PACK INSERT FOR MALAYSIA

ITOVEBI®

3mg and 9mg Film-Coated Tablets

Inavolisib

Composition

Active substances
Inavolisib.

Excipients
Microcrystalline Cellulose, Lactose 316 Spray Dried, Sodium Starch Glycolate, Magnesium Stearate.

One 3 mg film-coated tablet contains max. 0.17mg sodium.
One 9 mg film-coated tablet contains max. 0.51mg sodium.

Tablet coating:
Polyvinyl Alcohol Partially Hydrolysed, Titanium dioxide, Macrogol, Talc, Iron Oxide Red, Iron Oxide Yellow (only in 9 mg film-coated tablet).

Pharmaceutical form and active substance quantity per unit

Film-coated tablets containing 3 mg inavolisib and 9 mg inavolisib.

3 mg film-coated tablet:
Each 3 mg film-coated tablet contains 3 mg inavolisib. Itovebi 3 mg film-coated tablets are red and round convex-shaped with “INA 3” embossed on one side.

9 mg film-coated tablet:
Each 9 mg film-coated tablet contains 9 mg inavolisib. Itovebi 9 mg film-coated tablets are pink and oval-shaped with “INA 9” embossed on one side.

Indications/Uses

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.

Dosage/Administration

General information
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 that have been identified using a validated assay (see "Clinical Efficacy"). PIK3CA mutation status should be established prior to initiation of Itovebi therapy.

Recommended dosage
The recommended dose of Itovebi is 9 mg taken orally once daily independently of meals.

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 a 7-day break in treatment, to comprise a complete cycle of 28 days. Please refer to the Information for Healthcare Professionals for palbociclib and fulvestrant (500 mg) for the complete 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.

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

Missed/delayed administration
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 then be taken again at the usual time. If the patient vomits after taking the Itovebi dose, she should not take an additional dose on that day and should resume the usual dosing schedule the next day at the usual time.

Dose adjustment following undesirable effects/interactions
Management of adverse reactions may require temporary interruption, a 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	Modified Dose
Starting dose	9 mg/day
First dose reduction	6 mg/day
Second dose reduction	3 mg/day[a]
[a] Itovebi treatment should be permanently discontinued if patients are unable to tolerate the 3 mg daily dose.	

Hyperglycaemia
Before initiating treatment with Itovebi, fasting plasma glucose (FPG)/fasting blood glucose (FBG) and HbA1C levels should be measured, and plasma/blood glucose levels should be optimised in all patients (see “Warnings and Precaution”).

Evaluate patients for renal impairment prior to and during treatment with Itovebi (see “Special Dosage Instructions, Renal Impairment” and “Pharmacokinetic Properties”).

After initiating treatment with Itovebi, fasting glucose (FPG or FBG) levels in the patient should be monitored or self-monitored based on the recommended schedule (see "Warnings and precautions").

Table 2: Dose Adjustment and Management for Hyperglycaemia

Fasting Glucose Levels[a]	Recommendation[b]
> ULN to 160 mg/dL (>ULN to 8.9 mmol/L)	• No dose adjustment of Itovebi required. • Consider dietary modifications (e.g., low carbohydrate diet) and ensure adequate hydration. • Consider initiating or intensifying oral anti-hyperglycaemic medication[c] for patients with risk factors for hyperglycaemia[d].
> 160 to 250 mg/dL (> 8.9 - 13.9 mmol/L)	• Interrupt Itovebi until fasting glucose level decreases to ⩽ 160 mg/dL (⩽ 8.9 mmol/L). • Initiate or intensify anti-hyperglycaemic medication[c, e]. • Resume Itovebi at the same dose level. • If fasting glucose level persists at > 200 - 250 mg/dL (> 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.
> 250 to 500 mg/dL (> 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 ⩽ 160 mg/dL (⩽ 8.9 mmol/L) within 7 days, resume Itovebi at the same dose level. • If fasting glucose level decreases to ⩽ 160 mg/dL (⩽ 8.9 mmol/L) within ⩾ 8 days, resume Itovebi at the next dose level down (see Table 1). • If fasting glucose level of > 250 to 500 mg/dL (> 13.9 - 27.8 mmol/L) recurs within 30 days, interrupt Itovebi until fasting glucose level decreases to ⩽ 160 mg/dL (⩽ 8.9 mmol/L). Resume Itovebi at the next dose level down (see Table 1).
> 500 mg/dL (> 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 ⩽ 160 mg/dL (⩽ 8.9 mmol/L), resume Itovebi at the next dose level down (see Table 1). • If fasting glucose level of > 500 mg/dL (> 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 the 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 "Warnings and precautions"). [c] Initiate suitable anti-hyperglycaemic medication, 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 Information for Healthcare Professionals for recommendations on dosing and dose titration, including local hyperglycaemia treatment guidelines. Metformin was recommended in the INAVO120 study as the preferred initial agent (see "Undesirable effects"). [d] Risk factors for hyperglycaemia include, but are not limited to, (pre)diabetes, HbA1C ⩾ 5.7%, BMI ⩾ 30 kg/m^2, an age of ⩾ 45 years, a medical history of gestational diabetes, and a family history of diabetes mellitus (see "Warnings and precautions"). [e] In the INAVO120 study, short-term insulin was permitted to control blood glucose levels, with the aim of only maintaining blood glucose levels on oral agents once the acute episode has resolved.	

Stomatitis

Table 3: Dose Modification and Management for Stomatitis

Grade[a]	**Recommendation**
Grade 1	• No adjustment of Itovebi required. • Initiate or intensify appropriate medical therapy (e.g., corticosteroid-containing mouthwash) as clinically indicated.
Grade 2	• 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	• Withhold Itovebi until recovery to Grade < 1. • Initiate or intensify appropriate medical therapy. Resume Itovebi at one lower dose level.
Grade 4	• Permanently discontinue Itovebi.
[a] Based on CTCAE version 5.0.	

Other Adverse Reactions

Table 4: Dose Adjustment and Management for Other Adverse Reactions

Grade[a]	**Recommendation**
For all grades: Initiate supportive therapy and monitor as clinically indicated.	
Grade 1	• No dose adjustment of Itovebi required.
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 the next dose level down based on the clinical evaluation (see Table 1).
Grade 3, recurrent OR Grade 4, non-life-threatening	• Interrupt Itovebi until recovery to Grade ≤ 1. • Resume Itovebi at the next dose level down (see Table 1).
Grade 4, life-threatening	• Permanently discontinue Itovebi.
a Based on CTCAE version 5.0.	

Special dosage instructions

Children and adolescents

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

Elderly patients

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

Analyses of the safety of Itovebi in a comparison between patients aged ⩾ 65 years and younger patients suggest a higher incidence of Itovebi dose adjustments/interruptions (79.2% versus 68.1%). The number of patients aged ⩾ 75 years is insufficient to assess whether there are any differences in safety or efficacy.

No dose adjustment of Itovebi is required in patients aged ⩾ 65 years. For details on data for elderly patients, see “Warnings and precautions”.

The incidence of serious adverse events (SAEs) in the Itovebi + palbociclib + fulvestrant arm was higher in patients aged over 65 years than in patients aged under 65 years (41.7% vs 21.0%), as was as the incidence of fatalities due to toxicity (16.7% vs. 1.4%). In addition, serious treatment-emergent adverse events (TEAEs), TEAEs leading to discontinuation of treatment and TEAEs resulting in dose adjustments/interruption were observed in patients aged over 65 years when compared to patients aged under 65 years.

Patients with renal disorders

No dose adjustment is required in patients with mild renal disorders (eGFR 60 to < 90 mL/min) based on the population pharmacokinetic analysis. The recommended dose for Itovebi in patients with moderate renal insufficiency (eGFR 30 to < 60 mL/min based on CKD-EPI) is 6 mg orally once daily. The safety and efficacy of Itovebi have not been established in patients with severe renal disorders based on the population pharmacokinetic analysis. For details on data on renal disorders, see section "Pharmacokinetics: Patients with renal disorders”. Itovebi is known to be excreted via the kidneys, and the risk of adverse reactions may be greater in patients with impaired renal function.

Patients with hepatic disorders

No dose adjustment is required in patients with mild hepatic disorders (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 disorders. For details on data on hepatic disorders, see “Warnings and precautions”.

Contraindications

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

Warnings and precautions

Hyperglycaemia

Severe cases of hyperglycaemia, including life-threatening or fatal ketoacidosis, have been reported in patients treated with Itovebi.

Hyperglycaemia was managed with anti-hyperglycaemic medication (see “Undesirable effects: Description of specific adverse reactions and additional information”).

Before initiating treatment with Itovebi, fasting glucose levels (FPG and FBG) and HbA1C levels should be measured, 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, confusion, difficulty breathing or increased appetite with weight loss) and to immediately contact a healthcare professional if these symptoms occur. Prior to and during treatment patients should be evaluated for renal impairment (see "Special populations, Patients with renal impairment" and "Pharmacokinetics"). Prior to and during treatment optimal hydration should be maintained. All patients should be instructed to make lifestyle changes (e.g., change in diet, exercise programme).

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 a week for the next 3 weeks (Day 8 to 28), as well as once every 2 weeks for the next 8 weeks, once every 4 weeks thereafter, and as clinically indicated. HbA1C 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, HbA1C $\geqslant$ 5.7%, BMI $\geqslant$ 30 kg/m^2, an age of $\geqslant$ 45 years, a medical history of gestational diabetes, and a family history of diabetes mellitus, fasting glucose levels should be monitored as clinically indicated more frequently or by patients themselves at home, if applicable. Anti-hyperglycaemic treatment should be initiated or adjusted as required (see " Dosage/Administration"). Metformin prophylaxis was recommended for patients with risk factors for hyperglycaemia in the INAVO120 study.

The safety of Itovebi in patients with Type 1 diabetes mellitus or Type 2 diabetes mellitus requiring ongoing systemic therapy has 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 optimized. Consultation with a healthcare professional experienced in the treatment of hyperglycaemia should be considered before initiating Itovebi.

Only limited data are available for patients with fasting blood glucose levels of 126-140 mg/dL and an HbA1c value of between 6-7%.

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 or who experience hyperglycaemia.

Based on the severity of the hyperglycaemia, Itovebi may require a dose interruption, reduction of the dose, or discontinuation, as described in Table 2 (see “Dosage/Administration”).

Stomatitis

Cases of stomatitis have been reported in patients being treated with Itovebi (see "Undesirable effects: Description of specific adverse reactions and additional information"). Based on the severity of the stomatitis, Itovebi may require a dose interruption, reduction of the dose or discontinuation (see Table 3).

Corticosteroid mouthwash was recommended for prophylaxis of stomatitis for all patients in clinical studies.

Patients should be advised to start using an alcohol-free corticosteroid mouthwash at the first signs of stomatitis and to avoid mouthwashes containing alcohol or peroxide - as they may exacerbate the symptoms (see "Undesirable effects: Description of specific adverse reactions and additional information"). Changes in diet (e.g., avoiding spicy foods) should be considered.

Embryo-foetal toxicity
Based on animal experiments and the pharmacological activity of inavolisib, Itovebi is expected to harm the foetus when administered to pregnant women (see “Preclinical Data: Reproductive toxicity”). Pregnant women should be advised of the potential risk to the foetus. Women of child-bearing age should be advised to use effective contraception during treatment with Itovebi and for 1 week after the last dose of Itovebi (see “Pregnancy, lactation”).

Lactose
Patients with the rare hereditary galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not use this medicine.

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per daily dose (9 mg film-coated tablets), that is to say essentially "sodium-free".

Diarrhoea
Cases of diarrhoea have been reported in patients being treated with Itovebi. Such cases were frequently observed and severe diarrhoea may occur. Based on the severity of the diarrhoea, Itovebi may require a dose interruption, a reduction of the dose or discontinuation, as described in Table 4. Patients should be advised to start anti-diarrhoeal treatment, increase oral fluids, and notify their healthcare professionals if diarrhoea occurs while taking Itovebi (see "Undesirable effects: Description of specific adverse reactions and additional information").

Infections and infestations
Infections have been reported in patients being treated with Itovebi, including Covid-19, urinary tract infections and pneumonia. Patients should be monitored for signs and symptoms of infections and, based on severity, dosing of Itovebi may be interrupted or reduced, or discontinued permanently (see Table 4).

Patients previously treated with CDK46i (adjuvant)
No conclusive efficacy data are available for patients who have received prior CDK4/6 inhibitors due to the small sample size.

Interactions

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

Effects of inavolisib on the pharmacokinetics of other agents

CYP substrates
In vitro studies suggest a low likelihood of time-dependent inhibition and induction of CYP3A4, and no potential to inhibit or induce the other CYP enzymes that were tested (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6) at clinically relevant concentrations. Physiologically based pharmacokinetic modelling predicted that inavolisib has no clinically relevant impact on the exposure of a sensitive CYP3A4 substrate, midazolam.

Transporters
In vitro studies have shown that inavolisib does not appear to have the potential to inhibit any of the transporters that were 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 agents on the pharmacokinetics of inavolisib
CYP inhibitors/inducers

Clinical study results show that the predominant metabolites of inavolisib are not mediated by CYP 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, no clinically relevant drug-drug interactions are to be expected between inhibitors or inducers of P-gp and/or BCRP and inavolisib.

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

Pregnancy, lactation

Women of child-bearing age
Women of child-bearing age should be advised to carry out a pregnancy test before starting treatment with Itovebi.

Contraception in women and men
Female patients should be advised to use a reliable non-hormonal contraceptive method during treatment with Itovebi and for 1 week after the last dose of Itovebi (see "Warnings and precautions").

Pregnancy
There are no, or only limited, data available on the use of inavolisib in pregnant women. Based on observations in animals and on the mechanism of action, inavolisib may harm the foetus if administered to pregnant women. Animal experiments revealed reproductive toxicity for inavolisib (see "Preclinical data"). The use of inavolisib as a monotherapy or in combination with palbociclib is not recommended during pregnancy and in women of child-bearing age who are not using any contraception. The patient must be advised of the potential risk to the foetus if she becomes pregnant during treatment.

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

Lactation
It is not known whether inavolisib is excreted in human breast milk. A risk to the new-born/child cannot be excluded. Itovebi should not be used during breast-feeding or for one week after the last dose.

Fertility
No clinical studies have been conducted to evaluate the effect of Itovebi on fertility. Based on animal experiments, inavolisib may impact fertility in females and males (see "Preclinical data").

Effects on ability to drive and use machines

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

Undesirable effects

Summary of the safety profile
The overall safety profile of Itovebi is based on pooled data from 335 patients with locally advanced or metastatic breast cancer who received 9 mg Itovebi once daily as monotherapy or combination therapy in the Phase 3, randomised INAVO120 study and non-randomised Phase 1 GO39374 study. The most common adverse reactions (reported at a frequency of $\geqslant$ 20%) were hyperglycaemia (63.3%), diarrhoea (57.6%), stomatitis (52.5%), nausea (44.2%), fatigue (42.4%), anaemia (33.7%), thrombocytopenia (33.7%), decreased appetite (29.9%), vomiting (29%), rash (27.2%), headache (26.9%), abdominal pain (21.5%) and alopecia (20.3%).

The most common grade 3 or 4 adverse reactions (reported at frequency of $\geqslant$ 2%) were hyperglycaemia (15.8%), thrombocytopenia (9.3%), anaemia (6.6%), stomatitis (4.2%), alanine

aminotransferase increased (3.9%), hypokalaemia (3.9%), fatigue (3.3%), diarrhoea (3.3%) and weight loss (2.7%). Serious adverse drug reactions reported in > 1% of patients receiving treatment with inavolisib plus palbociclib plus fulvestrant included urinary tract infections (1.5%).

Regardless of the causal relationship, Grade 5 adverse reactions were reported in 9 (2.7%) patients in the pooled population. These included acute coronary syndrome, hypertrophic cardiomyopathy, gastrointestinal haemorrhage, death, Covid-19, peritonitis, cerebral haemorrhage, cerebrovascular accident and pleural effusion. None of the Grade 5 adverse reactions were reported in more than 1 patient.

In the same pooled population, dose reductions of Itovebi due to adverse reactions were reported in 51 (15.2%) patients. The most common adverse reactions (reported at frequency of ⩾ 2%) leading to a dose reduction of inavolisib were hyperglycaemia (5.4%) and stomatitis (3.9%).
Discontinuation of treatment due to adverse reactions occurred in 17 (5.1%) patients. The most common adverse reaction (reported in >1 patient) leading to discontinuation of treatment was hyperglycaemia (0.6%).

List of adverse reactions
The adverse reactions observed during treatment with Itovebi are classified according to MedDRA system organ class and conventional frequencies as follows: “very common” (⩾ 1/10), “common” (⩾ 1/100, < 1/10), “uncommon” (⩾ 1/1,000, < 1/100), “rare” (⩾ 1/10,000, < 1/1,000), “very rare” (< 1/10,000), “not known” (cannot be estimated from the available data), see Table 5:

Table 5: Adverse Drug Reactions

System Organ Class Adverse Reaction	Itovebi Monotherapy or Combination therapy N = 335			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	14.6	1.5*	7.4	0
Covid-19	Very Common	14.9	0.9	10	0.6
Blood and Lymphatic System Disorders					
Thrombocytopenia[a]	Very Common	33.7	9.3*	45.1	4.3
Anaemia[b]	Very Common	33.7	6.6*	36.4	1.9*
Neutrophils (total, absolute) decreased**	Very Common	95.1	82	97	78.8
Haemoglobin decreased**	Very Common	87.5	7.5	85.1	2.5*
Platelets decreased**	Very Common	83.8	15.6	71.4	3.7
Lymphocytes (absolute) decreased**	Very Common	72.1	9	68.2	14.4
Metabolism and Nutrition Disorders					
Hyperglycaemia[c]	Very Common	63.3	15.8*	9.9	0
Decreased appetite	Very Common	29.9	0.9	8.6	0
Hypokalaemia	Very Common	14.6	3.9*	6.2	0
Hypocalcaemia	Common	7.5	1.2*	2.5	0.6*

Glucose (fasting) increased**[i]	Very Common	85.4	12.1	42.9	0
Calcium decreased**	Very Common	41.9	3.1	31.7	3.7
Potassium decreased**	Very Common	37.5	6.2	20.5	0.6*
Sodium decreased**	Very Common	27.5	2.5	18.6	2.5
Magnesium decreased**	Very Common	26.9	0.6	20.5	0
Albumin decreased**	Very Common	25	0.6	18.1	0
Weight decreased	Very Common	18.2	2.7	0.6	0
Lipase (fasting) increased**	Very Common	16	1.4	6.9	0
Glucose (fasting) decreased**[i]	Common	6.4	0	3.2	0
Creatinine increased**	Very Common	37.5	1.9	29.8	1.2*
Blood insulin increased	Common	2.7	0	0.6	0
Nervous System Disorders					
Headache	Very Common	26.9	0.6	13.6	0
Eye Disorders					
Dry eye	Common	8.4	0	3.1	0
Gastrointestinal Disorders					
Stomatitis[d]	Very Common	52.5	4.2*	26.5	0
Diarrhoea	Very Common	57.6	3.3*	16	0
Nausea	Very Common	44.2	2.1*	16.7	0
Abdominal pain[e]	Very Common	21.5	1.2	0	0
Vomiting	Very Common	29	1.2*	4.9	1.2*
Dysgeusia[f]	Very Common	19.1	0	0	0
Dyspepsia	Very Common	10.1	0	2.5	0
Skin and Subcutaneous Tissue Disorders					
Rash[g]	Very Common	27.2	0.3	17.3	0
Alopecia	Very Common	20.3	0	5.6	0
Dry skin[h]	Very Common	14.3	0	4.3	0
General Disorders and Administration Site Conditions					
Fatigue	Very Common	42.4	3.3*	25.3	1.2*
Hepatobiliary disorders					
Alanine aminotransferase increased	Very Common	17.3	3.9*	13	1.2*

Pooled dataset includes INAVO120 (N = 162, grading according to CTCAE version 5.0) and GO39374 (N = 173, grading according to CTCAE version 4.0).
* Grade 4 events were observed.
** Only based on INAVO120 study; the denominator used to calculate the incidence in the Itovebi arm varied between 122 and 160 based on the number of patients with a baseline value and at least one post-treatment value, whereas the

denominator used to calculate the incidence in the placebo arm varied between 131 and 161 based on the number of patients with a baseline value and at least one post-treatment value.
[a] Includes platelet count decreased and thrombocytopenia.
[b] Includes anaemia and haemoglobin decreased.
[c] Includes hyperglycaemia, blood glucose increased, hyperglycaemic crisis, glycated serum protein increased, glucose tolerance impaired, diabetes mellitus, type 2 diabetes mellitus, and glycosylated haemoglobin increased.
[d] Includes aphthous ulcer, glossitis, glossodynia, lip ulceration, mouth ulceration, mucosal inflammation, and stomatitis.
[e] Includes abdominal pain, upper abdominal pain, and lower abdominal pain.
[f] Includes dysgeusia, ageusia, and hypogeusia.
[g] Includes dermatitis, dermatitis acneiform, dermatitis bullous, erythema, folliculitis, rash, rash erythematous, rash maculo-papular, rash papular, rash pruritic, and rash pustular.
[h] Includes dry skin, skin fissures, xerosis, and xeroderma.
[i] Grading according to CTCAE version 4.03.

Description of specific adverse reactions and additional information

Hyperglycaemia

In the INAVO120 study, hyperglycaemia of any grade was reported in 59.9% of patients treated with Itovebi in combination with palbociclib and fulvestrant; Grade 2 and Grade 3 events were reported in 38.3% and 5.6% of patients, respectively, and no Grade 4 events were reported (based on CTCAE version 5.0). Among the patients who experienced hyperglycaemia, the incidence of new-onset 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 sulphonylureas), SGLT2 inhibitors, thiazolidinediones, and DPP-4 inhibitors. In patients with fasting glucose levels > 160 mg/dL (> 8.9 mmol/L), with improvement in fasting glucose levels by at least one level (see Table 2) (n = 52), the median time to improvement was 8 days (range: 2 to 43 days).

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

Stomatitis and oral mucositis

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 an interruption of treatment with Itovebi in 9.9%, to a 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 the management of stomatitis.

Corticosteroid mouthwash was recommended for prophylaxis against 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

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 an interruption of treatment with Itovebi in 6.8%, to a dose reduction of Itovebi in 1.2%, and did not result in the discontinuation of Itovebi in any patients.

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

Undesirable effects from the post-marketing phase

The following adverse drug reactions have been identified from postmarketing experience with Itovebi (Table 6) based on spontaneous case reports and literature cases.

Table 6: Adverse Drug Reactions Reported from Post-Marketing Experience

System Organ Class **Adverse Reaction**	**Frequency Category**
Metabolism and Nutrition Disorders	
Ketoacidosis	Rare[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 reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Overdose

There are limited data on overdoses with Itovebi in clinical studies. Itovebi was administered at doses of up to 12 mg once daily in clinical studies.

The highest dose administered in the INAVO120 study was 18 mg in one patient. This case of an accidental overdose was resolved in one day and did not require either treatment or a dose adjustment of any study drugs.

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

Properties/Effects

ATC code
L01EM06

Mechanism of action
Inavolisib is an inhibitor of the alpha isoform of the phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) catalytic subunit (p110α; encoded by the PIK3CA gene). In addition, inavolisib promotes the degradation of mutated p110α (mutant degrader). The PI3K signalling 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 signalling pathway target proteins, 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 efficacy
Locally advanced or metastatic breast cancer
INAVO120
The efficacy of Itovebi in combination with palbociclib and fulvestrant was evaluated in a Phase III, randomised, double-blind, placebo-controlled study in adult patients with PIK3CA-mutated, HR-positive, HER2-negative, locally advanced or metastatic breast cancer, whose disease had progressed during or within 12 months of completing adjuvant endocrine therapy and who had not received prior systemic therapy for locally advanced or metastatic disease. The study excluded patients with fasting blood glucose levels $\geqslant$ 126 mg/dL ($\geqslant$ 7.0 mmol/L) and HbA1c values $\geqslant$ 6.0% ($\geqslant$ 42 mmol/mol), and patients on chronic corticosteroid therapy of $\geqslant$ 10 mg of prednisone per day or an equivalent dose of other anti-inflammatory corticosteroids or immunosuppressants for a chronic disease. Moreover, patients with type 1 diabetes mellitus or type 2 diabetes mellitus requiring ongoing systemic therapy at the start of study treatment were also excluded.

Patients with HIV and patients with symptomatic active lung disease, including pneumonitis, and patients with a history of leptomeningeal disease or carcinomatous meningitis were excluded from the study.

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. 92.6% of patients were enrolled by ctDNA testing (of these, 94.4% were tested using central ctDNA tests and 5.6% using local ctDNA tests). Central ctDNA tests were performed in all patients with FoundationOne®Liquid CDx (Foundation Medicine), with the exception of the Chinese patient population. 7.4% of patients were enrolled via local tissue testing.

62 short variant alterations in 13 codons of PIK3CA with preclinical and/or clinical evidence of their oncogenic potential and/or predictive response value were eligible for inclusion in INAVO120, including H1047D/I/L/N/P/Q/R/T/Y, G1049A/C/D/R/S, E545A/D/G/K/L/Q/R/V, E453A/D/G/K/Q/V, E542A/D/G/K/Q/R/V, K111N/R/E, Q546E/H/K/L/P/R, G106A/D/R/S/V, N345D/H/I/K/S/T/Y, G118D, C420R, R88Q, M1043I/T/V.

A total of 325 patients were randomised 1:1 to receive either 9 mg Itovebi (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. Randomisation 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%); secondary endocrine resistance 64.3%. Tamoxifen (56.9%) and aromatase inhibitors (50.2%) were the most commonly used adjuvant endocrine therapies; 82.8% of patients had received prior chemotherapy. Three patients (0.9%) had received prior treatment with a CDK4/6 inhibitor. 0.9% of patients had locally advanced breast cancer at study entry. 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) based on the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. The secondary efficacy outcome measures included overall survival (OS), which is the key secondary endpoint.

Efficacy results are summarised in Table 7.

Efficacy could not be demonstrated in patients who had previously received a CDK4/6 inhibitor due to the limited sample size.

Table 7: Efficacy Results in Patients with Locally Advanced or Metastatic Breast Cancer in INAVO120 (DCO 29 September 2023)

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	

CI = confidence interval;
[a] Based on RECIST version 1.1.

Data on overall survival (OS) are still immature. At the DCO date of 29 September 2023, the number of events was as follows:
- 42 OS events in the treatment arm.
- 55 OS events in the control arm.

Pharmacokinetics

The pharmacokinetics of inavolisib were investigated 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 after administration of a single dose of 9 mg.

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

No dose-response relationship was observed for the efficacy of inavolisib. Dose-response relationships were observed for hyperglycaemia (CTCAE Grade $\geqslant$ 2) at doses of 3 mg to 12 mg (0.3 to 1.3 times the recommended dosage) and anaemia (CTCAE Grade $\geqslant$ 2) at the recommended dosage of 9 mg.

Absorption
The time to maximum plasma concentration (Tmax) 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 fasting conditions. The geometric mean accumulation ratio was 2.04 for 9 mg once daily dosing.

The absolute bioavailability of inavolisib was 76%.

No clinically significant effect of food on the exposure to inavolisib was observed. The geometric mean ratio (GMR) (90% CI) for the AUC_{0-24} after a meal in comparison to the fasting condition 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} after a meal in comparison to the fasting condition 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 ranged from 27% to 75% (mouse, 75%; rat, 40%; rabbit, 47%; dog, 31%; monkey, 27%; and human, 37%) and did not appear to be concentration-dependent over the concentration range that was tested (0.1 - 10 µM). In humans, the estimated volume of distribution at steady state after oral administration is 155 L and the blood-to-plasma ratio is approximately 0.794.

Metabolism
Minimal metabolism of inavolisib was detected *in vitro* in rat, dog, and human liver microsome incubations.

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

Elimination
Following oral administration of a single radiolabelled 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.

Kinetics in specific patient groups
Children and adolescents
No studies have been conducted to investigate the pharmacokinetics of inavolisib in paediatric patients.

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

Renal impairment
Population pharmacokinetic analyses indicated that mild renal impairment is not a significant covariate of exposure to Itovebi. The pharmacokinetics of inavolisib in patients with mild renal impairment (CrCl 60 to < 90 mL/min) were similar to those in patients with normal renal function. The pharmacokinetics of inavolisib were investigated in subjects with moderate renal insufficiency (N = 7), corresponding to an eGFR ranging between 30 and 59 ml/min, as well as in 7 control subjects with normal renal function. The $AUC_{0-\infty}$ and C_{max} for inavolisib were increased by 73% and 11%, respectively, in patients with moderate renal insufficiency in comparison to healthy control subjects (eGFR ≥ 90 mL/min).

The effect of severe renal impairment on the pharmacokinetics of Itovebi has not been established.

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

Preclinical data

Repeated dose toxicity
Adverse reactions that were not observed in clinical studies, but were observed in animals at levels of exposure similar to those in the clinical application, and which were possibly relevant to the clinical application, included inflammation in dogs and degeneration of the lens of the eye in rats. The inflammation is in keeping with the expected pharmacological effects of PI3K inhibition, was generally dose-dependent and reversible, and was viewed as possible to monitor clinically and/or clinically manageable. The degeneration of the lens fibres observed in some rats (at $\geqslant$ 3.6 times the AUC exposure at a clinical dose of 9 mg) was viewed as irreversible.

Genotoxicity
Inavolisib was not mutagenic in the bacterial mutagenesis assay.

Inavolisib showed clastogenicity *in vitro*; however, there was no evidence of genotoxicity (clastogenicity, aneugenicity, or DNA damage) induced *in vivo* by inavolisib in the micronucleus and comet study in rats at doses up to a maximum tolerated dose (MTD) of 16.1 times the exposure at a clinical dose of 9 mg.

Carcinogenicity
No carcinogenicity studies have been conducted with inavolisib.

Reproductive toxicity
No dedicated fertility studies have been conducted with inavolisib.

In male rats, dose-dependent atrophy of the prostate and seminal vesicle was observed, as well as decreased organ weights without a microscopic correlate in the epididymis and testis (at $\geqslant$ 0.4 times the AUC exposure at a clinical dose of 9 mg). In the 1-month toxicity study conducted in dogs, focal inspissation of seminiferous tubule contents and multinucleated spermatids in the testis were observed, as well as epithelial degeneration/necrosis in the epididymis (at $\geqslant$ 2 times the AUC exposure at a clinical dose of 9 mg). However, in the 3-month toxicity study conducted in dogs at similar exposures, there were no inavolisib-related microscopic findings in the testes or epididymides, or effects on sperm concentration, motility, or morphology.

In the 4-week toxicity study conducted in rats, minimal to mild and reversible atrophy in the uterus and vagina were observed in female rats, as well as a decrease in the size of ovarian follicles (at $\geqslant$ 1.1

times the exposure at a clinical dose of 9 mg). Findings suggestive of an interruption/alteration of the oestrus cycle were observed (at ⩾ 1.5 times the exposure at a clinical dose of 9 mg) in the 3-month toxicity study conducted in rats. Potential effects on the female reproductive cycle are expected to be reversible in a clinical setting.

An embryo-foetal development study conducted in Sprague Dawley rats identified inavolisib-related dose-dependent effects on embryo-foetal development (at ⩾ 0.8 times the exposure at a clinical dose of 9 mg) that included decreases in foetal body weight and placental weight, post-implantation loss, lower foetal viability, and teratogenicity (external, visceral, and skeletal malformations in the foetus). The NOAEL was 0.24 times the exposure at a clinical dose of 9 mg.

Other information

Shelf life
Do not use this medicine after the expiry date ("EXP") stated on the pack.

Special precautions for storage
Keep out of the reach of children.

Do not store above 30 °C.

Disposal of unused/expired medicinal products
The release of medicines into the environment should be minimised. Medicinal products should not be disposed of in wastewater. Avoid disposal in household waste.

Dispose of unused medicinal products and/or waste in accordance with local requirements.

Packs
Itovebi 3 mg film-coated tablets: 28 (4 blister packs with 7 film-coated tablets)
Itovebi 9 mg film-coated tablets: 28 (4 blister packs with 7 film-coated tablets)

Medicine: Keep out of reach of children

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