ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Itovebi 3 mg film-coated tablets
Itovebi 9 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Itovebi 3 mg film-coated tablets

Each film-coated tablet contains 3 mg of inavolisib.

Excipient(s) with known effect
Each film-coated tablet contains 22 mg of lactose.

Itovebi 9 mg film-coated tablets

Each film-coated tablet contains 9 mg of inavolisib.

Excipient(s) with known effect
Each film-coated tablet contains 66 mg of lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Itovebi 3 mg film-coated tablets

Red, round convex-shaped film-coated tablet with an “INA 3” debossing on one side. Approximate diameter: 6 mm.

Itovebi 9 mg film-coated tablets

Pink, oval film-coated tablet with an “INA 9” debossing on one side. Approximate size: 13 mm (length), 6 mm (width).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Itovebi, in combination with palbociclib and fulvestrant, is indicated for the treatment of adult patients with *PIK3CA*-mutated, oestrogen receptor (ER)-positive, HER2-negative, locally advanced or metastatic breast cancer, following recurrence on or within 12 months of completing adjuvant endocrine treatment (see section 5.1).

Patients previously treated with a CDK 4/6 inhibitor in the (neo)adjuvant setting should have had an interval of at least 12 months between termination of CDK 4/6 inhibitor treatment and the detection of recurrence.

In pre/perimenopausal women and in men, endocrine therapy should be combined with a luteinising hormone-releasing hormone (LHRH) agonist.

4.2 Posology and method of administration

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

Patients with ER-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 in a tumour or plasma specimen using a CE-marked *in vitro* diagnostic (IVD) medical device with the corresponding intended purpose (see section 5.1). If a CE-marked IVD is not available, an alternative validated test should be used. If a mutation is not detected in one specimen type, a mutation might be detected in the other specimen type, if available.

Posology

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 1, 15, and 29, then once monthly thereafter. Please refer to the Summary of Product Characteristics (SmPC) of palbociclib and fulvestrant for more information.

Treatment of pre/perimenopausal women and men with Itovebi should also include an LHRH agonist in accordance with local clinical practice.

Duration of treatment

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

Delayed or missed doses

Patients should be encouraged to take their dose at approximately the same time each day. If a dose of Itovebi is missed, it can be taken within 9 hours after the time it is usually taken. After more than 9 hours, the dose should be skipped for that day. On the next day, Itovebi should be taken at the usual time. If the patient vomits after taking the Itovebi dose, the patient should not take an additional dose on that day and should resume the usual dosing schedule the next day at the usual time.

Dose modifications

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 level	Dose and schedule
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. Dose modification guidance for specific adverse reactions is presented in Tables 2-4.

Hyperglycaemia

Table 2: Dose modification and management for hyperglycaemia

Fasting glucose levels[a]	**Recommendation**
> 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-hyperglycaemic treatment[b] for patients with risk factors for hyperglycaemia[c].
> 160 to 250 mg/dL (> 8.9 – 13.9 mmol/L)	• Interrupt Itovebi until fasting glucose level decreases to ≤ 160 mg/dL (≤ 8.9 mmol/L). • Initiate or intensify anti-hyperglycaemic treatment[b]. • Resume Itovebi at the same dose level. • If fasting glucose level persists > 200 – 250 mg/dL (> 11.1 – 13.9 mmol/L) for 7 days under appropriate anti-hyperglycaemic treatment, consultation with a healthcare professional experienced in the treatment of hyperglycaemia is recommended.
> 250 to 500 mg/dL (> 13.9 – 27.8 mmol/L)	• Interrupt Itovebi. • Initiate or intensify anti-hyperglycaemic treatment[b]. • 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 levels[a]	Recommendation
> 500 mg/dL (> 27.8 mmol/L)	• Interrupt Itovebi. • Initiate or intensify anti-hyperglycaemic treatment[b]. • 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 (fasting plasma glucose [FPG] or fasting blood glucose [FBG]) should be checked prior to initiation of treatment. Fasting glucose levels referenced in this table reflect hyperglycaemia grading according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

[b] Initiate applicable anti-hyperglycaemic treatments such as metformin, sodium-glucose cotransporter-2 (SGLT2) inhibitors, insulin sensitisers (such as thiazolidinediones), dipeptidyl peptidase-4 (DPP-4) inhibitors, or insulin, and review the respective prescribing information for dosing and dose titration recommendations, including local hyperglycaemia treatment guidelines. Metformin was recommended in the INAVO120 study as the preferred initial agent. See sections 4.4 and 4.8.

[c] See section 4.4 for risk factors for hyperglycaemia.

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[a]	Recommendation
For all grades: Initiate supportive therapy and monitor as clinically indicated.	
Grade 3, first event	• Interrupt Itovebi until recovery to Grade ≤ 1. • Resume Itovebi at the same dose level or at one lower dose level based on clinical evaluation (see Table 1).
Grade 3, recurrent OR Grade 4, non-life-threatening	• Interrupt Itovebi until recovery to Grade ≤ 1. • Resume Itovebi at one lower dose level (see Table 1).
Grade 4, life-threatening	• Permanently discontinue Itovebi.
[a] Based on CTCAE version 5.0.	

Special populations

Paediatric population

The safety and efficacy of Itovebi in children and adolescents aged 0 – 17 years have not been established. No data are available.

Elderly

No dose adjustment of Itovebi is required in patients ≥ 65 years of age based on population pharmacokinetic analysis. There are limited data in patients ≥ 65 years of age (see section 5.2).

Renal impairment

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. No dose adjustment is required 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 severe renal impairment (see section 5.2).

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 established in patients with moderate to severe hepatic impairment (see section 5.2).

Method of administration

Itovebi is for oral use. The tablets can be taken with or without food. The tablets should be swallowed whole and not chewed, crushed, dissolved, or divided.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Hyperglycaemia

The safety and efficacy of Itovebi in patients with Type 1 diabetes mellitus or Type 2 diabetes mellitus requiring ongoing anti-hyperglycaemic therapy have not been studied as these patients were excluded from the INAVO120 study. Only 1 patient with Type 2 diabetes was included in the Itovebi arm of the INAVO120 study, which should be considered when Itovebi is prescribed to patients with diabetes mellitus. Patients with a history of diabetes mellitus may require intensified anti-hyperglycaemic

treatment and more frequent fasting glucose testing during Itovebi treatment. Treatment with Itovebi should not be initiated until fasting glucose levels are optimised. Consultation with a healthcare professional experienced in the treatment of hyperglycaemia should be considered before initiating Itovebi.

Hyperglycaemia has been frequently reported in patients treated with Itovebi. Severe cases of hyperglycaemia, including ketoacidosis with fatal complications, have occurred.

In the INAVO120 study, hyperglycaemia was managed with anti-hyperglycaemic treatment and adjustments of Itovebi as clinically indicated (see section 4.8). Short-term insulin may be used as rescue treatment for hyperglycaemia. There is limited experience in patients receiving insulin when being treated with Itovebi. A potential for hypoglycaemia with anti-hyperglycaemic medicinal products (e.g., insulin, sulfonylureas) should be considered when used to manage hyperglycaemia prior to Itovebi being interrupted or discontinued.

Before initiating treatment with Itovebi, patients should be advised of the signs and symptoms of hyperglycaemia (e.g., excessive thirst, urinating more often, blurred vision, mental confusion, difficulty breathing, or increased appetite with weight loss) and to immediately contact a healthcare professional if these symptoms occur. Optimal hydration should be maintained prior to and during treatment.

Patients should be tested for fasting glucose levels (FPG or FBG) and HbA_{1C} prior to treatment with Itovebi and at regular intervals during treatment (see Table 5). Initiation of fasting glucose monitoring at home should be considered for patients who have risk factors for hyperglycaemia or who experience hyperglycaemia. Metformin premedication can be considered in patients with risk factors for hyperglycaemia. All patients should be instructed on lifestyle changes (e.g., dietary modifications, physical activity).

Table 5: Schedule of fasting glucose monitoring and HbA_{1C}

	Recommended schedule for the monitoring of fasting glucose and HbA_{1C} levels in all patients treated with Itovebi
At screening, before initiating treatment with Itovebi	Test for fasting glucose levels (FPG or FBG) and HbA_{1C} levels and optimise the patient's blood glucose level (see Table 2).
After initiating treatment with Itovebi	Monitor/self-monitor fasting glucose 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*. Consider monitoring/self-monitoring fasting glucose levels more frequently as clinically indicated* in patients with risk factors for hyperglycaemia including, 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. More frequent fasting glucose testing is required in patients with concomitant use of corticosteroids, intercurrent infections, or other conditions which may require intensified glycaemia 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. Initiate or adjust anti-hyperglycaemic treatment as required (see section 4.2).

	Recommended schedule for the monitoring of fasting glucose and HbA_{1C} levels in all patients treated with Itovebi
	HbA_{1C} should be monitored every 3 months.
If hyperglycaemia develops after initiating treatment with Itovebi	Monitor fasting glucose more closely as clinically indicated*. Based on the severity of the hyperglycaemia, Itovebi dosing may be interrupted, reduced, or discontinued as described in Table 2 (see section 4.2).
	During anti-hyperglycaemic treatment, 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*.
* All glucose monitoring should be performed at the physician's discretion as clinically indicated.	

Stomatitis

Stomatitis has been reported in patients treated with Itovebi (see section 4.8). 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 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.

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

Use in patients who previously received a CDK4/6 inhibitor

Information on the efficacy of the combination of Itovebi, palbociclib, and fulvestrant is very limited in patients who previously received a CDK4/6 inhibitor as part of neoadjuvant or adjuvant treatment. Efficacy may be lower in such patients.

Lactose

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose glucose-galactose galactose malabsorption should not take this medicine.

Sodium

This medicine contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

CYP inhibitors and inducers

Clinical study results indicated that the predominant metabolites of inavolisib are not mediated by CYP enzymes, and that hydrolysis was the major metabolic pathway. This suggests a low likelihood of clinically relevant interactions between inavolisib and CYP inhibitors or inducers.

CYP substrates

Inavolisib induces CYP3A and is a time-dependent inhibitor of CYP3A *in vitro*. Therefore, inavolisib should be used with caution in combination with sensitive CYP3A4 substrates with a narrow

therapeutic index (e.g., alfentanil, astemizole, cisapride, cyclosporine, quinidine, sirolimus, tacrolimus) as inavolisib may increase or decrease the systemic exposure of these substrates.

In addition, inavolisib induces CYP2B6, CYP2C8, CYP2C9, and CYP2C19 *in vitro*. Therefore, inavolisib should be used with caution in combination with sensitive substrates of these enzymes with a narrow therapeutic index (e.g., paclitaxel, warfarin, phenytoin, S-mephenytoin) as inavolisib may decrease their systemic exposure and consequently lead to decreased efficacy.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Females

Patients should be advised to use effective non-hormonal contraception during treatment with Itovebi and for 1 week after the last dose of Itovebi.

Males

It is not known if inavolisib is present in semen. To avoid potential foetal 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.

Pregnancy

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 foetus.

There are no or limited amount of data from the use of inavolisib in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Itovebi is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

It is unknown whether inavolisib/metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. Breast-feeding should be discontinued during treatment with Itovebi and for 1 week after the last dose of Itovebi.

Fertility

No human data on the effect of inavolisib on fertility are available. Based on animal studies, inavolisib may impact fertility in females and males of reproductive potential (see section 5.3).

4.7 Effects on ability to drive and use machines

Itovebi has minor influence on the ability to drive or use machines because fatigue has been reported during treatment with Itovebi.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions in patients who received Itovebi were hyperglycaemia (59.9%), stomatitis (51.2%), diarrhoea (48.1%), thrombocytopenia (48.1%), fatigue (37.7%), anaemia (37%), nausea (27.8%), decreased appetite (23.5%), rash (22.8%), headache (21%), weight decreased (17.3%), vomiting (14.8%), and urinary tract infection (13%).

The most common serious adverse reactions reported in patients who received Itovebi were anaemia (1.9%), diarrhoea (1.2%), and urinary tract infection (1.2%).

Permanent discontinuation of Itovebi due to an adverse reaction occurred in 3.1% of patients. The adverse reactions leading to permanent discontinuation of Itovebi were hyperglycaemia (1.2%), stomatitis (0.6%), alanine transaminase (ALT) increased (0.6%), and weight decreased (0.6%).

Tabulated list of adverse drug reactions

Adverse drug reactions, based on data from 162 patients with locally advanced or metastatic breast cancer who received Itovebi in combination with palbociclib and fulvestrant in the INAVO120 Phase 3, randomised study, and from post-marketing surveillance are listed by MedDRA system organ class in Table 6. The median duration of Itovebi treatment at the time of the analysis was 9.2 months (range: 0 to 38.8 months).

Within each system organ class, the adverse reactions are ranked by frequency, with the most frequent reactions first. 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), not known (cannot be estimated from available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 6: Adverse drug reactions observed in patients treated with Itovebi

System organ class Adverse reaction	**Itovebi + palbociclib + fulvestrant N=162**		
	Frequency category (all grades)	**All grades (%)**	**Grade 3-4 (%)**
Infections and infestations			
Urinary tract infection	Very common	13	1.2*
Blood and lymphatic system disorders			
Thrombocytopenia	Very common	48.1	14.2
Anaemia	Very common	37	6.2*
Metabolism and nutrition disorders			
Hyperglycaemia[a]	Very common	59.9	5.6*
Decreased appetite	Very common	23.5	0
Hypokalaemia	Very common	16	2.5
Hypocalcaemia	Common	8.6	1.2*
Ketoacidosis	Uncommon[b]	–	–
Nervous system disorders			
Headache	Very common	21	0
Eye disorders			
Dry eye	Common	8.6	0
Gastrointestinal disorders			
Stomatitis[c]	Very common	51.2	5.6*
Diarrhoea	Very common	48.1	3.7*
Nausea	Very common	27.8	0.6*
Abdominal pain	Very Common	15.4	0.6*

System organ class Adverse reaction	Itovebi + palbociclib + fulvestrant N=162		
	Frequency category (all grades)	**All grades (%)**	**Grade 3-4 (%)**
Vomiting	Very common	14.8	0.6*
Dysgeusia	Common	8.6	0
Dyspepsia	Common	8	0
Skin and subcutaneous tissue disorders			
Rash[d]	Very common	22.8	0
Alopecia	Very common	18.5	0
Dry skin[e]	Very common	13	0
Dermatitis[f]	Common	2.5	0
Folliculitis	Common	1.2	0
General disorders and administration site conditions			
Fatigue	Very common	37.7	1.9*
Investigations			
Alanine aminotransferase increased	Very common	17.3	3.7*
Weight decreased	Very common	17.3	3.7*
Blood insulin increased	Common	6.2	0

Grading according to CTCAE version 5.0.

* No Grade 4 events were observed.

[a] Includes hyperglycaemia, blood glucose increased, hyperglycaemic crisis, glycated serum protein increased, glucose tolerance impaired, diabetes mellitus, Type 2 diabetes mellitus, and glycosylated haemoglobin increased.

[b] Adverse reaction reported during post-marketing experience. 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 Itovebi in clinical trials.

[c] Includes aphthous ulcer, glossitis, glossodynia, lip ulceration, mouth ulceration, mucosal inflammation, and stomatitis.

[d] Includes rash, rash erythematous, rash maculo-papular, rash papular, rash pruritic, and rash pustular.

[e] Includes dry skin, skin fissures, xerosis, and xeroderma.

[f] Includes dermatitis, dermatitis acneiform, and dermatitis bullous.

Description of selected adverse drug reactions

Hyperglycaemia

In the INAVO120 study, hyperglycaemia of any grade was reported in 59.9% of patients treated with Itovebi in combination with palbociclib and fulvestrant; Grade 2 and Grade 3 events were reported in 38.3% and 5.6% of patients, respectively (based on CTCAE version 5.0). Among the patients who experienced hyperglycaemia, the rate of new onset of hyperglycaemia events was highest during the first two months of treatment with a median time to first onset of 7 days (range: 2 to 955 days).

In the 97 patients who received Itovebi in combination with palbociclib and fulvestrant and experienced hyperglycaemia, 74.2% (72/97) received anti-hyperglycaemic medicines including SGLT2 inhibitors, thiazolidinediones, and DPP-4 inhibitors for prophylaxis or treatment of hyperglycaemia. All patients who received anti-hyperglycaemic medicines received metformin as a

single agent or in combination with other anti-hyperglycaemic medicines (i.e., insulin, DPP-4 inhibitors, and sulfonylureas); and 11.3% (11/97) received insulin (see section 4.4).

In patients with fasting glucose levels > 160 mg/dL (> 8.9 mmol/L) with at least one level (see Table 2) improvement in fasting blood glucose levels (n=52), the median time to improvement was 8 days (range: 2 to 43 days).

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

Stomatitis

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. Among patients who experienced stomatitis, 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 (see section 4.4).

Diarrhoea

Diarrhoea was reported in 48.1% of patients treated with Itovebi in combination with palbociclib and fulvestrant; Grade 1 events were reported in 27.8% of patients, Grade 2 events in 16.7% of patients, and Grade 3 events in 3.7% of patients. Among patients who experienced diarrhoea, the median time to first onset was 15 days (range: 2 to 602 days).

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

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

Elderly

Analysis of the safety of Itovebi comparing patients ≥ 65 years of age (14.8%) to younger patients (85.2%) suggests a higher incidence of Itovebi dose modification/interruptions (79.2% versus 68.1%).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 the national reporting system listed in Appendix V.

4.9 Overdose

The highest dose of Itovebi administered in the INAVO120 study was 18 mg in one patient. This event of accidental overdose 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, PI3K inhibitors, ATC Code: not yet assigned

Mechanism of action

Inavolisib is an 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 signalling pathway is commonly dysregulated in HR-positive breast cancer, often due to activating *PIK3CA* mutations. With its dual mechanism of action, inavolisib inhibits the activity of downstream PI3K pathway targets, including AKT, resulting in reduced cellular proliferation and induction of apoptosis in *PIK3CA*-mutated breast cancer cell lines.

Clinical efficacy and safety

Locally advanced or metastatic breast cancer

The patients in this setting, based on data from the INAVO120 study, are defined as endocrine-resistant patients (disease recurrence on or within 12 months of adjuvant endocrine treatment completion) who have not received prior treatment for their locally advanced or metastatic disease.

INAVO120

The efficacy of Itovebi in combination with palbociclib and fulvestrant was evaluated in a Phase 3, randomised, double-blind, placebo-controlled study in adult patients with *PIK3CA*-mutated, HR-positive, HER2-negative, locally advanced or metastatic breast cancer whose disease progressed during or within 12 months of completing adjuvant endocrine therapy (endocrine-resistant) and who have not received prior systemic therapy for locally advanced or metastatic disease. The study included patients who received prior (neo)adjuvant endocrine therapy including a CDK4/6 inhibitor if the progression event was > 12 months since completion of the CDK4/6 inhibitor portion of (neo)adjuvant therapy, and who had HbA_{1C} < 6% and fasting blood glucose < 126 mg/dL. The study excluded patients with Type 1 diabetes mellitus or Type 2 diabetes mellitus requiring ongoing anti-hyperglycaemic therapy at the start of study treatment, patients who received prior treatment with fulvestrant (except as part of neoadjuvant therapy with treatment duration ≤ 6 months), and patients with known and untreated, or active CNS metastases (progressing or requiring anticonvulsants or corticosteroids for symptomatic control).

PIK3CA mutation status was prospectively determined through testing of plasma-derived circulating tumour DNA (ctDNA) using a next-generation sequencing (NGS) assay (FoundationOne® Liquid CDx assay or PredicineCARE™) performed at a central laboratory (87.4%), or in local laboratories (12.6%) using various validated polymerase chain reaction (PCR) or NGS assays on tumour tissue or plasma. The following *PIK3CA* mutations at the indicated amino acid positions were eligible for inclusion: H1047D/I/L/N/P/Q/R/T/Y, G1049A/C/D/R/S, E545A/D/G/K/L/Q/R/V, E453A/D/G/K/Q/V, E542A/D/G/K/Q/R/V, K111N/R/E, Q546E/H/K/L/P/R, G106A/D/R/S/V, N345D/H/I/K/S/T/Y, G118D, C420R, R88Q, and M1043I/T/V. At least one eligible *PIK3CA* mutation was identified in at least one of these amino acid positions in each of the enrolled patient specimens. Based on results from the central FoundationOne® Liquid CDx assay, the most common *PIK3CA* alterations were short variants at amino acids H1047 (n=115, 42.6%), E545 (n=58, 21.5%), and E542 (n=39, 14.4%). There were 25 patients whose specimens harboured more than one *PIK3CA* alterations (i.e., multiple *PIK3CA* mutations), and 33 with less common *PIK3CA* alterations.

A total of 325 patients were randomised 1:1 to receive either Itovebi 9 mg (n=161) or placebo (n=164) orally once daily, in combination with palbociclib and fulvestrant, until disease progression or

unacceptable toxicity. In addition, pre/perimenopausal women and men received an LHRH agonist throughout therapy. Randomisation was stratified by presence of visceral disease (yes or no), endocrine resistance (primary or secondary), and geographic region (North America/Western Europe, Asia, other).

The baseline demographic and disease characteristics were: median age 54 years (range: 27 to 79 years, 18.2% were ≥ 65 years of age); 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. Three (0.9%) patients received prior CDK4/6 inhibitor therapy. The demographics and baseline disease characteristics were balanced and comparable between study arms.

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

Efficacy results are summarised in Table 7, Figure 1, and Figure 2. INV-assessed PFS results were supported by consistent results from blinded independent central review (BICR) assessment.

Table 7: Efficacy results in patients with locally advanced or metastatic breast cancer in INAVO120

Efficacy endpoint	**Itovebi + palbociclib + fulvestrant N=161**	**Placebo + palbociclib + fulvestrant N=164**
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	
Overall survival[b,c]		
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[b,d]		
Patients with CR or PR, n (%)	101 (62.7)	46 (28)
95% CI	(54.8, 70.2)	(21.3, 35.6)
p-value	<0.0001	
Duration of response[b]		
Median DOR, months (95% CI)	19.2 (14.7, 28.3)	11.1 (8.5, 20.2)

CI = confidence interval; CR = complete response; PR = partial response

[a] Per RECIST version 1.1. Based on primary analysis (clinical cutoff date: 29 September 2023).

[b] Based on final overall survival analysis (clinical cutoff date: 15 November 2024).

[c] The prespecified boundary for statistical significance was p < 0.0469.

[d] Per RECIST version 1.1. 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

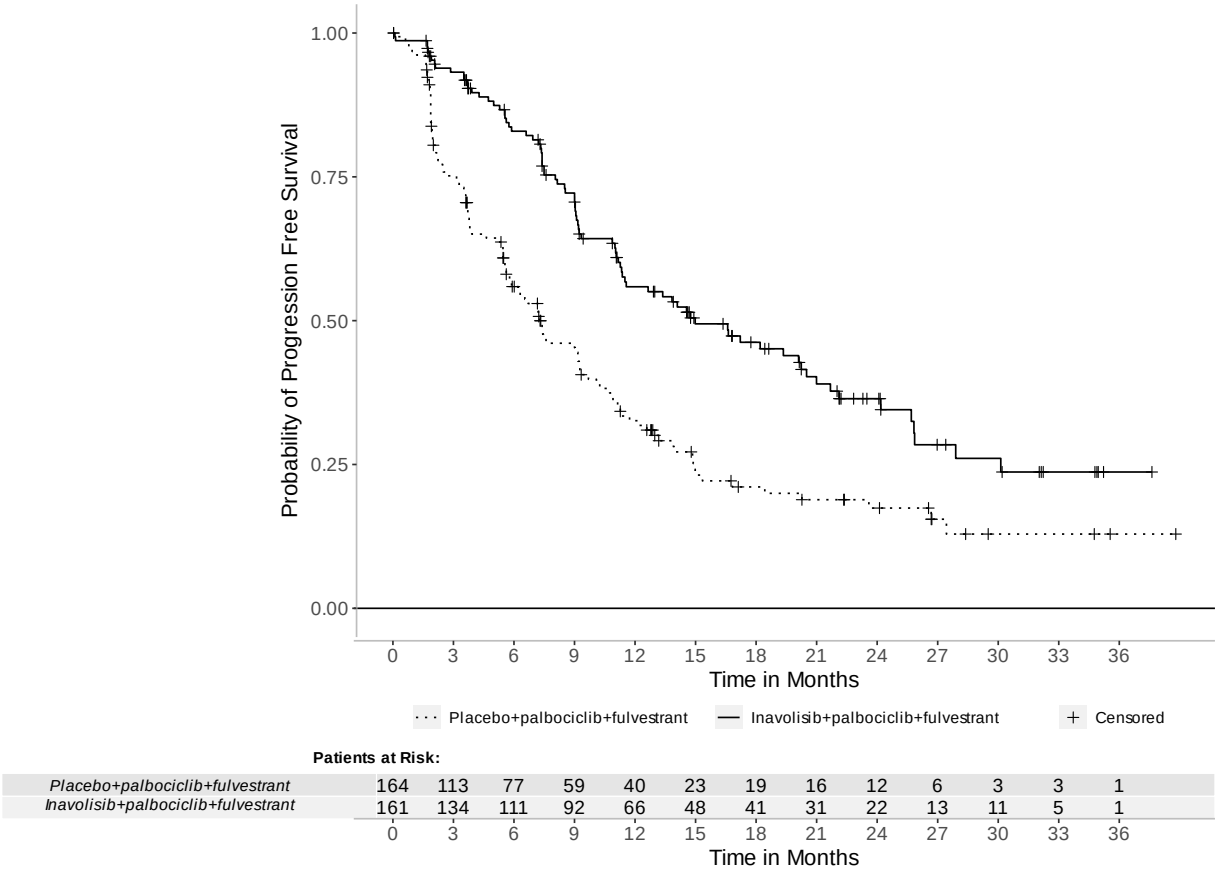
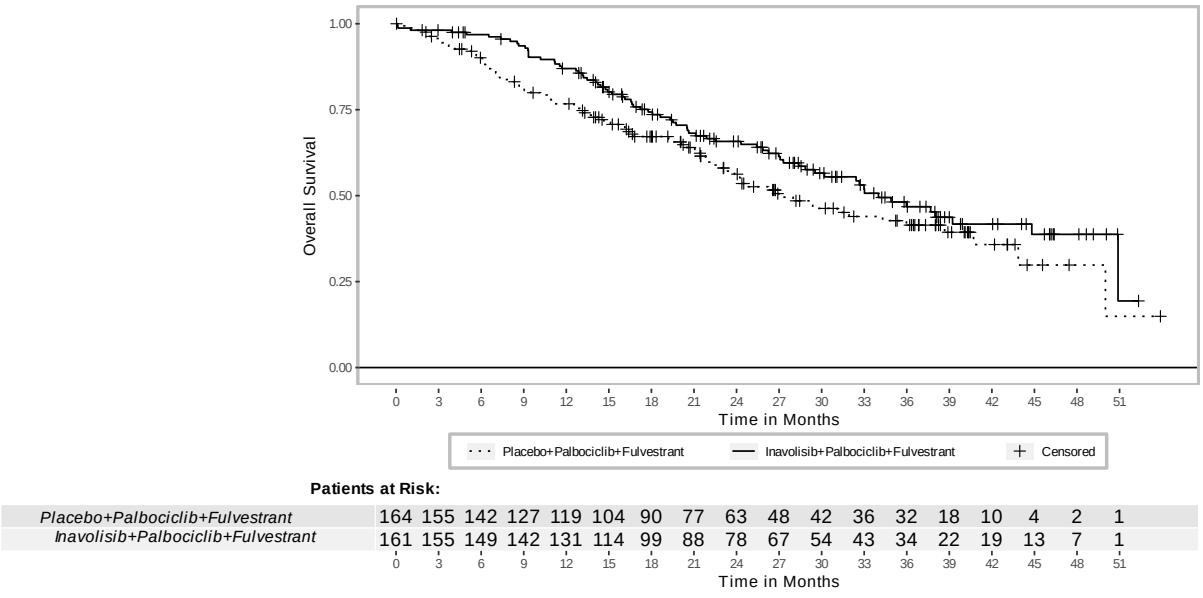


Figure 2 Overall survival in patients with locally advanced or metastatic breast cancer in INAVO120



Paediatric population

The European Medical Agency has waived the obligation to submit the results of studies with Itovebi in all subsets of the paediatric population in breast cancer (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

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

Inavolisib pharmacokinetics are presented as geometric mean (geometric coefficient of variation [geo CV]%) following administration of the approved recommended dosage unless otherwise specified. Based on population pharmacokinetics analysis, the inavolisib steady-state AUC was 1 019 h*ng/mL (29%) and C_{max} was 67 ng/mL (28%). Steady-state concentrations were predicted to be attained by day 5.

With 9 mg once daily dosing, the geometric mean accumulation ratio was about 2-fold.

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 daily dosing of inavolisib, under fasted conditions.

The absolute oral bioavailability of inavolisib was 76%.

Food effect

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

Distribution

Plasma protein binding of inavolisib in humans is 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 (26%) based on population pharmacokinetics analysis.

Biotransformation

Following oral administration of a single radio-labeled 9 mg dose of inavolisib to healthy subjects, parent drug was the most prominent drug-related compound in plasma and urine. Hydrolysis was the major metabolic pathway. No specific hydrolysis enzymes involved in the metabolism of inavolisib were identified.

Elimination

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

In clinical studies, based on population pharmacokinetics analysis, the geometric mean of the individual elimination half-life estimates for inavolisib was 15 hours (24%) following a single 9 mg dose. The estimated total clearance of inavolisib is 8.8 L/hr (29%).

Linearity/non-linearity

Limited data suggest dose proportionality within the dose range tested (6 to 12 mg) for single-dose C_{max} and AUC_{0-24} and steady-state AUC_{0-24}; however, for steady-state C_{max}, the data suggest non-proportionality.

Drug-drug interactions

Clinical study results indicated that the predominant metabolites of inavolisib are not mediated by CYP enzymes, suggesting a low likelihood of clinically relevant interactions between inavolisib and CYP inhibitors or inducers. Moreover, *in vitro* results indicated that inavolisib does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 enzymes.

In vitro studies have shown that inavolisib does not appear to have the potential to inhibit any of the relevant drug transporters tested. Furthermore, inavolisib is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) *in vitro*. However, based on the overall pharmacokinetic characteristics of inavolisib, inhibitors or inducers of P-gp and/or BCRP are not expected to cause a clinically relevant drug-drug interaction with inavolisib.

Special populations

Elderly

No clinically relevant differences in inavolisib pharmacokinetics were noted between patients 65 years of age and older and those under 65 years based on population pharmacokinetic analysis. Of the 162 patients who received Itovebi in the INAVO120 study, 24 patients were ≥ 65 years of age.

Renal impairment

Population pharmacokinetic analyses indicated that mild renal impairment is not a clinically relevant 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. Inavolisib AUC and C_{max} were 73% and 11% higher in patients with moderate renal impairment compared to patients with normal renal function (eGFR ≥ 90 mL/min), respectively. The effect of severe renal impairment on inavolisib pharmacokinetics has not been established.

Hepatic impairment

Population pharmacokinetic analyses indicated that mild hepatic impairment is not a clinically relevant 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 to severe hepatic impairment on inavolisib pharmacokinetics has not been studied.

5.3 Preclinical safety data

Genotoxicity

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 times the exposure at a clinical dose of 9 mg.

Carcinogenicity

No carcinogenicity studies with inavolisib have been conducted.

Developmental toxicity

An embryo-foetal development study in Sprague-Dawley rats identified inavolisib-related dose-dependent effects on embryo-foetal development that included decreases in foetal body weight and placental weight, post-implantation loss, lower foetal viability, and teratogenicity (foetal external, visceral, and skeletal malformations), with the maternal exposure at NOAEL being 0.2 times the exposure at a clinical dose of 9 mg.

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 ≥ NOAEL of 0.4 times the exposure at a clinical dose of 9 mg). These findings were reversible. In male dogs, focal inspissation of seminiferous tubule contents and multinucleated spermatids in the testis and epithelial degeneration/necrosis in the epididymis were observed following 4 weeks of dosing (at ≥ 2 times the exposure at a clinical dose of 9 mg). Following 3 months of dosing at up to 1.2 times the exposure at a clinical dose of 9 mg, a reversible decrease in total sperm count was observed with a no observed adverse effect level (NOAEL) of 0.4 times the exposure at a clinical dose of 9 mg but there were no inavolisib-related microscopic findings in the testes or epididymides or effects on sperm concentration, motility, or morphology.

In female rats, minimal to mild atrophy in the uterus and vagina, decreased ovarian follicles, and findings suggestive of an interruption/alteration of the oestrus cycle were observed (at ≥ 1.2 times the exposure at a clinical dose of 9 mg), with a NOAEL of 0.5 times the exposure at a clinical dose of 9 mg. These findings were not observed following the recovery period in the 4-week toxicity study. Recovery was not assessed in the 3-month study in rats.

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. Minimal lens fiber degeneration observed in some rats (at ≥ 3.6 times the exposure at a clinical dose of 9 mg) was considered irreversible.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Itovebi 3 mg and 9 mg tablet core

Lactose monohydrate
Magnesium stearate (E470b)
Microcrystalline cellulose (E460)
Sodium starch glycolate

Itovebi 3 mg film-coating

Polyvinyl alcohol, partially hydrolysed
Titanium dioxide (E 171)
Macrogol
Talc (E 553b)
Iron oxide red (E 172)

Itovebi 9 mg film-coating

Polyvinyl alcohol, partially hydrolysed
Titanium dioxide (E 171)
Macrogol
Talc (E 553b)
Iron oxide red (E 172)
Iron oxide yellow (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Alu/Alu (aluminium/aluminium) perforated unit-dose blisters in cartons of 28 × 1 film-coated tablets.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1942/001
EU/1/25/1942/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Roche Pharma AG
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Itovebi 3 mg film-coated tablets
inavolisib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 3 mg inavolisib.

3. LIST OF EXCIPIENTS

Also contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

28 × 1 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1942/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

itovebi 3 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Itovebi 3 mg tablets
inavolisib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Mon. Tue. Wed. Thu. Fri. Sat. Sun.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Itovebi 9 mg film-coated tablets
inavolisib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 9 mg inavolisib.

3. LIST OF EXCIPIENTS

Also contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

28 × 1 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1942/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

itovebi 9 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Itovebi 9 mg tablets
inavolisib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Mon. Tue. Wed. Thu. Fri. Sat. Sun.

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Itovebi 3 mg film-coated tablets
Itovebi 9 mg film-coated tablets
inavolisib

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Itovebi is and what it is used for

What Itovebi is

Itovebi contains the active substance inavolisib, which belongs to a group of medicines called PI3K inhibitors.

What Itovebi is used for

Itovebi is used to treat adults with a type of breast cancer called:
- ER-positive (oestrogen receptor-positive)
- HER2-negative (human epidermal growth factor receptor 2-negative)

It is used in patients whose cancer has returned whilst receiving hormonal anti-cancer therapy or within 12 months of completing hormonal anti-cancer therapy. Itovebi is used when a patient's cancer:
- has a change (mutation) in a gene called '*PIK3CA*', and
- has spread to nearby tissue or lymph nodes or to other parts of the body ('metastatic').

In patients who have previously received treatment with a 'CDK 4/6 inhibitor' medicine, there should be at least 12 months since stopping treatment with the 'CDK 4/6 inhibitor' medicine and when the breast cancer has come back.

Before starting treatment with Itovebi, your doctor will test your cancer for a *PIK3CA* mutation.

How Itovebi works

Itovebi works by blocking the effects of a protein called ‘p110 alpha’. This protein is produced by the *PIK3CA* gene. A mutation in this gene may cause cancer cells to grow and multiply more rapidly. By blocking the protein, Itovebi can reduce growth and spread of the cancer and help to destroy cancer cells.

What other medicines Itovebi is given with

Itovebi is used in combination with ‘palbociclib’ and ‘fulvestrant’, which are medicines used to treat breast cancer.

In women who have not reached menopause and in men, treatment with Itovebi will also be combined with a medicine called a luteinising hormone-releasing hormone (LHRH) agonist.

Please read the Package Leaflet for these medicines for further information.

2. What you need to know before you take Itovebi

Do not take Itovebi

- if you are allergic to inavolisib or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor or pharmacist before taking Itovebi if you have ever had:
- high levels of sugar in your blood, diabetes, or signs of high blood sugar levels (hyperglycaemia), such as feeling very thirsty and dry mouth, needing to pass urine more often than usual, producing greater amounts of urine than usual, feeling tired, feeling sick (nausea), increased appetite with weight loss, blurred vision, and/or feeling lightheaded
- kidney problems

Tell your doctor straight away if you develop symptoms of any of the following side effects while taking Itovebi (see ‘Serious side effects’ in section 4 for more information):
- High blood sugar levels (hyperglycaemia) – your doctor may tell you to drink more water during treatment with Itovebi
- Inflammation of the lining of the mouth (stomatitis)

Your doctor may need to treat these symptoms, pause your treatment, reduce your dose, or permanently stop your treatment with Itovebi.

Monitoring during your treatment with Itovebi

Your doctor will do blood tests before and regularly during treatment with Itovebi. This is to monitor your blood sugar levels.

Your doctor may also ask you to monitor your blood sugar at home during treatment with Itovebi.
- Your doctor will tell you exactly when to test your blood sugar..
- This will be needed more often in the first 4 weeks of treatment. If you are not sure how to test your blood sugar, talk to a doctor, pharmacist, or nurse.

Based on the results, your doctor will take any necessary actions - such as prescribing a medicine to lower blood sugar levels. If necessary, your doctor may decide to pause treatment with Itovebi - or

reduce your Itovebi dose to decrease your blood sugar levels. Your doctor may also decide to stop Itovebi treatment permanently.

Children and adolescents

This medicine should not be given to children and adolescents below 18 years of age. This is because Itovebi has not been studied in this age group.

Other medicines and Itovebi

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This is because Itovebi may increase or reduce the effectiveness of some medicines. This includes medicines obtained without a prescription and herbal medicines.

In particular, tell your doctor or pharmacist if you are taking:
- alfentanil (medicine to treat pain and for anaesthesia)
- astemizole (medicine to treat allergies)
- cisapride (medicine to treat heartburn and acid reflux)
- paclitaxel (medicine to treat various cancers)
- quinidine (medicine to treat certain types of irregular heartbeats)
- warfarin (medicine to treat or prevent blood clots)
- medicines to prevent seizures or fits (such as phenytoin and S-mephenytoin)
- medicines that affect the immune system (cyclosporine, sirolimus, and tacrolimus)

The medicines listed here may not be the only ones that could interact with Itovebi. Ask your doctor or pharmacist if you are not sure whether your medicine is one of the medicines listed above.

Pregnancy

- You should not take Itovebi if you are pregnant. This is because it is possible that Itovebi could harm your unborn baby.
- If you are able to become pregnant, your doctor will check you are not already pregnant before starting you on treatment with Itovebi. This may include having a pregnancy test.
- If you become pregnant while taking the medicine, tell your doctor right away.
- If you or your partner are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Contraception for men and women

- If you are a woman who is able to become pregnant, you should use a non-hormonal method of birth control during treatment and for 1 week after stopping Itovebi. Ask your doctor or pharmacist about suitable methods.
- If you are male and have a female partner who are or can become pregnant, you should use a condom during treatment and for 1 week after stopping Itovebi.

Breast-feeding

- You should not breast-feed while taking Itovebi and for 1 week after stopping Itovebi. This is because it is not known if this medicine can pass into breast milk and harm your baby.

Driving and using machines

Itovebi may affect your ability to drive and use machines. If you feel tired while taking Itovebi, take special care when driving or using tools or machines. You should not drive or use machines until you are sure that your ability to perform such activities is not affected.

Itovebi contains lactose and sodium

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

This medicine contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially ‘sodium-free’.

3. How to take Itovebi

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

How much Itovebi to take

The usual starting dose of Itovebi is 9 mg taken once a day.

Your doctor will decide on the right dose for you. However, you may be prescribed:
- 6 mg once a day, or
- 3 mg once a day

Depending on how you respond to the treatment with Itovebi, your doctor may adjust your Itovebi dose. If you have certain side effects, your doctor may ask you to change to a lower dose, to pause treatment for a time, or to stop treatment.

How to take Itovebi

Take Itovebi once a day with or without food. Taking Itovebi at the same time each day will help you to remember when to take your medicine.

Itovebi tablets should be swallowed whole; they should not be chewed, crushed or split before swallowing. You should not swallow any tablet that is broken, cracked or otherwise damaged as you may not be taking the full dose.

How long to take Itovebi

Keep taking Itovebi every day for as long as your doctor tells you.

This is a long-term treatment - possibly lasting for months or years. Your doctor will regularly monitor your condition to check that the treatment is having the desired effect.

If you have questions about how long to take Itovebi, talk to your doctor or to your pharmacist.

If you take more Itovebi than you should

If you take more Itovebi than you should, talk to your doctor or go to the hospital straight away. Take the medicine pack and the package leaflet with you.

If you forget to take Itovebi

If you miss a dose of Itovebi, you may still take it up to 9 hours after the time you should have taken it.
- If it has been more than 9 hours from the time you should have taken it, skip the dose for that day.
- The next day, take the dose at your usual time.

Do not take a double dose to make up for a forgotten dose.

If you vomit right after taking a dose of Itovebi

If you vomit after taking a dose of Itovebi, do not take an extra dose on that day. Take your regular dose of Itovebi at your usual time the next day.

If you stop taking Itovebi

Do not stop taking Itovebi unless your doctor tells you to stop or you have serious side effects (see section 4 'Possible side effects'). This is because stopping treatment may make your illness worse.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Talk to your doctor if you experience the following side effects during treatment with Itovebi. Your doctor may need to treat these symptoms, temporarily pause your treatment, reduce your dose, or permanently stop your treatment with Itovebi.

Serious side effects

If you have any of these side effects, stop taking this medicine and tell your doctor straight away:
- High blood sugar (hyperglycaemia) (very common; may affect more than 1 in 10 people), symptoms include:
    - difficulty breathing
    - nausea and vomiting (lasting more than 2 hours)
    - stomach pain, feeling very thirsty or dry mouth
    - passing urine more often than usual or passing greater amounts of urine than usual,
    - blurred vision
    - unusually increased appetite
    - weight loss, fruity-smelling breath
    - flushed face and dry skin, and feeling unusually sleepy or tired
- Inflammation of the lining of the mouth (stomatitis) (very common; may affect more than 1 in 10 people), symptoms include:
    - pain
    - redness
    - swelling
    - ulcers in the mouth
- A serious complication of high blood sugar that involves high blood levels of ketones that can make blood more acidic (ketoacidosis) (uncommon; may affect up to 1 in 100 people), symptoms may include:
    - difficulty breathing
    - headache
    - nausea
    - vomiting

Other side effects

Tell your doctor or pharmacist if you notice any of the following side effects or if they get worse:

Very common (may affect more than 1 in 10 people)

- diarrhoea
- low levels of platelets (helps the blood to clot), which may cause unusual bruising or bleeding (thrombocytopenia)
- tiredness
- low levels of red blood cells (anaemia), which may cause tiredness, feeling unwell, and pale skin
- feeling sick (nausea)
- rash
- loss of appetite
- headache
- hair loss or hair thinning (alopecia)
- weight loss
- increased levels of alanine aminotransferase (a type of liver enzyme) seen in blood test
- low levels of potassium seen in blood test
- abdominal pain
- vomiting
- dry skin
- urinary tract infection

Common (may affect up to 1 in 10 people)

- low levels of calcium seen in blood test
- dry eye
- indigestion (dyspepsia)
- high levels of insulin (a hormone that helps the body use sugar for energy) seen in blood test
- disturbed sense of taste (dysgeusia)
- skin inflammation with rash (dermatitis)
- infection or inflammation of hair follicles (folliculitis)

Tell your doctor or pharmacist if you notice any of these side effects or if they get worse.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Itovebi

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the blister after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not use this medicine if you notice any damage to the packaging or if there are any signs of tampering, or if the tablet is broken, cracked, or otherwise not intact.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Itovebi contains

- The active substance is inavolisib.
- Each 3 mg film-coated tablet contains 3 mg inavolisib.
- Each 9 mg film-coated tablet contains 9 mg inavolisib.

The other ingredients are:
- Tablet core (3 mg and 9 mg film-coated tablets): lactose monohydrate, magnesium stearate (E 470b), microcrystalline cellulose (E 460), sodium starch glycolate (see section 2 ‘Itovebi contains lactose and sodium’).
- Film-coating (3 mg film-coated tablets): polyvinyl alcohol, partially hydrolysed; titanium dioxide (E 171); macrogol; talc (E 553b); and iron oxide red (E 172).
- Film-coating (9 mg film-coated tablets): polyvinyl alcohol, partially hydrolysed; titanium dioxide (E 171); macrogol; talc (E 553b); iron oxide red (E 172); and iron oxide yellow (E 172).

What Itovebi looks like and contents of the pack

Itovebi 3 mg film-coated tablets (tablets) are red and round convex-shaped with an “INA 3” debossing on one side. Approximate diameter: 6 mm.

Itovebi 9 mg film-coated tablets (tablets) are pink and oval-shaped with an “INA 9” debossing on one side. Approximate size: 13 mm (length), 6 mm (width).

The Itovebi film-coated tablets are provided in cartons containing 28 × 1 film-coated tablets in perforated unit-dose blisters.

Marketing Authorisation Holder

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Manufacturer

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This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu