolisib exhibited dose-proportional pharmacokinetics in patients with locally advanced or metastatic breast cancer over a dose range of 6 mg to 12 mg.

The exposure-response correlation for the efficacy of inavolisib was not observed. Exposure-response relationships were observed for hyperglycaemia (CTCAE Grade ≥ 2) at doses of 3 mg to 12 mg (0.3 to 1.3 times the recommended dosage) and anemia (CTCAE Grade ≥ 2) at the recommended dosage of 9 mg.

Absorption

The time to maximum plasma concentration (T_{max}) was reached after a median of 3 hours (range: 0.5 to 4 hours) at steady state following 9 mg once daily dosing of inavolisib, under fasted conditions.

With 9 mg once daily dosing, the geometric mean accumulation ratio was 2.04.

The absolute bioavailability of inavolisib was 76%.

No clinically significant effect of food on inavolisib exposure was observed. The geometric mean ratio (GMR) (90% CI) for AUC_{0-24} comparing the fed to the fasted state was 0.895 (0.737 – 1.09) after a single dose and 0.876 (0.701 – 1.09) at steady state. The GMR (90% CI) for C_{max} comparing the fed to the fasted state was 0.925 (0.748 – 1.14) after a single dose and 0.910 (0.712 – 1.16) at steady state.

Distribution

Plasma protein binding of inavolisib is 37%. In humans, the estimated steady state oral volume of distribution is 155 L and the blood-to-plasma ratio is approximately 0.794.

Metabolism

Minimal metabolism of inavolisib was detected *in vitro* in human liver microsome incubations.

Following oral administration of a single radiolabeled 9 mg dose of inavolisib to healthy subjects, parent drug was the most prominent drug-related compound in plasma and urine. Total metabolites in the excreta accounted for 42% (35% in faeces and 7% in urine) of the dose.

Excretion

Following oral administration of a single radiolabeled 9 mg dose of inavolisib to healthy subjects, 48.5% of the administered dose was recovered in urine (40.4% unchanged) and 48% in faeces (10.8% unchanged).

In clinical studies, the geometric mean of the individual elimination half-life estimate for inavolisib was 16.4 hours following a single 9 mg dose. The estimated total clearance of inavolisib is 8.83 L/hr.

Pharmacokinetics in Special Populations

Paediatric Population

No studies have been conducted to investigate the pharmacokinetics of inavolisib in paediatric patients.

Geriatric Population

No differences in inavolisib pharmacokinetics were noted between patients 65 years of age and older and those under 65 years based on population pharmacokinetic analysis.

Renal Impairment

No clinically significant differences in the pharmacokinetics of inavolisib were observed in patients with mild renal impairment compared to patients with normal renal function. Inavolisib AUC and C_{max} were 73% and 11% higher in patients with moderate renal impairment compared to patients with normal renal function (eGFR ≥ 90 mL/min), respectively. The effect of severe renal impairment (eGFR < 30 mL/min) on the pharmacokinetics of Itovebi is unknown.

Hepatic Impairment

Population pharmacokinetic analyses indicated that mild hepatic impairment is not a significant covariate on Itovebi exposure. The pharmacokinetics of inavolisib in patients with mild hepatic impairment (total bilirubin > ULN to ≤ 1.5 x ULN or AST > ULN and total bilirubin ≤ ULN) were similar to those in patients with normal hepatic function. The effect of moderate to severe hepatic impairment on Itovebi pharmacokinetics has not been studied.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Inavolisib was not mutagenic in the bacterial mutagenicity assay.

Inavolisib was clastogenic *in vitro* in a human lymphocyte micronucleus assay; however, there was no evidence of inavolisib-induced *in vivo* genotoxicity (clastogenicity, aneugenicity, or DNA damage) in the micronucleus and comet study in rats at daily oral doses up to 40 mg/kg resulting in exposures (AUC) 16 times the exposure at a clinical dose of 9 mg.

Inavolisib does not pose a genotoxic risk in humans.

Carcinogenicity

No carcinogenicity studies with inavolisib have been conducted.

Other

Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use, included inflammation in dogs and eye lens degeneration in rats. The inflammation is consistent with the anticipated pharmacological effects of PI3K inhibition, was generally dose-dependent and reversible, and is considered to be clinically monitorable and/or manageable. Lens fibre degeneration observed

in some rats at 10 mg/kg/day (≥ 3.6 times the exposure at a clinical dose of 9 mg based on AUC) was considered irreversible.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Microcrystalline cellulose
Lactose
Sodium starch glycollate
Magnesium stearate
Polyvinyl alcohol
Titanium dioxide
Macrogol/polyethylene glycol
Purified talc
Iron oxide red
Iron oxide yellow (9 mg tablet only)

6.2 INCOMPATIBILITIES

Refer to section 4.5 Interactions with other medicines and other forms of interactions.

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 below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

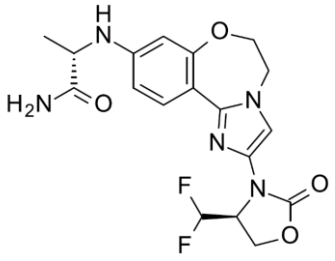
Itovebi 3 mg and 9 mg film-coated tablets are supplied in cartons of 28 tablets (4 aluminium blister cards, each with 7 tablets, per carton).

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

The release of pharmaceuticals in the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Any unused medicine or waste material should be disposed of by taking to a local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure:



CAS number: 2060571-02-8

Chemical name: (2*S*)-2-[[2-[(4*S*)-4-(difluoromethyl)-2-oxo-1,3-oxazolidin-3-yl]-5,6-dihydroimidazo[1,2-d][1,4]benzoxazepin-9-yl]amino]propenamide

Empirical formula: $C_{18}H_{19}F_2N_5O_4$

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

Roche Products Pty Limited
ABN 70 000 132 865
Level 8, 30-34 Hickson Road
Sydney NSW 2000
AUSTRALIA

Medical enquiries: 1800 233 950

9 DATE OF FIRST APPROVAL

26 March 2025

10 DATE OF REVISION

15 October 2025

- **SUMMARY TABLE OF CHANGES**

Section Changed	Summary of new information
4.6	Addition of breast-feeding restriction within 1 week of completing treatment.
4.8	Increase of adverse reaction frequency (from post-marketing data) of ketoacidosis from 'rare' to 'uncommon.'