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TAB-ITO-2025 12

Itovebi®

inavolisib

1. DESCRIPTION

1.1 THERAPEUTIC / PHARMACOLOGIC CLASS OF DRUG

Pharmacotherapeutic group: Antineoplastic agents, PI3K inhibitors

ATC Code: L01EM06

1.2 TYPE OF DOSAGE FORM

Film-coated tablet

1.3 ROUTE OF ADMINISTRATION

Oral

1.4 STERILE / RADIOACTIVE STATEMENT

Not applicable

1.5 QUANTITATIVE AND QUALITATIVE COMPOSITION

1.5.1 Active Ingredients

Active ingredient: inavolisib

Itovebi 3 mg film-coated tablet is red and round convex-shaped with an "INA 3" debossing on one side. Each 3 mg film-coated tablet contains 3 mg inavolisib.

Itovebi 9 mg film-coated tablet is pink and oval-shaped with an "INA 9" debossing on one side. Each 9 mg film-coated tablet contains 9 mg inavolisib.

1.5.2 Excipients

Tablet Core- Microcrystalline Cellulose (PH-102), Lactose 316 Spray Dried, Sodium Starch Glycolate, Magnesium Stearate

Film-Coating Mixture- Purified Water, Polyvinyl Alcohol, Partially Hydrolyzed, Titanium Dioxide, Macrogol/Polyethylene Glycol, Talc and Iron Oxide Red (for the 3mg tablet) and Iron Oxide Red and Iron Oxide Yellow (for the 9mg tablet)

2. CLINICAL PARTICULARS

2.1 THERAPEUTIC INDICATION(S)

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.

2.2 DOSAGE AND ADMINISTRATION

2.2.1 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.

2.2.2 Dose Recommendation

The recommended dose of 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 prescribing information for palbociclib and fulvestrant being used for 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.

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

2.2.3 Duration of Treatment

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

2.2.4 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.

2.2.5 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.

Hyperglycemia

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 optimized in all patients. Evaluate patients for renal impairment prior to treatment with Itovebi (see section 2.2.6.3 Special Dosage Instructions, Renal Impairment and section 3.2 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 2.4.1 *Warnings and Precautions, General*).

Table 2: Dose Modification and Management for Hyperglycemia

Fasting Glucose Levels[a]	Recommendation[b]
> ULN to 160 mg/dL (>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-hyperglycemic medications[c] for patients with risk factors for hyperglycemia[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-hyperglycemic medication[c,e]. • Resume Itovebi at the same dose level.
> 250 to 500 mg/dL (> 13.9 – 27.8 mmol/L)	• Interrupt Itovebi. • Initiate or intensify anti-hyperglycemic 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) in ≥ 8 days, resume Itovebi at one lower dose level (see Table 1). • If fasting glucose level > 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 one lower dose level (see Table 1).
> 500 mg/dL (> 27.8 mmol/L)	• Interrupt Itovebi. • Initiate or intensify anti-hyperglycemic 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 one lower dose level (see Table 1). • If fasting glucose level > 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 initiation of treatment. Fasting glucose levels referenced in this table reflect hyperglycemia 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 2.4.1 *Warnings and Precautions, General*).

[c] Initiate applicable anti-hyperglycemic medications, such as metformin, sodium-glucose cotransporter-2 (SGLT2) inhibitors, dipeptidyl peptidase-4 [DPP-4] inhibitors, or insulin sensitizers (such as thiazolidinediones), and review the respective prescribing information for dosing and dose titration recommendations, including local hyperglycemia treatment guidelines. Metformin was recommended in the INAVO120 study as the preferred initial agent. See section 2.6.1 *Description of selected adverse drug reactions*.

[d] Risk factors for hyperglycemia include, but are not limited to, (pre)diabetes, HbA_{1C} ≥ 5.7%, BMI ≥ 30 kg/m^2, ≥ 45 years of age, history of gestational diabetes, and family history of diabetes mellitus (see section 2.4.1 *Warnings and Precautions, General*).

[e] In the INAVO120 study, short-term insulin was allowed to control blood glucose levels with a goal of maintaining blood glucose levels on only oral agents once the acute episode 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 (see Table 1).
Grade 3	• Withhold Itovebi until recovery to Grade ≤ 1. • Initiate or intensify appropriate medical therapy. Resume Itovebi at one lower dose level (see Table 1).
Grade 4	• Permanently discontinue Itovebi.
[a] Based on CTCAE version 5.0.	

Other Adverse Reactions

Table 4: Dose Modification and Management for Other Adverse Reactions

Grade[a]	Recommendation
For all grades: Initiate supportive therapy and monitor as clinically indicated.	
Grade 1	• No 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 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.	

2.2.6 Special Dosage Instructions

2.2.6.1 Pediatric Use

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

2.2.6.2 Geriatric Use

No dose adjustment of Itovebi is required in patients ≥ 65 years of age. For details on geriatric data, see section 2.5.5 *Geriatric Use.*

2.2.6.3 Renal Impairment

No dose adjustment is required in patients with mild renal impairment (eGFR ≥ 60 to < 90mL/min). The recommended starting dose of Itovebi for patients with moderate renal impairment (eGFR 30 to < 60 mL/min) is 6 mg orally once daily, and 3 mg orally once daily for patients with severe renal impairment (eGFR < 30 mL/min). For details on renal impairment data, see section 2.5.6 *Renal Impairment*.

2.2.6.4 Hepatic Impairment

No dose adjustment is required in patients with mild hepatic impairment (total bilirubin > ULN to ≤ 1.5 × 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 2.5.7 Hepatic Impairment.

2.3 CONTRAINDICATIONS

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

2.4 WARNINGS AND PRECAUTIONS

2.4.1 General

Hyperglycemia

Severe cases of hyperglycemia, including complications such as life-threatening ketoacidosis, have been reported in patients treated with Itovebi.

The safety of Itovebi in patients with Type 1 diabetes mellitus or Type 2 diabetes mellitus requiring ongoing anti-hyperglycemic therapy has not been studied. Patients with a history of well-controlled Type 2 diabetes mellitus may require intensified anti-hyperglycemic 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 hyperglycemia should be considered before initiating Itovebi.

Hyperglycemia was managed with anti-hyperglycemic medication (see section 2.6.1 *Description of selected adverse reactions*).

Before initiating treatment with Itovebi, fasting glucose levels (FPG or FBG) and HbA_{1C} levels should be tested, and fasting glucose levels should be optimized in all patients. Patients should also be advised of the signs and symptoms of hyperglycemia (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 hyperglycemia including, but not limited to, (pre)diabetes, HbA_{1C} ≥ 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-hyperglycemic treatment should be initiated or adjusted as required (see section 2.2.5 *Dose Modification*). Metformin prophylaxis was recommended for patients with risk factors for hyperglycemia in the INAVO120 study.

If a patient experiences hyperglycemia after initiating treatment with Itovebi, fasting glucose levels should be monitored more closely as clinically indicated. During treatment with anti-hyperglycemic 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 hyperglycemia or who experience hyperglycemia.

Based on the severity of the hyperglycemia, Itovebi may require dose interruption, reduction, or discontinuation as described in Table 2 (see section 2.2.5 *Dose Modification*). All patients should be instructed on lifestyle changes (e.g., dietary modifications, physical activity).

Stomatitis

Stomatitis has been reported in patients treated with Itovebi (see section 2.6.1 Description of selected adverse reactions). Based on the severity of stomatitis, Itovebi dosing may be interrupted, reduced, or permanently discontinued (see Table 3). Corticosteroid mouthwash was recommended for prophylaxis of stomatitis for all patients in clinical studies.

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 2.6.1 Description of selected adverse reactions). Dietary modifications (e.g., avoiding spicy foods) should be considered.

Embryo-fetal 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 3.3.3 *Developmental Toxicity*). 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 1 week after the last dose of Itovebi (see section 2.5.1 *Females and Males of Reproductive Potential*).

Diarrhoea

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

Diarrhea 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-diarrheal 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 diarrhea. Advise patients to increase oral fluids and start anti-diarrheal treatment at the first sign of diarrhea while taking Itovebi. Withhold, reduce dose, or permanently discontinue Itovebi based on severity (see section 2.2 *Dosage and Administration).*

2.4.2 Drug Abuse and Dependence

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

2.4.3 Ability to Drive and Use Machines

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

2.5 USE IN SPECIAL POPULATIONS

2.5.1 Females and Males of Reproductive Potential

2.5.1.1 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 3.3.4 *Fertility*).

2.5.1.2 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.

2.5.1.3 Contraception

Female

Patients should be advised to use effective non-hormonal contraception during treatment with Itovebi and for 1 week after the last dose of Itovebi (see section 2.4.1 *Warnings and Precautions, 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 1 week after the last dose of Itovebi (see section 2.4.1 *Warnings and Precautions, General*).

2.5.2 Pregnancy

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 3.3.3 *Developmental Toxicity*).

2.5.2.1 Labor and Delivery

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

2.5.3 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.

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

2.5.5 Geriatric Use
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 suggest 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.

2.5.6 Renal Impairment
No dose adjustment is required in patients with mild renal impairment (eGFR 60 to < 90 mL/min) based on population pharmacokinetic analysis. The recommended starting dose of Itovebi for patients with moderate renal impairment (eGFR 30 to < 60 mL/min based on CKD-EPI) is 6 mg orally once daily. The recommended starting dose of Itovebi for patients with severe renal impairment (eGFR < 30 mL/min based on CKD-EPI) is 3 mg orally once daily. See section 2.2.6.3 *Special Dosage Instructions, Renal Impairment* and section 3.2.5.3 *Pharmacokinetics in Special Populations, Renal Impairment.*

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

2.5.7 Hepatic Impairment
No dose adjustment is required in patients with mild hepatic impairment (total bilirubin > ULN to ≤ 1.5 × 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 2.2.6 *Special Dosage Instructions* and section 3.2.5 *Pharmacokinetics in Special Populations*.

2.6 UNDESIRABLE EFFECTS
2.6.1 Clinical Trials
2.6.1.1 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, randomized study. The median duration of Itovebi treatment at the time of the analysis was 9.2 months (range: 0 to 38.8 months).

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 5. 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 5: 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
Anemia[b]	Very Common	37	6.2*	36.4	1.9*
Metabolism and Nutrition Disorders					
Hyperglycemia[c]	Very Common	59.9	5.6*	9.9	0
Decreased appetite	Very Common	23.5	0	8.6	0
Hypokalemia	Very Common	16	2.5	6.2	0
Hypocalcemia	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
Diarrhea	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.
[b] Includes anemia and hemoglobin decreased.
[c] Includes hyperglycemia, blood glucose increased, hyperglycemic 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 papular, 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

Hyperglycemia

In the INAVO120 study, hyperglycemia 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 hyperglycemia, the rate of new onset of hyperglycemia 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-hyperglycemic medication including metformin as a single agent or in combination with other anti-hyperglycemic medication (i.e., insulin, DPP-4 inhibitors, and sulfonylureas), SGLT2 inhibitors, thiazolidinediones, and DPP-4 inhibitors. In patients with fasting glucose levels > 160 mg/dL (> 8.9 mmol/L) with at least one level (see Table 2) improvement in fasting glucose levels (n=52), the median time to improvement from the first event was 8 days (range: 2 to 43 days).

Hyperglycemia 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

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.

Diarrhea

Diarrhea 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 diarrhea events were reported. The median time to first onset was 15 days (range: 2 to 602 days).

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

2.6.1.2 Laboratory Abnormalities
Table 6 summarizes treatment-emergent shifts from baseline in laboratory abnormalities in the INAVO120 study.

Table 6: Laboratory Abnormalities with a ≥ 2% (All Grades or Grade 3-4) Higher Incidence in the ItovebiArm in INAVO120

Laboratory Abnormality	Itovebi + Palbociclib + Fulvestrant[a]		Placebo + Palbociclib + Fulvestrant[b]	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Hematology				
Neutrophils (total, absolute) decreased	95.1	82	97	78.8
Hemoglobin 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
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.

2.6.2 Postmarketing Experience
The following adverse drug reactions have been identified from postmarketing experience with Itovebi (Table 7) 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 7: Adverse Drug Reactions Reported from Post-Marketing Experience

System Organ Class Adverse Reaction	Frequency Category
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.

2.7 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.

2.8 INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION
No pharmacokinetic drug-drug interaction studies have been conducted with Itovebi.

Effects of inavolisib on other drugs

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 tested (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6) at clinically relevant concentrations. Physiologically based pharmacokinetic modeling 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 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

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, 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.

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS
3.1 PHARMACODYNAMIC PROPERTIES
3.1.1 Mechanism of Action
Inavolisib is a highly potent and selective 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 tumor growth, which was more pronounced in combination with a CDK4/6 inhibitor (palbociclib) and endocrine therapy.

3.1.2 Clinical / Efficacy Studies
3.1.2.1 Locally advanced or metastatic breast cancer
INAVO120

The efficacy of Itovebi in combination with palbociclib and fulvestrant was evaluated in a Phase 3, randomized, 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 tumor 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 tumor tissue or plasma.

A total of 325 patients were randomized 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% 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 Tumors (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 8, Figure 1, and Figure 2. INV-assessed PFS results were supported by consistent results from blinded independent central review (BICR) assessment.

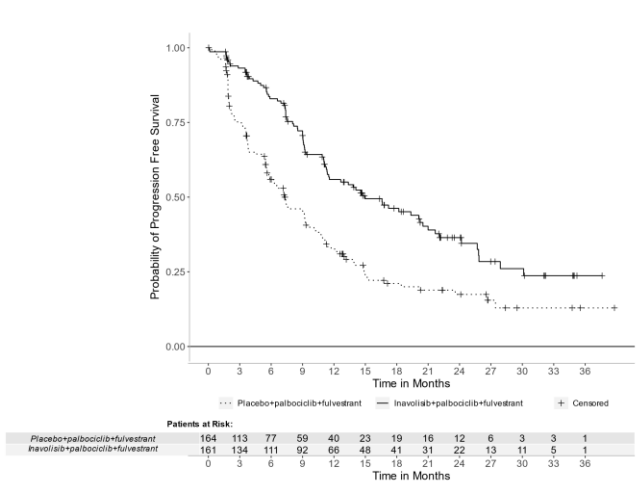
Table 8 Efficacy Results in Patients with Locally Advanced or Metastatic Breast Cancer in INAVO120

Efficacy Endpoint	Itovebi + Palbociclib + Fulvestrant N=161	Placebo + Palbociclib + Fulvestrant N=164
Primary Endpoint		
INV-Assessed Progression-Free Survival[a,b]		
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[c,d]		
Patients with event, n (%)	72 (44.7)	82 (50)

Median, months (95% CI)	34 (28.4, 44.8)	27 (22.8, 38.7)
Hazard ratio (95% CI)	0.67 (0.48, 0.94)	
p-value	0.0190	
Objective Response Rate[a,c,e]		
Patients with CR or PR, n (%)	101 (62.7)	46 (28)
95% CI	(54.8, 70.2)	(21.3, 35.6)
Difference in response rate, % (95% CI)	34.7 (24.5, 44.8)	
p-value	< 0.0001	
Best Overall Response[a,c,f]		
Patients with CR or PR, n (%)	109 (67.7)	53 (32.3)
95% CI	(59.9, 74.8)	(25.2, 40.1)
Difference in response rate, % (95% CI)	35.4 (25.2, 45.6)	
p-value	< 0.0001	
Duration of Response[a,c]		
Median DOR, months (95% CI)	19.2 (14.7, 28.3)	11.1 (8.5, 20.2)
Clinical Benefit Rate[c]		
Patients, n (%)	131 (81.4)	85 (51.8)
95% CI	(74.5, 87.1)	(43.9, 59.7)
Difference in response rate, % (95% CI)	29.5 (19.8, 39.3)	
p-value	< 0.0001	

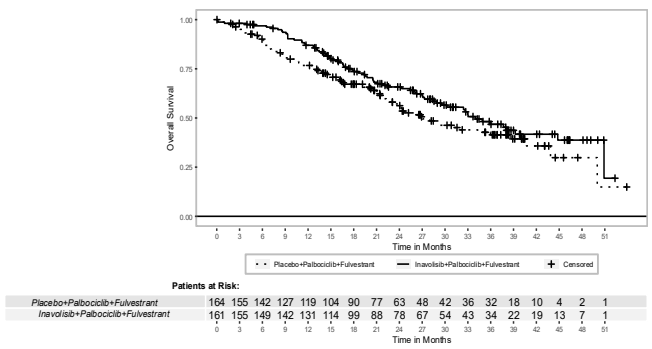
CI = confidence interval; CR = complete response; PR = partial response
[a] Per RECIST version 1.1.
[b] Based on primary analysis (clinical cutoff date: 29 September 2023).
[c] Based on final overall survival analysis (clinical cutoff date: 15 November 2024).
[d] The prespecified boundary for statistical significance was p < 0.0469.
[e] 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.
[f] 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).

Figure 2 Overall Survival in Patients with Locally Advanced or Metastatic Breast Cancer in INAVO120 (Final Analysis)



Patient-Reported Outcomes

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, was median 30.9 months [95% CI: 16.6, NE] in the Itovebi arm versus 18.1 months [95% CI: 13.1, NE] in the placebo arm.

Other patient-reported endpoints were measured by the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30) for 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) were observed in the Itovebi and placebo arms, respectively. No changes of 10 points or greater from baseline mean score was observed during the course of treatment. Additionally, median time to a confirmed ≥ 10-point, clinically meaningful deterioration was: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), and role function (25.7 [95% CI: 18.4, NE] and 24.2 [95% CI: 7.4, NE] months) in the Itovebi and placebo arms, respectively.

Patients also reported on seven selected symptomatic toxicities (diarrhea, 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 randomized 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, diarrhea, 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 diarrhea (Table 9). Rash was reported in 53.9% and 40.5% of patients in the Itovebi and placebo arms, respectively, post-baseline.

Table 9 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
Diarrhea (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, both arms (≥ 90% in each arm) reported increased levels of bother, mostly at levels 'moderate'/'somewhat' or less.

3.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetics of inavolisib were characterized in patients with locally advanced or metastatic *PIK3CA*-mutated solid tumors, 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 hyperglycemia (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.

3.2.1 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 AUC0-24 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 Cmax 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.

3.2.2 Distribution

Plasma protein binding of inavolisib ranged from 27% to 75% bound (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 tested (0.1 − 10 μM). In humans, the estimated steady state oral volume of distribution is 155 L and the blood-to-plasma ratio is approximately 0.794.

3.2.3 Metabolism

Minimal metabolism of inavolisib was detected in vitro in rat, dog, and 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 feces and 7% in urine) of the dose. Hydrolysis was the major metabolic pathway.

3.2.4 Elimination

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 feces (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.

3.2.5 Pharmacokinetics in Special Populations

3.2.5.1 Pediatric Population

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

3.2.5.2 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.

3.2.5.3 Renal Impairment

Population pharmacokinetic analyses indicated that mild renal impairment is not a significant covariate on Itovebi exposure. The pharmacokinetics of inavolisib in patients with mild renal impairment (eGFR 60 to < 90 mL/min) were similar to those in patients with normal renal function. Inavolisib AUC and C_{max} were 73% and 11% higher in patients with moderate renal impairment (eGFR 30 to < 60 mL/min), and 123% and 33% higher in patients with severe renal impairment (eGFR < 30 mL/min), respectively, when compared to patients with normal renal function (eGFR ≥ 90 mL/min).

3.2.5.4 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 × 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.

3.3 NONCLINICAL SAFETY

3.3.1 Genotoxicity and Mutagenicity

Inavolisib was not mutagenic in the bacterial mutagenesis assay.

Inavolisib showed clastogenicity in vitro; 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 doses up to a maximum tolerated dose (MTD) of 16.1 times the exposure at a clinical dose of 9 mg.

3.3.2 Carcinogenicity

No carcinogenicity studies with inavolisib have been conducted.

3.3.3 Development Toxicity

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

3.3.4 Fertility

No dedicated fertility studies with inavolisib have been conducted.

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 ≥ 0.4 times the exposure at a clinical dose of 9 mg). In the 1-month toxicity study in dogs, focal inspissation of seminiferous tubule contents and multinucleated spermatids in the testis and epithelial degeneration/necrosis in the epididymis were observed (at ≥ 2 times the exposure at a clinical dose of 9 mg). However, there were no inavolisib-related microscopic findings in the testes or epididymides or effects on sperm concentration, motility, or morphology in the 3-month dog toxicity study at similar exposures.

In female rats, minimal to mild and reversible atrophy in the uterus and vagina and decreased ovarian follicles were observed (at ≥ 1.1 times the exposure at a clinical dose of 9 mg) in the 4-week rat toxicity study. Findings suggestive of an interruption/alteration of the estrus cycle were observed (at ≥ 1.5 times the exposure at a clinical dose of 9 mg) in the 3-month rat toxicity study. Potential effects on female reproductive system cycling are expected to be reversible in a clinical setting.

3.3.5 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 pharmacologic effects of PI3K inhibition, was generally dose-dependent and reversible, and is considered to be clinically monitorable and/or manageable. Lens fiber degeneration observed in some rats (at ≥ 3.6 times the exposure at a clinical dose of 9 mg) was considered irreversible.

4. PHARMACEUTICAL PARTICULARS

4.1 STORAGE

As registered locally.
Store below 30°C (86°F).

Blister: Store in the original package in order to protect from moisture.

4.1.1 Shelf Life

As registered locally.

Blister: This medicine should not be used after the expiry date (EXP) shown on the blister packaging.

4.2 SPECIAL INSTRUCTIONS FOR USE, HANDLING AND DISPOSAL

4.2.1 Packs

Itovebi 3 mg and 9 mg Blister Pack

Alu/alu (aluminum/aluminium) blister sealed into a blister containing 7 film-coated tablets. Each carton contains 28 film-coated tablets (4 blisters per carton).

4.2.2 Disposal of Unused/Expired Medicines

The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Medicine: keep out of reach of children

Current at Dec 2025

Roche F. Hoffmann-La Roche Ltd, Basel, Switzerland