ITOVEBI®
Inavolisib film-coated tablets
For oral use
3 mg and 9 mg
Antineoplastic agent

Part 1: Health Professional Information

1 Indications

ITOVEBI® (inavolisib film-coated tablets), in combination with palbociclib and fulvestrant, is indicated for:

- the treatment of adult patients with endocrine-resistant, *PIK3CA*-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer, following recurrence on or after completing adjuvant endocrine treatment (see *14 Clinical Trials*).

2 Contraindications

- ITOVEBI is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see *6 Dosage Forms, Strengths, Composition and Packaging*.

3 Serious Warnings and Precautions Box

- **Hyperglycemia.** Severe case of hyperglycemia, including complications such as life-threatening ketoacidosis, have been reported in patients treated with ITOVEBI. ITOVEBI should not be administered to patients until their blood glucose levels are well controlled and stable. The safety of ITOVEBI in patients with Type 1 diabetes mellitus, or Type 2 diabetes mellitus requiring ongoing anti-hyperglycemic treatment have not been studied. Metformin prophylaxis is recommended for patients with risk factors for hyperglycemia.

4 Dosage and Administration

4.1 Dosing Considerations

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

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 test. *PIK3CA* mutation status should be established prior to initiation of ITOVEBI therapy.

The use of ITOVEBI is not recommended in patients with moderate (eGFR ≥ 30 to < 60 mL/min based on CKD-EPI) or severe (eGFR < 30 mL/min based on CKD-EPI) renal impairment.

4.2 Recommended Dose and Dosage Adjustment

Dose Recommendation:
The recommended dose of ITOVEBI is 9 mg taken orally once daily with or without food.

ITOVEBI should be administered in combination with palbociclib and fulvestrant. The recommended dose of palbociclib is 125 mg taken orally once daily for 21 consecutive days followed by 7 days off treatment to comprise a complete cycle of 28 days. The recommended dose of fulvestrant is 500 mg administered

intramuscularly on Days 0, 14, and 28, then every 28 days thereafter. Refer to the prescribing information for palbociclib and fulvestrant 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.

Duration of Treatment:

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

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.

The recommended dosage modifications of ITOVEBI for adverse reactions are summarized in Table 2.

Table 2: Dose Modification and Management for Adverse Reactions

Adverse Reaction	Severity	Recommendation
Hyperglycemia[b]	Fasting glucose level[a] > 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-hyperglycemic medications[c] for patients with risk factors for hyperglycemia[d]
	Fasting glucose level > 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.

Adverse Reaction	Severity	Recommendation
		• If fasting glucose level persists > 200 – 250 mg/dL (> 11.1 – 13.9 mmol/L) for 7 days under appropriate anti-hyperglycemic treatment, consultation with a healthcare professional experienced in the treatment of hyperglycemia is recommended.
	Fasting glucose 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*).
	Fasting glucose level > 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.
Stomatitis	Grade[f] 1	• No adjustment of ITOVEBI required. • Initiate or intensify appropriate medical therapy (e.g., corticosteroid-containing mouthwash) as clinically indicated.
	Grade[f] 2	• Withhold ITOVEBI until recovery to Grade ≤ 1. • Initiate or intensify appropriate medical therapy. Resume ITOVEBI at the same dose level.

Adverse Reaction	Severity	Recommendation
		• For recurrent Grade 2 stomatitis, withhold ITOVEBI until recovery to Grade ≤ 1, then resume ITOVEBI at one lower dose level (see *Table 1*).
	Grade [f] 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 [f] 4	• Permanently discontinue ITOVEBI
Diarrhea	Grade[f] 1	• No adjustment of ITOVEBI required. • Initiate appropriate medical therapy and monitor as clinically indicated.
	Grade [f] 2	• Withhold ITOVEBI until recovery to Grade ≤ 1, then resume ITOVEBI at the same dose level. • Initiate or intensify appropriate medical therapy and monitor as clinically indicated. • For recurrent Grade 2 diarrhea, withhold ITOVEBI until recovery to Grade ≤ 1, then resume ITOVEBI at one lower dose level (see *Table 1*).
	Grade [f] 3	• Withhold ITOVEBI until recovery to Grade ≤ 1, then resume ITOVEBI at one lower dose level (see *Table 1*). • Initiate or intensify appropriate medical therapy and monitor as clinically indicated.
	Grade [f] 4	• Permanently discontinue ITOVEBI.
Hematologic toxicities	Grade[f] 1, 2, or 3	• No adjustment of ITOVEBI required. • Monitor complete blood count and for signs or symptoms of hematologic toxicities as clinically indicated.
	Grade [f] 4	• Withhold ITOVEBI until recovery to Grade ≤ 2. • Resume ITOVEBI at the same dose level or reduce to one lower dose level as clinically indicated (see *Table 1*).
Other Adverse Reactions[g]	Grade[f] 1	• No adjustment of ITOVEBI required.
	Grade [f] 2	• Consider interruption of ITOVEBI, if clinically indicated, until recovery to Grade ≤ 1. • Resume ITOVEBI at the same dose level
	Grade [f] 3, first event	• Interrupt ITOVEBI until recovery to Grade ≤ 1.

Adverse Reaction	Severity	Recommendation
		• Resume ITOVEBI at the same dose level or at one lower dose level based on clinical evaluation (see *Table 1*).
	Grade [f] 3, recurrent	• Interrupt ITOVEBI until recovery to Grade ≤ 1. • Resume ITOVEBI at one lower dose level (see *Table 1*).
	Grade [f] 4	• Permanently discontinue ITOVEBI.

ULN = upper limit of normal

[a]Fasting glucose levels referenced in this table reflect hyperglycemia grading according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

[b] 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. After initiating treatment with ITOVEBI, patient fasting glucose (FPG or FBG) levels should be monitored or self-monitored based on the recommended schedule (see *7 Warnings and Precautions, Endocrine and Metabolism*). Metformin prophylaxis was recommended for patients with risk factors for hyperglycemia in the INAVO120 study (see *7 Warnings and Precautions, Endocrine and Metabolism, Hyperglycemia*).

[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) or dipeptidyl peptidase-4 [DPP-4] inhibitors, 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 *8.2 Clinical Trial Adverse Reactions*.

[d] Risk factors for hyperglycemia include, but are not limited to, (pre)diabetes, $HbA_{1C} \geq 5.7\%$, BMI ≥ 30 kg/m^2, ≥ 45 years of age, history of gestational diabetes, and family history of diabetes mellitus (see *7 Warnings and Precautions, Endocrine and Metabolism, Hyperglycemia*).

[e] In the INAVO120 study, short-term insulin was allowed to control blood glucose levels when oral agents were inadequate, with the objective of returning to oral-only treatment after the acute episode resolved.

[f] Based on CTCAE version 5.0.

[g] For all grades: Initiate supportive therapy and monitor as clinically indicated.

Pediatric Use (<18 years)

The safety and efficacy of ITOVEBI in pediatric patients (< 18 years of age) have not been established (see sections *7.1.3 Pediatrics* and *10.3 Pharmacokinetics*).

Geriatric Use (≥ 65 years)

No dose adjustment of ITOVEBI is recommended in patients ≥ 65 years of age. For details on geriatric data, see *7.1.4 Geriatrics* (≥ 65 years of age) and *10.3 Pharmacokinetics*.

Renal Impairment

No dose adjustment is recommended in patients with mild renal impairment (eGFR ≥ 60 to < 90 mL/min). The safety and efficacy of ITOVEBI have not been established in patients with moderate (eGFR ≥ 30 to < 60 mL/min based on CKD-EPI) or severe (< 30 mL/min based on CKD-EPI) renal impairment. The use of ITOVEBI is not recommended in patients with moderate or severe renal impairment (See *10.3 Pharmacokinetics, Renal Insufficiency*).

Hepatic Impairment

No dose adjustment is recommended 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 *10.3 Pharmacokinetics, Hepatic Insufficiency*.

4.3 Administration

Advise patients to take ITOVEBI at approximately the same time each day.

Swallow ITOVEBI tablet(s) whole. Do not chew, crush, or split prior to swallowing.

4.4 Missed Dose

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.

5 Overdose

There is limited experience of overdose with ITOVEBI in clinical trials.

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

6 Dosage Forms, Strengths, Composition and Packaging

Table 3: Dosage Forms, Strengths, and Composition

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Tablets 3 mg inavolisib	Lactose, magnesium stearate, microcrystalline cellulose, sodium starch glycolate, Opadry II red 85F250110-CN (Iron oxide red, polyethylene glycol, polyvinyl alcohol, purified water*, talc, titanium dioxide)
	Tablet 9 mg inavolisib	Lactose, magnesium stearate, microcrystalline cellulose, sodium starch glycolate, Opadry II pink 85F240025-CN (Iron oxide red, Iron oxide yellow, polyethylene glycol, polyvinyl alcohol, purified water*, talc, titanium dioxide)

*Removed during processing

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.

Packaging:

ITOVEBI 3 mg and 9 mg Blister Card
Alu/alu (aluminum/aluminium) blister sealed into a blister card containing 7 film-coated tablets. Each carton contains 28 film-coated tablets (4 blister cards per carton).

7 Warnings and Precautions

Dependence, Tolerance and/or Abuse Liability

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

Driving and Operating Machinery

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

Endocrine and Metabolism

Hyperglycemia: Severe cases of hyperglycemia, including ketoacidosis, have been reported in patients treated with ITOVEBI.

Delayed or without appropriate treatment, ketoacidosis could be fatal. Ketoacidosis with a fatal outcome has occurred in the postmarketing setting.

The safety of ITOVEBI in patients with Type 1 diabetes mellitus, or Type 2 diabetes mellitus requiring ongoing anti-hyperglycemic treatment have 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.

Consultation with a healthcare professional experienced in the treatment of hyperglycemia should be considered before initiating ITOVEBI. Fasting glucose monitoring at home should be considered for patients who have risk factors for hyperglycemia or who experience hyperglycemia.

Before initiating treatment with ITOVEBI, test fasting glucose levels (FPG or FBG), HbA_{1C} levels. ITOVEBI should not be initiated until fasting glucose is optimized (see *Monitoring and Laboratory Tests*). Patients should 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.

Anti-hyperglycemic treatment should be initiated or adjusted as required (see *4.2 Recommended Dose and Dosage Adjustment*). In patients with risk factors for hyperglycemia, metformin prophylaxis was allowed in the INAVO120 study. Therefore, metformin prophylaxis is similarly recommended for ITOVEBI in patients with risk factors for hyperglycemia.

Based on the severity of the hyperglycemia, ITOVEBI may require dose interruption, reduction, or discontinuation as described in Table 2 (see *4.2 Recommended Dose and Dosage Adjustment*). All patients should be instructed on lifestyle changes (e.g., dietary modifications, physical activity).

In the INAVO120 study, adverse reactions of hyperglycemia of any grade was reported in 60% of patients treated with ITOVEBI in combination with palbociclib and fulvestrant; Grade 2 and Grade 3 events were reported in 38% and 6% of patients respectively.

In INAVO120, 46% (74/162) of patients who received ITOVEBI were treated with oral anti-hyperglycemic medications and 7% (11/162) were treated with insulin to manage increased fasting glucose. In patients who experienced increased fasting glucose of > 8.9 mmol/L, 96% (52/54) had an improvement in fasting glucose of at least one grade level with a median time to improvement of 8 days (range: 2 to 43 days).

Among patients with hyperglycemia, the median time to first onset was 7 days (range: 2 to 955 days). Hyperglycemia led to dose interruption in 28%, to dose reduction in 2.5%, and to discontinuation of ITOVEBI in 1.2% of patients.

Gastrointestinal

Stomatitis: Severe cases of stomatitis can occur in patients treated with ITOVEBI. Based on the severity of stomatitis, ITOVEBI dosing may be interrupted, reduced, or permanently discontinued (see *Table 2*).

Stomatitis occurred in 51% of patients treated with ITOVEBI in combination with palbociclib and fulvestrant, including Grade 3 events in 6% of patients. The median time to first onset was 13 days (range: 1 to 610 days). Stomatitis led to interruption of ITOVEBI in 10%, to dose reduction in 3.7%, and to discontinuation of ITOVEBI in 0.6% of patients.

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

Patients should be advised to start an alcohol-free corticosteroid mouthwash and to avoid alcohol- or peroxide-containing mouthwashes as they may exacerbate the condition. Dietary modifications (e.g., avoiding spicy foods) should be considered.

Monitor patients for signs and symptoms of stomatitis. Withhold, reduce dose, or permanently discontinue ITOVEBI based on severity (see *4.2 Recommended Dose and Dosage Adjustment*).

Diarrhea: 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 2 events in 16.7%, and 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 antidiarrheal treatment at the first sign of diarrhea while taking ITOVEBI. Withhold, reduce dose, or permanently discontinue ITOVEBI based on severity (see *4.2 Recommended Dose and Dosage Adjustment*).

Monitoring and Laboratory Tests

Hyperglycemia

Increased fasting glucose occurred in 85% of patients treated with ITOVEBI, including 22% of patients with Grade 2 (FPG > 8.9 to 13.9 mmol/L), 12% with Grade 3 (FPG > 13.9 to 27.8 mmol/L), and 0.6% with Grade 4 (FPG > 27.8 mmol/L) events according to CTCAE v4.03 (See *Table 6*).

Patients should be monitored for hyperglycemia (see *Table 4*).

Table 4: Recommended Schedule for Monitoring Fasting Glucose and HbA1c Levels

	Recommended schedule for the monitoring of fasting glucose and HbA1c levels in all patients treated with ITOVEBI	**Recommended schedule for the monitoring of fasting glucose and HbA1c levels in patients with risk factors for hyperglycemia[a] treated with ITOVEBI**
At screening, 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.	
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.	Fasting glucose levels should be monitored or self-monitored more frequently as clinically indicated. Metformin prophylaxis is recommended for patients with risk factors for hyperglycemia. More frequent fasting glucose testing is required in patients with concomitant use of corticosteroids, intercurrent infections, or other conditions which may require intensified glycemia management to prevent worsening of impaired glucose metabolism and potential complications, including diabetic ketoacidosis. Monitoring of HbA_{1C} and ketones (preferably in blood), in addition to fasting glucose, is recommended in these patients.
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.	

[a] Risk factors for hyperglycemia include, but not limited to, (pre)diabetes, $HbA_{1C} \geq 5.7\%$, BMI ≥ 30 kg/m^2, ≥ 45 years of age, history of gestational diabetes, and family history of diabetes mellitus.

Renal

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

Reproductive Health

Fertility

There are no clinical studies conducted to evaluate the effect of ITOVEBI on fertility. Based on animal studies, inavolisib may impact fertility in both females and males of reproductive potential (see *16 Non-Clinical Toxicology, Reproductive and Developmental Toxicology*).

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 *7.1 Special Populations*).

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 effective contraception during treatment with ITOVEBI and for 1 week after the last dose of ITOVEBI.

Pregnancy Testing

The pregnancy status of females of reproductive potential should be verified prior to initiating ITOVEBI (see *7.1 Special Populations*).

7.1 Special Populations

7.1.1 Pregnancy

There are no clinical data available on the use of ITOVEBI during pregnancy. Based on animal studies and the mechanism of action, ITOVEBI is expected to cause harm to the developing fetus and/ or result in a loss of pregnancy. Studies in pregnant animals demonstrated that ITOVEBI lead to decreased fetal body and placental weight, post-implantation loss, fetal death, and teratogenicity (see *16 Non-Clinical Toxicology*). Therefore, ITOVEBI should not be used during pregnancy.

If ITOVEBI is used during pregnancy or if a patient becomes pregnant while on treatment or a female is impregnated by a male partner being treated with ITOVEBI, the pregnant individual must be informed of the potential hazard to the fetus. Women of child bearing potential should avoid becoming pregnant by using effective non-hormonal contraception during treatment and for at least 1 week after the last dose of ITOVEBI.

Labour and Delivery

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

7.1.2 Breast-feeding

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, women should not breastfeed during ITOVEBI treatment and for 1 week after the last dose.

7.1.3 Pediatrics (< 18 years of age)

Pediatrics (< 18 years of age): No data are available in pediatric patients. The safety and efficacy of ITOVEBI in pediatric patients have not been established.

7.1.4 Geriatrics (≥ 65 years of age)

Geriatrics (≥ 65 years of age): 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.

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%).

Clinical studies of ITOVEBI did not include sufficient number of patients ≥ 65 years of age to assess whether there are differences in safety or efficacy.

8 Adverse Reactions

8.1 Adverse Reaction Overview

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 most common adverse reactions (ADRs) in patients treated with ITOVEBI in combination with palbociclib and fulvestrant (reported at a frequency ≥ 20%) were, hyperglycemia, stomatitis, diarrhea, thrombocytopenia, fatigue, anemia, nausea, rash, decreased appetite, and headache. Serious adverse events occurred in 24% of patients receiving ITOVEBI plus palbociclib and fulvestrant. Serious adverse reactions in ≥ 1% of patients receiving ITOVEBI plus palbociclib and fulvestrant included anemia (1.9%), diarrhea (1.2%), and urinary tract infection (1.2%).

Fatal adverse events occurred in 3.7% of patients who received ITOVEBI with palbociclib and fulvestrant, including (0.6% each) acute coronary syndrome, cerebral hemorrhage, cerebrovascular accident, COVID-19 infection, and gastrointestinal hemorrhage. None of the fatal adverse events were assessed as related to study treatment.

Adverse events led to permanent discontinuation of ITOVEBI in 6.2% of patients. The adverse events leading to discontinuation of ITOVEBI were hyperglycemia (1.2%), and (0.6% each) stomatitis, gastric ulcer, intestinal perforation, anal abscess, ALT increased, decreased weight, bone pain, musculoskeletal pain, transitional cell carcinoma, and acute kidney injury.

Adverse events led to dose interruptions of ITOVEBI in 69.1%% of patients, most frequently (≥ 2%) from hyperglycemia (28%), neutropenia (23%), COVID-19 infection (16%), stomatitis (10%), diarrhea (6.8%), thrombocytopenia (4.9%), anemia (4.3%), upper respiratory tract infection (4.3%), decreased white blood count (3.7%), pyrexia (3.1%), nausea (2.5%), and fatigue (2.5%).

Dose reductions of ITOVEBI due to adverse events occurred in 14% of patients. The most frequent adverse reactions leading to dose reduction of ITOVEBI in ≥ 2% of patients were stomatitis (3.7%) and hyperglycemia (2.5%).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials, therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

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 (≥ 10% 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	
	All Grades n (%)	Grade 3-4 n (%)	All Grades n (%)	Grade 3-4 n (%)
Blood and Lymphatic System Disorders				
Thrombocytopenia[a]	78 (48)	23 (14)	73 (45)	7 (4)
Anemia[b]	60 (37)	10 (6)*	59 (36)	3 (2)*
Gastrointestinal Disorders				
Stomatitis[c]	83 (51)	9 (6)*	43 (27)	0
Diarrhea	78 (48)	6 (4)*	26 (16)	0
Nausea	45 (28)	1 (1)*	27 (17)	0
Vomiting	24 (15)	1 (1)*	8 (5)	2 (1)*
General Disorders and Administration Site Conditions				
Fatigue	61 (38)	3 (2)*	41 (25)	2 (1)*
Infections and Infestations				
COVID-19	37 (23)	3 (2)	17 (11)	1 (1)
Urinary Tract Infection	21 (13)	2 (1)*	12 (7)	0
Investigations				
Alanine aminotransferase increased	28 (17)	6 (4)*	21 (13)	2 (1)*
Weight decreased	28 (17)	6 (4)*	1 (1)	0
Metabolism and Nutrition Disorders				
Hyperglycemia[d]	97 (60)	9 (6)*	16 (10)	0
Decreased appetite	38 (24)	0	14 (9)	0
Hypokalemia	26 (16)	4 (3)	10 (6)	0
Nervous System Disorders				
Headache	34 (21)	0	22 (14)	0
Skin and Subcutaneous Tissue Disorders				
Rash[e]	41 (25)	0	28 (17)	0
Alopecia	30 (19)	0	9 (6)	0
Dry skin[f]	21 (13)	0	7 (4)	0

System Organ Class Adverse Reaction	ITOVEBI + Palbociclib + Fulvestrant n=162		Placebo + Palbociclib + Fulvestrant n=162	
	All Grades n (%)	Grade 3-4 n (%)	All Grades n (%)	Grade 3-4 n (%)
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 aphthous ulcer, glossitis, glossodynia, lip ulceration, mouth ulceration, mucosal inflammation, and stomatitis. [d] Includes hyperglycemia, blood glucose increased, hyperglycemic crisis, glycated serum protein increased, glucose tolerance impaired, diabetes mellitus, Type 2 diabetes mellitus, and glycosylated hemoglobin increased. [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.				

In Table 5 in addition to hyperglycemia, stomatitis, and diarrhea, an increase in Grade 3-4 adverse events with the addition of ITOVEBI to the combination of palbociclib and fulvestrant occurred in the following adverse drug reactions: urinary tract infection, thrombocytopenia, anemia, hypokalemia, nausea, fatigue, alanine aminotransferase increased, and weight decreased.

8.3 Less Common Clinical Trial Adverse Reactions

Other clinically relevant adverse reactions occurring in < 10% of patients treated with ITOVEBI in combination with palbociclib and fulvestrant or with < 5% (all grades) or < 2% (Grade 3-4) greater incidence in the ITOVEBI arm than the placebo arm are presented below:

Metabolism and Nutrition Disorders: Hypocalcemia (all grades: 9%; Grade 3: 1%; no Grade 4 events).

Eye Disorders: Dry eye (all grades: 9%; Grade 3-4: 0%).

Gastrointestinal Disorders: Abdominal pain, including abdominal pain, abdominal pain upper, abdominal pain lower (all grades: 15%; Grade 3: 1%; no Grade 4 events); dysgeusia, including dysgeusia, ageusia, and hypogeusia (all grades: 9%; Grade 3-4: 0%); dyspepsia (all grades: 8%; Grade 3-4: 0%)

Investigations: Blood insulin increased (all grades: 6%; Grade 3-4: 0%)

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

The following table 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 ITOVEBI Arm in INAVO120

Laboratory Abnormality	ITOVEBI + Palbociclib + Fulvestrant[a]		Placebo + Palbociclib + Fulvestrant[b]	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Hematology				
Glucose (fasting) increased[c]	85.4	12.1	42.9	0
Hemoglobin decreased	87.5	7.5*	85.1	2.5*
Lymphocytes (absolute) decreased	72.1	9	68.2	14.4
Neutrophils (total, absolute) decreased	95.1	82	97	78.8
Platelets decreased	83.8	15.6	71.4	3.7
Chemistry				
ALT increased	34.4	3.1*	28.6	1.2*
Albumin decreased	25	0.6*	18.1	0
Calcium decreased	41.9	3.1	31.7	3.7
Creatinine increased	37.5	1.9*	29.8	1.2*
Glucose (fasting) decreased[c]	6.4	0	3.2	0
Lipase (fasting) increased	16	1.4*	6.9	0
Magnesium decreased	26.9	0.6	20.5	0
Potassium decreased	37.5	6.2	20.5	0.6*
Sodium decreased	27.5	2.5*	18.6	2.5

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.

8.5 Post-Market Adverse Reactions

The following adverse drug reaction has been identified from post marketing experience with ITOVEBI based on spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Metabolism and Nutrition Disorders: Ketoacidosis, including a fatal outcome (frequency unknown).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

Pusat Farmakovigilans/MESO Nasional
Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat, Narkotika, Psikotropika, Prekursor dan Zat Adiktif
Badan Pengawas Obat dan Makanan

Address: Jl. Percetakan Negara No. 23, Jakarta Pusat, 10560
Email: pv-center@pom.go.id
Website: https://e-meso.pom.go.id

PT Roche Indonesia
Patient Safety
Email: indonesia.safety@roche.com
Phone: +62 21 3041 3000
Website: https://medinfo.roche.com/id/id.html

9 Drug Interactions

9.1 Drug Interactions Overview

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.

Inavolisib is a time-dependent inhibitor and an inducer of CYP3A. It is also an inducer of CYP2B6.

Inavolisib is a substrate of P-gp and BCRP.

9.2 Drug-Behaviour Interactions

There are no drug-behavioural interactions known at this time.

9.3 Drug-Drug Interactions

No pharmacokinetic drug-drug interaction clinical studies have been conducted with inavolisib.

Effects of inavolisib on other drugs

CYP Substrates

In vitro studies show that inavolisib is a time-dependent inhibitor and an inducer of CYP3A. It is also an inducer of CYP2B6. Inavolisib does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 and does not induce CYP1A2 at clinically relevant concentrations.

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

Transporters

In vitro studies have shown that inavolisib is not a substrate of OATP1B1, OATP1B3, OCT1, OCT2, OAT3, OAT1, MATE1, or MATE2K, but is a substrate of P-gp and BCRP.

9.4 Drug-Food Interactions

No clinically meaningful effect of food on inavolisib exposure was observed in a clinical study.

9.5 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.6 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 Clinical Pharmacology

10.1 Mechanism of Action

Inavolisib is a selective inhibitor of the phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) with activity predominantly against the catalytic subunit alpha isoform protein (p110α; encoded by the *PIK3CA* gene). In vitro, inavolisib lead to the degradation of mutated p110α, inhibited the activity of downstream PI3K pathway target (AKT), 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 increased when combined with the CDK4/6 inhibitor palbociclib and the endocrine therapy fulvestrant, as compared to any treatment alone or in doublet combinations.

10.2 Pharmacodynamics

Exposure-Response Relationships

The exposure-response relationship for the efficacy of inavolisib has not been fully characterized.

Higher systemic exposure of inavolisib was associated with higher incidence of Grade ≥ 2 anemia, Grade ≥ 2 hyperglycemia, and inavolisib dose modification due to adverse event.

Cardiac Electrophysiology

The ability of inavolisib to prolong the QT interval was assessed in a pharmacokinetic-pharmacodynamic analysis of 172 patients with locally advanced or metastatic *PIK3CA*-mutated solid tumours given 3 mg to 12 mg once daily dosing of inavolisib in an open-label, multi-arm uncontrolled study. At the recommended ITOVEBI dose, a mean increase in the QTc interval of > 20 ms is unlikely.

10.3 Pharmacokinetics

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 3 mg to 12 mg daily and in healthy subjects at 9 mg single dose.

Inavolisib pharmacokinetics are presented as geometric mean (geometric coefficient of variation [geo CV]%) following administration of the approved recommended dosage unless otherwise specified. The inavolisib steady-state AUC is 1,010 h*ng/mL (25%) and C_{max} is 69 ng/mL (27%). Inavolisib exhibited dose-proportional pharmacokinetics (steady-state AUC_{0-24} is proportional with dose) in patients with locally advanced or metastatic breast cancer over a dose range of 6 mg to 12 mg (0.7 to 1.3 times the recommended dose). Steady-state concentrations are predicted to be attained by day 5.

Table 7: Summary of Inavolisib Pharmacokinetic Parameters in Patients with Locally Advanced or Metastatic Breast Cancer

PK Parameter	**Steady State C_{max} (ng/mL)**	**Steady State T_{max} (h)**	**Single dose $t_{½}$ (h)**	**Steady State $AUC_{0-\tau}$ (h*ng/mL)**	**CL (L/hr)**	**Vd (L)**
Geometric Mean (Geo CV%)	69 (27%)	3 (0.5 to 4)	15 (22%)	1,010 (25%)	8.83 (29%)	155 (26%)

Parameters are presented as geometric mean values [geometric coefficient of variation (geo CV)%] or median (min to max) for T_{max}.

$AUC_{0-\tau}$: area under the curve from time zero to τ (τ = 24 hour for Inavolisib); C_{max}: maximum concentration; $t_{½}$: terminal half-life; T_{max}: time to reach C_{max}; V_d: apparent (oral) volume of distribution; CL: clearance

Parameters presented are derived using the population pharmacokinetics modelling except for the steady state T_{max} which is based on observed non-compartmental analysis.

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.

Distribution:

Plasma protein binding of inavolisib was 37% bound and did not appear to be concentration-dependent over the concentration range tested (0.1 - 10 µM). In humans, the estimated apparent (oral) volume of distribution is 155 L (26%) and the blood-to-plasma ratio is 0.794.

Metabolism:

Minimal metabolism of inavolisib was detected *in vitro* in human liver microsome incubations. This minimal oxidative metabolism appeared to be mediated by CYP3A4/5.

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 with no oxidative metabolites detected in plasma and representing approximately 2% of the dose in urine and feces.

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 15 hours (22%) following a single 9 mg dose. The estimated total clearance of inavolisib is 8.83 L/hr (29%).

Special Populations and Conditions

- **Pediatrics:** No data are available in pediatric patients; therefore, the safety and efficacy of inavolisib in this population have not been established. No studies have been conducted to investigate the pharmacokinetics of inavolisib in pediatric patients.

- **Geriatrics:** No clinically significant differences in inavolisib pharmacokinetics were noted between patients 65 years of age and older and those under 65 years based on population pharmacokinetic analysis.

- **Ethnic origin:** No clinically significant differences in inavolisib pharmacokinetics were noted based on the covariate of race (Asian or all others, with the majority Caucasian) according to population pharmacokinetic analysis.

- **Hepatic Insufficiency:** Population pharmacokinetic analyses indicated that mild hepatic impairment is not a significant covariate on inavolisib 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 (AST any value and total bilirubin 1.5-3.0 ULN) to severe (AST any value and total bilirubin > 3.0 ULN) hepatic impairment on inavolisib pharmacokinetics has not been studied.

- **Renal Insufficiency:** Population pharmacokinetic analyses indicated that mild renal impairment is not a significant covariate on inavolisib 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. The effect of moderate (eGFR ≥ 30 to < 60 mL/min based on CKD-EPI) and severe (eGFR < 30 mL/min) renal impairment on ITOVEBI pharmacokinetics has not been established. The use of ITOVEBI is not recommended in patients with moderate or severe renal impairment (see *4.2 Recommended Dose and Dosage Adjustment, Renal Impairment).*

- **Obesity:** No clinically significant differences in inavolisib pharmacokinetics were noted based on body weight (39 to 159 kg) according to population pharmacokinetic analysis.

11 Storage, Stability and Disposal

Store at room temperature, below 30°C.

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

12 Special Handling Instructions

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.

Part 2: Scientific Information

13 Pharmaceutical Information

Drug Substance

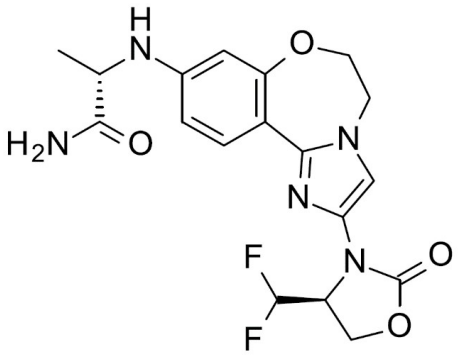
Proper/ Common name: inavolisib

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

Molecular formula and molecular mass: $C_{18}H_{19}F_2N_5O_4$.

407.37 g/mol, 407.37 (M_r) (free form)

Structural formula:



Physicochemical properties: White to off-white, greyish pink, greyish orange, or greyish yellow powder or powder with lumps

At lower pH-values, solubility of inavolisib increases. At pH 1, the solubility increases with time and equilibrium is not reached within the first 4 hour.

Aqueous Media or Buffer	pH Medium	pH, 24 h	Solubility at 37°C, 4 h (mg/mL)	Solubility at 37°C, 24 h (mg/mL)
0.1 N HCl	1.09	1.17	2.41	8.14
50 mM Acetate Buffer	4.50	4.47	0.06	0.05
50 mM Phosphate Buffer	6.80	6.78	0.05	0.04

14 Clinical Trials

14.1 Clinical Trials by Indication

Locally Advanced or Metastatic Breast Cancer

INAVO120

Study Demographics and Trial Design

Table 8: Summary of Patient Demographics for INAVO120 in Locally Advanced or Metastatic Breast Cancer Patients

Study #	Study Design	Dosage, route of administration and duration	Study subjects (n)	Median age (Range)	Sex n (%)
INAVO120	Phase 3, randomized, double-blind, placebo-controlled	ITOVEBI 9 mg/placebo QD PO + palbociclib 125 mg QD PO (21/7) + fulvestrant 500 mg Q4W IM (Days 0 and 14 of first 28-day cycle, and then Day 0 of each following 28-day cycle) Until PD or unacceptable toxicity	Total: n = 325 ITOVEBI + Palbo + Fulv: n = 161 Pbo+Palbo+Fulv: n = 164	54 years (range: 27-79)	F: 319 (98.2) M: 6 (1.8)

Fulv= fulvestrant; IM = intramuscular; Palbo = palbociclib; PD = progressive disease; PO = per oral; QD = once daily; Q4W = every 4 weeks.

The efficacy of ITOVEBI in combination with palbociclib and fulvestrant was evaluated in a Phase III, 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 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 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).

Primary endocrine resistance was defined as relapse while on the first 2 years of adjuvant endocrine therapy (ET) and secondary endocrine resistance was defined as relapse while on adjuvant ET after at least 2 years or relapse within 12 months of completing adjuvant ET.

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), and duration of response (DOR).

INAVO120

Study Results

Efficacy results are summarized in Table 9, and Figure 1. INV-assessed PFS results were supported by consistent results from blinded independent central review (BICR) assessment.

Table 9: **Efficacy Results in Patients with Locally Advanced or Metastatic Breast Cancer in INAVO120**

Efficacy Endpoint	**ITOVEBI + Palbociclib + Fulvestrant n=161**	**Placebo + Palbociclib + Fulvestrant n=164**
Primary Endpoint		
INV-Assessed Progression-Free Survival[a]		
Patients with event, n (%)	82 (50.9)	113 (68.9)
Median, months (95% CI)	15 (11.3, 20.5)	7.3 (5.6, 9.3)
Hazard ratio (95% CI)	0.43 (0.32, 0.59)	
p-value	< 0.0001	
Secondary Endpoints		
Overall Survival[b]		
Patients with event, n (%)	42 (26.1)	55 (33.5)
Median, months (95% CI)	NE (27.3, NE)	31.1 (22.3, NE)
Hazard ratio (95% CI)	0.64 (0.43, 0.97)	
p-value	0.0338	
Objective Response Rate[a,c]		
Patients with CR or PR, n (%)	94 (58.4)	41 (25)
95% CI	(50.4, 66.1)	(18.6, 32.3)
Duration of Response		
Median DOR, months (95% CI)	18.4 (10.4, 22.2)	9.6 (7.4, 16.6)

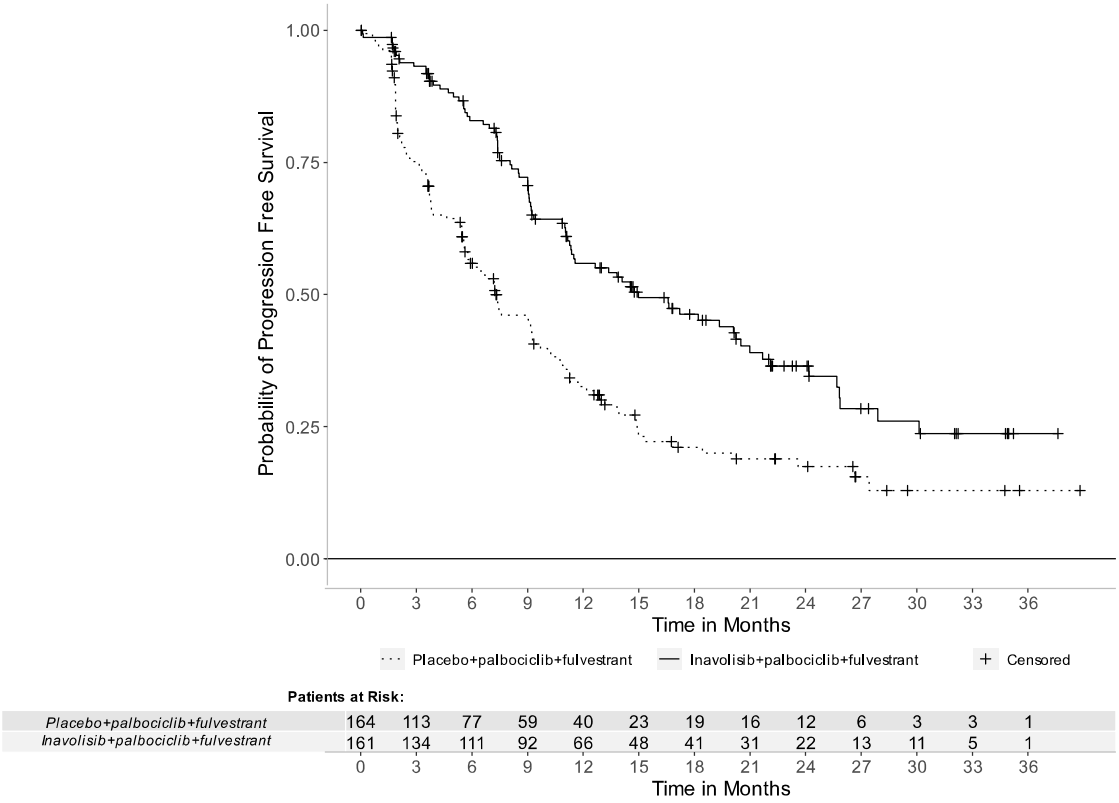
CI = confidence interval; CR = complete response; NE = not evaluable; PR = partial response

[a] Per RECIST version 1.1.

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

Efficacy Endpoint	ITOVEBI + Palbociclib + Fulvestrant n=161	Placebo + Palbociclib + Fulvestrant n=164
[c] ORR is defined as the proportion of patients with a CR or PR on two consecutive occasions ≥ 4 weeks apart, as determined by the investigator.		

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



The study met its primary endpoint of (INV)-assessed PFS. Addition of ITOVEBI to the combination of palbociclib and fulvestrant demonstrated a statistically significant improvement in median PFS, by reducing the risk of disease progression or death by 57% in patients with *PIK3CA*-mutated, HR-positive, HER2-negative LA/mBC (Stratified hazard ratio [HR] = 0.43 [95% CI: 0.32, 0.59], p < 0.0001). Prespecified PFS analyses per investigator assessment showed a generally consistent treatment effect in favour 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). At interim analysis, while the key secondary endpoint, OS, was not statistically significant, it is supportive of the primary endpoint.

Patient-Reported Outcomes

Patients 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 10). Rash was reported in 53.9% and 40.5% of patients in the ITOVEBI and placebo arms, respectively, post-baseline.

Table 10: 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'.

15 Microbiology

No microbiological information is required for this drug product.

16 Non-Clinical Toxicology

General Toxicology

The key inavolisib effects observed in repeat dose toxicity studies included hyperglycemia and body weight loss in rats and dogs, inflammation in dogs, bone marrow hypocellularity, atrophy of glandular and reproductive tissues, eye lens degeneration in rats, lymphoid depletion, and lens fiber swelling and lens cortex vacuolation in the eye in dogs. The NOAEL were 1.5 mg/kg/day and 0.3 mg/kg/day in rats and dogs, respectively, which corresponds to 0.44 times and 0.56 times the human exposure at a clinical dose of 9 mg.

Findings were generally dose-dependent and reversible, considered to be clinically monitorable and/or manageable. Lens fiber swelling and lens vacuolation in dogs (at ≥ 0.56 times the human exposure at a clinical dose of 9 mg) were reversible. Lens fiber degeneration observed in rats (at ≥ 3.6 times the human exposure at a clinical dose of 9 mg) was considered irreversible.

Carcinogenicity

No carcinogenicity studies with inavolisib have been conducted.

Genotoxicity

Inavolisib was not mutagenic in the bacterial mutagenesis assay.

Inavolisib showed clastogenicity in an *in vitro assay in human lymphocytes*; 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 human exposure at a clinical dose of 9 mg.

Reproductive and Developmental Toxicology

An embryo-fetal development study in Sprague Dawley rats identified inavolisib-related dose dependent effects on embryo-fetal development (at ≥ 0.8 times the human 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 including edema, anasarca, absent eye bulge, microphthalmia, fused thoracic arch, and kyphosis of the vertebral column).

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 human exposure at a clinical dose of 9 mg). In the 1-month toxicity study in dogs, focal inspissation of seminiferous tubule contents, multinucleated spermatids in the testis, and epithelial degeneration/necrosis in the epididymis were observed (at ≥ 2 times the human exposure at a clinical dose of 9 mg). Multinucleated spermatids in the testis persisted through the 4-week recovery period. 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 human exposure at a clinical dose of 9 mg) in the 4-week toxicity

study. Findings suggestive of an interruption/alteration of the estrus cycle were observed (at ≥ 1.5 times the human exposure at a clinical dose of 9 mg) in the 3-month rat toxicity study.

Special Toxicology

Inavolisib did not show phototoxicity potential in the *in vitro* BALB/c 3T3 mouse fibroblast assay.

17 Packs

Itovebi 3 mg
Box, 4 blisters @ 7 film-coated tablets — Reg. No: DKIXXXXXXXXXX

Itovebi 9 mg
Box, 4 blisters @ 7 film-coated tablets — Reg. No: DKIXXXXXXXXXX

18 Date of Latest Marketing Authorisation

Date of latest marketing authorisation:

19 Date of Revision of The Product Information

Date of revision of the Product Information:

Medicine: keep out of reach and sight of children
Obat: Jauhkan dari jangkauan dan pandangan anak-anak
On medical prescription only
Harus dengan resep dokter

Made by:
F. Hoffmann-La Roche Ltd., Kaiseraugst, Switzerland

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

Imported by:
PT Menarini Indria Laboratories, Bekasi, Indonesia

Distributed by:
PT Roche Indonesia, Jakarta, Indonesia

This PI draft has been reviewed and approved for submission by Safira Rizky on 08-Jul-2026

INFORMASI PRODUK UNTUK PASIEN

ITOVEBI
Inavolisib
Tablet salut selaput
3 mg dan 9 mg

BACALAH BROSUR INI AGAR OBAT ANDA DAPAT DIGUNAKAN SECARA AMAN DAN EFEKTIF

Informasi produk untuk pasien ini ditujukan untuk individu yang akan mengonsumsi **ITOVEBI**, baik itu Anda sendiri maupun orang yang berada dalam perawatan Anda. Bacalah informasi ini dengan saksama. Simpanlah brosur ini karena Anda mungkin perlu membacanya kembali di masa mendatang.

Informasi produk untuk pasien ini merupakan sebuah ringkasan dan tidak mencakup seluruh informasi mengenai obat ini. Apabila Anda memiliki pertanyaan lebih lanjut atau memerlukan informasi tambahan mengenai **ITOVEBI**, bicarakanlah dengan dokter, apoteker atau perawat Anda.

Kotak Peringatan Serius dan Tindakan Pencegahan

ITOVEBI dapat menyebabkan efek samping serius yang meliputi:

- Kasus **hiperglikemia** (kadar gula darah tinggi) yang berat, termasuk komplikasi seperti **ketoasidosis**. Ketoasidosis adalah kondisi serius yang terjadi ketika tubuh tidak dapat menggunakan gula secara semestinya dan mulai memecah lemak untuk menghasilkan energi. Proses ini menyebabkan produksi asam yang disebut keton, yang dapat menumpuk hingga mencapai kadar yang berbahaya. Dokter yang menangani Anda akan memeriksa kadar gula darah Anda sebelum dan selama pengobatan dengan ITOVEBI. Dokter Anda akan memberi tahu kapan Anda harus mengonsumsi ITOVEBI berdasarkan kadar gula darah Anda. Pastikan Anda meminum air dalam jumlah yang cukup sebelum dan selama pengobatan dengan ITOVEBI. Dokter yang menangani Anda akan memantau kadar gula darah Anda dan mengobati Anda sesuai kebutuhan. Dokter Anda mungkin akan memberikan Anda obat bernama metformin.

  Lihat tabel "**Efek samping serius dan apa yang harus dilakukan**" di bawah ini, untuk informasi lebih lanjut mengenai efek samping serius ini dan efek samping serius lainnya.

Apa kegunaan ITOVEBI:

ITOVEBI digunakan bersama palbociclib dan fulvestrant untuk mengobati kanker payudara pada orang dewasa. Kanker payudara tersebut merupakan kanker yang:

- resistan terhadap terapi endokrin (muncul kembali saat pasien mendapat atau setelah pasien menyelesaikan terapi hormonal)
- HR-positif (reseptor hormon positif)
- HER2-negatif (*human epidermal growth factor receptor 2* negatif),
- memiliki perubahan (mutasi) pada gen yang disebut '*PIK3CA*', dan
- telah menyebar ke jaringan atau kelenjar getah bening di sekitarnya, atau ke bagian tubuh lainnya

Sebelum mengonsumsi ITOVEBI, akan dilakukan pemeriksaan untuk memastikan apakah ITOVEBI tepat untuk Anda.

Bagaimana cara kerja ITOVEBI:

ITOVEBI bekerja dengan menghambat efek dari protein yang dihasilkan oleh gen *PIK3CA* yang bermutasi. Obat ini membantu menghancurkan sel kanker, dan memperlambat pertumbuhan serta penyebaran kanker.

Bahan-bahan yang terkandung dalam ITOVEBI adalah:

Zat aktif: inavolisib

Bahan-bahan lainnya: laktosa, magnesium stearate, selulosa mikrokristalina, natrium pati glikolat, *Opadry II Red 85F250110-CN* (*Iron oxide red*, polietilena glikol, polivinil alkohol, air yang dimurnikan, talk, titanium dioksida) untuk tablet 3 mg atau *Opadry II Pink 85F240025-CN* (*Iron oxide red*, *Iron oxide yellow,* polietilena glikol, polivinil alkohol, air yang dimurnikan, talk, titanium dioksida) untuk tablet 9 mg.

ITOVEBI memiliki beberapa bentuk dosis berikut ini:

Tablet: 3 mg dan 9 mg

Tampilan ITOVEBI dan isi dalam kemasan

Itovebi 3 mg tablet salut selaput merupakan tablet berwarna merah, berbentuk bulat cembung, dengan cetakan timbul "INA 3" pada satu sisi.

Itovebi 9 mg tablet salut selaput merupakan tablet berwarna merah muda, berbentuk oval, dengan cetakan timbul "INA 9" pada satu sisi.

Kemasan blister Itovebi 3 mg dan 9 mg

Itovebi dikemas dalam blister dan tersedia dalam dus berisi 28 tablet salut selaput (terdiri dari 4 blister, masing-masing berisi 7 tablet salut selaput).

Jangan mengonsumsi ITOVEBI jika:

Anda alergi terhadap inavolisib atau bahan lainnya dari ITOVEBI atau wadahnya.

Untuk membantu menghindari efek samping dan untuk memastikan penggunaan yang tepat, bicarakanlah dengan dokter, apoteker atau perawat Anda sebelum Anda mengonsumsi ITOVEBI. Diskusikan kondisi kesehatan atau gangguan apa pun yang mungkin sedang Anda alami, termasuk jika Anda:

- sedang hamil atau berencana untuk hamil. ITOVEBI dapat membahayakan bayi dalam kandungan Anda,
- mengalami gangguan ginjal,
- mengalami atau pernah mengalami kadar gula darah yang tinggi, diabetes, diabetes pada kehamilan, riwayat diabetes dalam keluarga,
- berusia 65 tahun atau lebih.

Peringatan lain yang harus Anda ketahui:

Stomatitis (seriawan, kemerahan dan pembengkakan pada selaput lendir mulut): ITOVEBI dapat menyebabkan stomatitis. Dokter Anda akan memantau tanda dan gejala stomatitis pada Anda. Dokter Anda mungkin menyarankan Anda untuk menggunakan obat kumur yang tidak mengandung alkohol dan menghindari konsumsi makanan tertentu.

Diare: ITOVEBI dapat menyebabkan diare berat. Hal ini dapat mengakibatkan dehidrasi dan gangguan ginjal. Dokter Anda akan memantau kadar elektrolit Anda dan memberikan pengobatan sesuai kebutuhan.

Pemeriksaan Darah untuk Hiperglikemia (kadar gula darah tinggi):

- Dokter Anda akan melakukan pemeriksaan darah sebelum, selama, dan setelah terapi dengan ITOVEBI. Hal ini dilakukan untuk memeriksa kesehatan darah dan kadar gula darah Anda.
- Dokter Anda mungkin akan meminta Anda untuk memeriksa kadar gula darah Anda di rumah. Dokter Anda akan memberi tahu Anda bagaimana caranya dan kapan waktu untuk memeriksa kadar gula darah Anda.
    - Selalu ikuti dengan saksama arahan dari dokter Anda untuk memeriksa kadar gula darah. Hal ini membantu mendeteksi secara dini apabila Anda memiliki kadar gula darah yang tinggi.
- Dokter Anda akan memberitahu Anda apabila kadar gula darah Anda tidak normal dan jika Anda membutuhkan terapi. Terapi dapat meliputi obat-obatan dan perubahan gaya hidup, seperti diet dan olah raga.
- Apabila Anda sedang mengonsumsi obat-obatan tertentu yang disebut kortikosteroid atau sedang mengalami infeksi, Anda mungkin perlu melakukan pemeriksaan kadar gula darah dengan lebih sering.

Kehamilan dan Menyusui:

- Apabila Anda sedang hamil, dapat menjadi hamil, atau berencana untuk hamil, terdapat risiko-risiko yang perlu Anda diskusikan dengan dokter Anda.
- Sebaiknya Anda tidak mengonsumsi ITOVEBI jika sedang hamil. Obat ini dapat membahayakan bayi dalam kandungan Anda.
- Dokter Anda mungkin akan melakukan tes kehamilan sebelum Anda mulai mengonsumsi ITOVEBI. Hasil pemeriksaan harus menunjukkan bahwa Anda tidak sedang hamil.
- Jika Anda merasa sedang hamil, menjadi hamil sewaktu mengonsumsi ITOVEBI, atau menjadi hamil dari pasangan laki-laki yang sedang mengonsumsi ITOVEBI, segera beritahukan kepada dokter Anda.
- Anda sebaiknya tidak menyusui sewaktu mengonsumsi ITOVEBI dan selama 1 minggu setelah dosis terakhir Anda.

Kontrasepsi untuk Wanita dan Pria:

- **Wanita:** Gunakan metode kontrasepsi non-hormonal selama terapi dan selama 1 minggu setelah dosis terakhir Anda. Tanyakan kepada dokter Anda mengenai kontrasepsi yang tepat untuk Anda.
- **Pria:** Gunakan kontrasepsi yang efektif setiap Anda melakukan hubungan seksual dengan wanita yang sedang hamil, mungkin hamil, atau dapat menjadi hamil. Tetap gunakan kontrasepsi yang efektif hingga 1 minggu setelah dosis terakhir Anda. Tanyakan kepada dokter Anda mengenai kontrasepsi yang tepat untuk Anda.
    - Jika pasangan seksual Anda menjadi hamil atau merasa mungkin hamil sewaktu Anda sedang menjalani terapi dengan ITOVEBI, segera beritahukan kepada dokter Anda.

Kesuburan untuk Wanita dan Pria:

Terapi dengan ITOVEBI dapat memengaruhi kemampuan Anda untuk memiliki anak. Jika Anda memiliki pertanyaan terkait hal ini, tanyakanlah kepada dokter Anda.

Anak-anak dan Remaja:

ITOVEBI tidak diperuntukkan bagi anak-anak dan remaja di bawah usia 18 tahun.

Obat-obatan lainnya dan ITOVEBI:

Beritahukan kepada dokter, apoteker atau perawat Anda tentang semua obat yang Anda konsumsi, termasuk obat-obatan, vitamin, mineral, suplemen alami, atau obat-obatan alternatif.

Bagaimana cara mengonsumsi ITOVEBI:

- Selalu konsumsi obat ini tepat sesuai anjuran dokter atau apoteker Anda. Apabila Anda merasa kurang yakin, pastikan kembali kepada dokter atau apoteker Anda.
- Konsumsi ITOVEBI dengan atau tanpa makanan, pada waktu yang sama setiap hari.
- Telan tablet secara keseluruhan. Jangan mengunyah, menghancurkan, atau membelah tablet tersebut.
- Konsumsi ITOVEBI selama dianjurkan oleh dokter atau apoteker Anda. Jangan menghentikan konsumsi obat kecuali apabila dokter Anda meminta Anda untuk menghentikan konsumsi obat ini.

Dosis biasa:

Dewasa: Konsumsi sesuai anjuran. Dokter Anda akan menentukan dosis yang tepat untuk Anda.

- Dokter Anda mungkin akan menurunkan dosis Anda, menghentikan terapi selama periode waktu tertentu, atau menghentikan terapi sepenuhnya. Hal ini mungkin terjadi apabila Anda mengalami efek samping yang serius.
- Anda juga akan mendapat terapi dengan palbosiklib dan fulvestran. Dokter Anda akan menentukan dosis dan jadwal terapi Anda.

Overdosis:

Apabila Anda merasa Anda atau pasien yang Anda rawat telah mengonsumsi ITOVEBI secara berlebihan, segera hubungi tenaga kesehatan atau unit gawat darurat rumah sakit.

Dosis yang terlewat:

- Apabila Anda melewatkan dosis ITOVEBI, Anda masih dapat mengonsumsinya hingga 9 jam setelah waktu konsumsi yang seharusnya.
- Jika sudah lebih dari 9 jam dari waktu yang seharusnya, lewatkan dosis untuk hari itu. Pada keesokan harinya, konsumsi obat pada jadwal minum obat Anda yang biasa.
- Jangan mengonsumsi dosis tambahan untuk mengganti dosis yang terlewat.
- Jika Anda muntah setelah mengonsumsi ITOVEBI, jangan mengonsumsi dosis tambahan pada hari tersebut. Konsumsi dosis rutin Anda pada waktu biasa di hari berikutnya.

Efek samping yang mungkin terjadi akibat mengonsumsi ITOVEBI:

Berikut ini bukanlah semua efek samping yang mungkin Anda alami saat mengonsumsi ITOVEBI. Jika Anda mengalami efek samping yang tidak ada pada daftar berikut, beritahukan kepada dokter atau apoteker Anda.

- Penurunan kadar trombosit/sel pembeku darah (*thrombocytopenia*)
- Kurang darah/penurunan sel darah merah (*anemia*)
- Sariawan (*stomatitis*)
- Diare
- Mual
- Muntah
- Kelelahan
- Infeksi COVID-19 atau gejala flu
- Infeksi saluran kemih
- Peningkatan kadar alanine aminotransferase
- Penurunan berat badan
- Kadar gula darah tinggi (*hyperglycemia*)
- Hilangnya nafsu makan
- Kadar kalium rendah dalam darah (*hypokalemia*)
- Sakit kepala
- Ruam
- Rambut rontok atau penipisan rambut (*alopecia*)
- Kulit kering

Kurang Umum
- Kadar kalsium rendah dalam darah (*hypocalcemia*)
- Mata kering
- Nyeri perut
- Perubahan rasa pada lidah atau penurunan indra pengecap (*dysgeusia*)
- Rasa tidak nyaman pada perut bagian atas (*dyspepsia*)
- Peningkatan kadar hormon insulin dalam darah

ITOVEBI dapat menyebabkan hasil pemeriksaan darah abnormal. Dokter Anda akan melakukan pemeriksaan darah sebelum, selama, dan setelah pengobatan Anda. Melalui hasil pemeriksaan tersebut, Dokter Anda akan mengetahui bagaimana efek ITOVEBI terhadap darah Anda.

Efek samping serius dan apa yang harus dilakukan

Frekuensi/Efek Samping/Gejala	Bicarakan dengan dokter, apoteker atau perawat Anda		Hentikan konsumsi obat ini dan segera cari bantuan medis
	Hanya pada kasus berat	Pada semua kasus	
Sangat Umum			
Hiperglikemia (kadar gula darah tinggi): kesulitan bernapas, kebingungan, mual dan muntah, nyeri perut, merasa sangat haus atau mulut kering (dehidrasi), buang air kecil lebih sering atau lebih banyak dari biasanya, penglihatan kabur, peningkatan nafsu makan yang tidak biasa, penurunan berat badan, bau napas seperti buah, wajah merah dan kulit kering, merasa luar biasa mengantuk atau lelah, dan merasa pusing.			✓
Stomatitis (seriawan, kemerahan dan pembengkakan pada selaput lendir mulut): gusi, lidah, mulut, atau tenggorokan yang nyeri, merah, mengkilap, atau bengkak, darah di mulut, kesulitan atau nyeri saat menelan atau berbicara, mulut kering, rasa terbakar ringan, atau nyeri saat makan, kemerahan dan pembengkakan pada selaput lendir mulut		✓	
Infeksi saluran kemih (infeksi pada sistem kemih meliputi ginjal, ureter, kandung kemih, dan uretra): Nyeri atau rasa terbakar saat buang air kecil, sering buang air kecil, adanya darah pada air seni, nyeri panggul, air seni berbau, air seni keruh		✓	
Umum			
Diare, mual, muntah (berat): dehidrasi, rasa haus, air seni berwarna gelap, penurunan jumlah air seni yang dikeluarkan, adanya darah pada air seni, dan peningkatan berat badan (akibat penumpukan cairan)		✓	
Tidak diketahui			
Ketoasidosis (penumpukan asam di dalam darah Anda): merasa sangat haus, sering buang air kecil, mual, merasa lemas, aroma napas yang berbau buah, kesulitan bernapas, dan kebingungan.			✓

Pelaporan efek samping

Bila Anda mengalami efek samping apa pun, beri tahu dokter, apoteker atau perawat Anda. Termasuk efek samping apapun yang mungkin terjadi tetapi tidak tertera pada brosur ini. Anda juga dapat melaporkan efek samping langsung melalui:

PT Roche Indonesia – Patient Safety
Email: indonesia.safety@roche.com
Tel: +62 21 3041 3000
Situs web: https://medinfo.roche.com/id/id.html

Dengan melaporkan efek samping, Anda dapat membantu memberikan lebih banyak informasi mengenai keamanan obat ini.

Penyimpanan:

- Simpan pada suhu ruang, di bawah suhu 30°C.
- Jauhkan dari pandangan dan jangkauan anak-anak.
- Jangan mengonsumsi obat ini setelah tanggal kedaluwarsa (EXP) yang tertera pada kemasan. Tanggal tersebut merujuk pada hari terakhir di bulan yang tertera. Jangan mengonsumsi obat ini apabila terdapat kerusakan pada kemasan atau jika terdapat tanda-tanda perusakan.
- Jangan membuang obat melalui saluran pembuangan air limbah atau sampah rumah tangga. Tanyakan kepada apoteker Anda bagaimana cara membuang obat-obatan yang sudah tidak digunakan. Tindakan ini akan membantu melindungi lingkungan.

Jika Anda membutuhkan informasi lebih lanjut mengenai ITOVEBI:

Tanyakan kepada dokter, apoteker atau perawat Anda.

Kemasan

Itovebi 3 mg
Dus, 4 blister @ 7 tablet salut selaput — Reg. No: DKIXXXXXXXXXX

Itovebi 9 mg
Dus, 4 blister @ 7 tablet salut selaput — Reg. No: DKIXXXXXXXXXX

Obat: Jauhkan dari jangkauan dan pandangan anak-anak
Harus dengan resep dokter

Diproduksi oleh:
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Untuk:
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