swissmedic

Date: 21 March 2025
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Itovebi

International non-proprietary name:	inavolisib
Pharmaceutical form:	film-coated tablets
Dosage strength(s):	3 mg, 9 mg
Route(s) of administration:	oral use
Marketing authorisation holder:	Roche Pharma (Schweiz) AG
Marketing authorisation no.:	69792
Decision and decision date:	approved on 31 January 2025

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

Table of contents

1 Terms, Definitions, Abbreviations

ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
BC	Breast cancer
BCRP	Breast cancer resistance protein
CCOD	Clinical cutoff date
CDK4/6	Cyclin-dependent kinase 4/6
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DOR	Duration of response
EC_{50}	Half-maximal effective dose
ECOG	Eastern Cooperative Oncology Group
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
ER	Exposure-response
ERA	Environmental risk assessment
FCT	Film-coated tablet
FDA	Food and Drug Administration (USA)
HER2	Human epidermal growth factor receptor 2
HPLC	High-performance liquid chromatography
HR	Hormone receptor
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
INN	International non-proprietary name
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MTD	Maximum tolerated dose
NE	Not estimable
NO(A)EL	No observed (adverse) effect level
ORR	Overall response rate
OS	Overall survival
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PFS	Progression-free survival
P-gp	P-glycoprotein
PI3K	Phosphatidylinositol-4,5-bisphosate-3-kinase
PIK3CA	gene coding for phosphatidylinositol-3-kinase catalytic subunit alpha
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
QD	quaque die (Latin: once a day)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for inavolisib in the above-mentioned medicinal product.

Project Orbis
The applicant requested a marketing authorisation procedure within the framework of Project Orbis. Project Orbis is coordinated by the FDA and provides a framework for concurrent submission and review of oncology products among international partners.

2.2 Indication and dosage

2.2.1 Requested indication

Inavolisib, in combination with palbociclib and endocrine therapy, is indicated for the treatment of adult patients with *PIK3CA*-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer, following recurrence on or after adjuvant therapy or progression on an endocrine-based regimen in the metastatic setting.

2.2.2 Approved indication

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

2.2.3 Requested dosage

Summary of the requested standard dosage:
Inavolisib 9 mg orally, once daily
Palbociclib 125 mg orally, once daily on days 1 to 21 of 28-day cycles
Endocrine therapy: see corresponding Information for healthcare professionals
In case of adverse events reduce dose of inavolisib to 6 mg once daily (first dose reduction) or to 3 mg once daily (second dose reduction).
Maintain treatment until progression of disease or unacceptable toxicity.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	29 April 2024
Formal control completed	2 May 2024
Preliminary decision	15 October 2024
Response to preliminary decision	15 December 2024
Final decision	31 January 2025
Decision	approval

3 Medical context

Breast cancer (BC) is the most frequently diagnosed cancer in women, with a global incidence estimated at 2.2 million new cases and nearly 700,000 deaths reported yearly. According to the Swiss Cancer Report 2021, between 2013 and 2017 BC was the most common cancer among women in Switzerland, with an average of over 6,200 new cases per year, accounting for nearly one-third of all female cancer diagnoses.

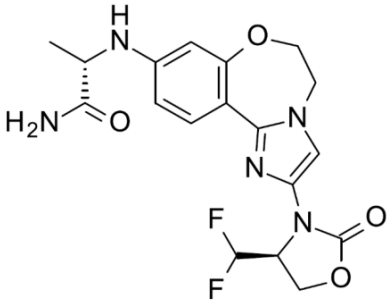
The hormone receptor-positive (HR-positive), human epidermal growth factor receptor 2-negative (HER2-negative) subtype is the most prevalent, making up about 70% of all BC cases. The 5-year survival rate for distant disease in HR-positive, HER2-negative locally advanced/metastatic BC is around 35% (SEER 2023). Around 35-40% of patients with HR-positive BC have tumours with phosphatidylinositol-3-kinase catalytic subunit alpha (PIK3CA) mutations.

Currently, patients with HR-positive, HER2-negative locally advanced/metastatic BC who have tumours with a PIK3CA mutation can receive, as first-line treatment, any standard-of-care therapy for HR-positive, HER2-negative locally advanced/metastatic BC, which includes sequential endocrine-based therapies combined with a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor or chemotherapy-based regimens in cases of endocrine refractoriness/resistance or rapid disease progression.

4 Quality aspects

4.1 Drug substance

INN:	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:	$C_{18}H_{19}F_2N_5O_4$
Molecular mass:	407.37 g/mol
Molecular structure:	



Physicochemical properties: Inavolisib is a white to off-white, greyish pink, greyish orange, or greyish yellow powder. It exhibits stereoisomerism due to the presence of two chiral centres. The isomer with S configuration at both centres is the active substance. The substance shows polymorphism. A thermodynamically stable crystalline form is manufactured. The substance is non-hygroscopic.
The drug substance demonstrates pH-dependent aqueous solubility, which is greatest at low pH.

Synthesis: The drug substance is synthesised from three starting materials in six linear steps, followed by recrystallisation and operations to obtain the specified particle size distribution. The synthesis of the drug substance is adequately described, and the process is controlled by appropriate in-process controls and tests for isolated intermediates. Confirmation of the chemical structure is provided by elemental and spectroscopic analysis.

Specification: The active substance specifications include tests for appearance, identification, assay (HPLC), organic impurities (HPLC), chiral impurities (HPLC), residual solvents (HS-GC), residue on ignition, particle size distribution and microbial quality. The specifications conform to the requirements outlined in the relevant ICH guidelines and are considered appropriate in order to ensure a consistent drug substance quality.

Stability: The drug substance is packaged in double low-density polyethylene (LDPE) bags. A stability study, according to the current guideline recommendations, was carried out. No significant change in any of the parameters was observed. Based on these results a satisfactory retest period was established for inavolisib drug substance.

4.2 Drug product

Description and composition: Inavolisib drug product is formulated as 3 mg and 9 mg immediate-release film-coated tablets (FCTs). The 3 mg formulation is a round convex, red FCT with an “INA 3” debossing on one side. The 9 mg formulation is an oval, pink FCT with an “INA 9” debossing on one side. The tablet cores consist of the pharmaceutical excipients microcrystalline cellulose, lactose, sodium starch glycolate and magnesium stearate. The tablets are film-coated with a mixture of partially hydrolysed polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc and iron oxide.

Pharmaceutical development: The development of the drug product followed an enhanced development approach that included elements of a quality by design and risk-based methodology.

Manufacture: The manufacturing process for the commercial drug product involves standard and conventional pharmaceutical operations and is described with a sufficient level of detail.

Specification: For the control of the finished product, adequate tests and criteria for release and at shelf-life are established. The specifications include the parameters of description (visual examination), identification (HPLC, UV), assay (HPLC), uniformity of dosage units (HPLC), degradation products (HPLC), water content (Karl Fischer titration) and dissolution testing. The test methods are adequately validated according to the recommendations of the current scientific guidelines.

Container closure system: The container closure system for the drug product consists of a cold-formed aluminium foil blister sealed with an aluminium lidding foil.

Stability: Appropriate stability data are presented for primary and supportive stability batches. Based on these data, a shelf-life and a storage recommendation (“Do not store above 30°C”) was established for the film-coated tablets.

4.3 Quality conclusions

Satisfactory and consistent quality of the drug substance and drug product has been demonstrated.

5 Nonclinical aspects

5.1 Pharmacology

Inavolisib is a potent inhibitor of the alpha isoform of the phosphatidylinositol-4,5-bisphosphate-3-kinase (PI3Kα) with a Ki of 0.038 nM, which is at least 300-fold more selective than other class I PI3K isoforms. Treatment of cells with inavolisib resulted in depletion of p110α protein in the breast cancer cell lines containing mutant PIK3CA, but not in cell lines with wild-type for PIK3CA. Inavolisib showed a greater reduction in levels of pathway markers such as pAKT and a greater increase in apoptosis in PIK3CA mutant cell lines than in wild-type cancer cells.
Inavolisib inhibited cellular proliferation of PIK3CA-mutated breast cancer cells *in vitro*, with median EC_{50} values in the nanomolar range. Combining inavolisib with fulvestrant or palbociclib in MCF-7 cells harbouring a hot-spot mutation in the p110α catalytic subunit of PI3K resulted in a modest additive effect. Inavolisib treatment inhibited the expression of the PI3K pathway phosphoprotein markers pAKT, pPRAS40 and pS6RP in a time- and dose-dependent manner in the HCC1954X1 breast cancer mouse model. Oral inavolisib administration dose-dependently inhibited tumour growth of KPL-4 or HCC1954X1 *PIK3CA*-mutated human breast cancer cells, with ED_{50} values of 2.91 and 5.42 mg/kg *in vivo*. A modest additive effect on MCF7 tumour growth inhibition was observed in combination studies of inavolisib with palbociclib and/or fulvestrant.

Inavolisib showed no off-target activity in an *in vitro* screening study.

Cardiovascular endpoints were assessed in dedicated safety pharmacology studies, and the central nervous and respiratory system endpoints were incorporated in the repeat-dose toxicology studies. No inavolisib-related adverse effects were seen at clinically relevant exposures.

5.2 Pharmacokinetics

Bioavailability after oral administration ranged from 57% to 100% in nonclinical species. The terminal half-life ranged from 0.72 h (mouse) to 4.75 h (dog), compared with a human $t_{1/2}$ value of 16.4 h. After repeated oral dosing in rats or dogs, both C_{max} and AUC increased with the dose. In rats, exposure was generally higher in females than in males.

Inavolisib showed 27%-75% plasma protein binding in human, monkey, dog, rat and mouse, and remained predominantly in plasma with low partition to red blood cells *in vitro*. In rats, ^{14}C-inavolisib-derived radioactivity was distributed to tissues and clearance from the body was slow. Brain penetration was negligible. There was significant distribution to melanin-containing tissues.

The turnover of inavolisib in rat, dog and human liver microsomes was low. No human-specific metabolites were identified. After a single oral dose, intact inavolisib was the most prominent drug-related compound in rat and human plasma. No metabolite accounted for more than 10% of the radioactivity in any matrix. The major elimination routes for inavolisib in humans and rats were both urinary and faecal excretion and metabolism.

Secretion into milk has not been studied. Because of the mode of action and the possibility of adverse effects, inavolisib is not recommended during lactation. This information is adequately stated in the Information for healthcare professionals.

5.3 Toxicology

The applicant's toxicology programme for inavolisib was based on ICH S9. The repeat-dose toxicity studies were conducted in rats and dogs, both of them being pharmacologically relevant animal species based on the similarity of *in vitro* metabolic profiles to that of humans and the anticipated PD effects of

inavolisib in these species. Inavolisib was administered orally, in accordance with the intended clinical route of administration. The duration of the repeat-dose toxicity studies (up to 13 weeks in rats and dogs and a 12-week recovery period in dogs) is appropriate for a product intended for the treatment of advanced cancer.

Single oral doses of up to 30 mg/kg in rats or 10 mg/kg in dogs were well tolerated, but repeated doses resulted in mortality in dogs at 5/3 mg/kg/day. Adverse effects of inavolisib administration in nonclinical species were observed on body weight, metabolism (hyperglycaemia and related microscopic changes), haematopoietic and inflammatory parameters, ocular system (lens degeneration), lymphoid organs, and male and female reproductive organs. All effects were observed at exposure levels close to or below the human exposure levels at therapeutic dose. They are consistent with the expected pharmacological effects of inavolisib.

Inavolisib was not mutagenic in the bacterial mutagenesis assay but induced micronuclei through a clastogenic mechanism in an *in vitro* lymphocyte micronucleus assay. Inavolisib was not genotoxic in an *in vivo* assay.

Inavolisib has not been tested for carcinogenicity, in accordance with ICH S9.

In line with ICH S9 guidelines, no fertility and early embryonic development or pre- and postnatal development toxicity studies were conducted. Based on the observed adverse effects on reproductive organs in the repeat-dose toxicity studies, inavolisib may affect male and female fertility. This is addressed in the Information for healthcare professionals. Maternal and embryofoetal toxicity were noted in pregnant rats. Embryofoetal adverse effects were observed at 2 mg/kg/day (decreased foetal body weight and placental weight) in addition to higher post-implantation loss, lower foetal viability, and malformations at 6 mg/kg. The NOAEL for embryofoetal toxicity was 0.6 mg/kg/day in the rat (exposure 0.24-fold the human AUC at the therapeutic dose) and 2 mg/kg/day for maternal toxicity (exposure 0.84-fold the human AUC at the therapeutic dose). Due to the identified embryofoetal toxicity, inavolisib is not recommended for use during pregnancy or in women of childbearing potential not using contraception, as addressed in the Information for healthcare professionals.

Inavolisib did not show phototoxicity potential in the 3T3 assay. Therefore, the phototoxicity risk is considered to be low.
According to the ERA, inavolisib does not pose a risk to the environment.

All relevant nonclinical safety findings are included in the nonclinical part of the safety specification of the RMP. The EMA granted a product-specific waiver for all subsets of the paediatric population.

5.4 Nonclinical conclusions

The submitted nonclinical documentation is considered sufficient to support the approval of inavolisib in the proposed indication. The submitted nonclinical data support the approval of Itovebi (inavolisib) for the proposed indication.

6 Clinical aspects

6.1 Clinical pharmacology

General aspects
The PK of inavolisib is based on a mass balance study GP42652 in healthy subjects and on data from two clinical studies GO39374 and WO41554 (INAVO120) in the intended patient population using a popPK approach. A total of 3863 PK observations from 336 patients were included in the model development.
The PK parameters of inavolisib are well described by a three-compartment model with 1st-order absorption, linear elimination and a proportional and additive mixed error model.

Overall, the PK of inavolisib is proportional to the dose over the dose range evaluated in study GO39374 (6 mg to 12 mg). With the proposed dosage regimen, an increase of approximately twofold (based on $AUC_{0\text{-}24h}$ or C_{max}) is observed when steady-state exposures are compared to those of a single dose.

ADME
Absorption
After oral administration of a 9 mg dose of inavolisib, with no food (no food effect was observed), the absolute bioavailability was determined at 76%. Maximal plasma concentrations were observed at a median time of 3.0 h post-dose.

Distribution
The volume of distribution of inavolisib was determined to be 155 L at steady state and 204 L during the terminal phase. Inavolisib appeared to be weakly bound to proteins (37% regardless of inavolisib concentration), mainly to albumin according to an *in vitro* study.

Metabolism and excretion
The predominant entity circulating in the plasma was inavolisib (95.1%). After a single 9 mg dose of inavolisib in healthy subjects, the elimination routes are urinary and faecal excretion in equal parts, with 48.5% of the dose found in the urine (40.4% in unchanged form) and 48% in the faeces (10.8% in unchanged form). Metabolism of inavolisib occurs predominantly via amidase hydrolysis and, to a lesser extent, by CYP3A4 and, to an even lesser extent, CYP3A5. Inavolisib has a systemic clearance of 8.83 L/h with an elimination half-life ($T_{1/2}$) of 16.4 days in a typical patient.

Special populations
In patients with mild renal impairment (eGFR 60-89 mL/min), no alteration in PK was expected based on a popPK analysis. Consequently, dose adjustment is not necessary. In a dedicated clinical study, exposure (AUC) to inavolisib in patients with moderate renal impairment (eGFR 30-59 mL/min) was significantly increased, requiring a dosage adjustment with a daily dose reduced to 6 mg instead of 9 mg. For subjects with severe renal impairment (eGFR < 30 mL/min), the use of inavolisib is not recommended due to a lack of data. Mild hepatic impairment (total bilirubin > ULN to ≤ 1.5 × ULN or AST > ULN and total bilirubin ≤ ULN) had no effect on inavolisib exposure. For moderate or severe hepatic impairment, no dose recommendation can be made due to a lack of data. Based on a popPK analysis, the covariates (age, body weight…) were not considered clinically relevant.

Interactions
Impact of other compounds on inavolisib PK
There was a low potential for PK-based interactions based on *in vitro* studies investigating the impact of other compounds on inavolisib-metabolising enzymes (CYP3A4 and, to a lesser extent, CYP3A5) and/or its transporters (P-gp and BCRP).

Impact of inavolisib on other compounds
The potential for inavolisib to interact with other compounds has been studied *in vitro,* in clinical interaction studies and with a PBPK model. Overall, inavolisib has a low potential for PK-based interactions with other compounds. No clinically significant interactions were identified.

Pharmacodynamics
Safety pharmacology
Based on the results of the concentration-ΔQTc modelling, summary statistics, the incidence of electrocardiogram (ECG) interval values and rhythm abnormalities, inavolisib administered at 9 mg daily (QD) does not cause a clinically significant QTcF prolongation that exceeds the regulatory threshold of concern (<10 ms) based on ECG data collected during the GO39374 (Phase I) study.

Relationship between Plasma Concentration and Effect – Efficacy
Exposure-response (ER) analyses revealed no relationship between inavolisib exposure (C_{max}, C_{min} or AUC) and clinical response markers: progression-free survival (PFS), overall response rate (ORR), best overall response (BOR), duration of response (DOR), clinical benefit rate (CBR), and time to first subsequent cancer therapy after study treatment (TFST).

Relationship between Plasma Concentration and Effect – Safety
Exposure-safety analyses revealed no relationship between inavolisib exposure (C_{max}, C_{min} or AUC) and all AEs of interest (Grade ≥2 hyperglycaemia, neutropenia, thrombocytopenia, diarrhoea, stomatitis; any Grade ≥3 AE; dose modification due to AE) even if trends between inavolisib exposure and AEs were observed on an *ad hoc* basis.

6.2 Dose finding and dose recommendation

The dose-finding Study GO39374 included a dose-escalation stage and a dose-expansion phase. In the dose-finding phase, inavolisib was administered both as a single agent and in combination therapy (hormone therapies, HER-2 inhibitors or metformin) in patients with locally advanced or metastatic PIK3CA-mutated solid tumours. The maximum tolerated dose (MTD) of inavolisib was determined to be 9 mg QD, as two patients experienced dose-limiting toxicities at the 12 mg QD dose level. No dose-limiting toxicities were reported in combination arms up to 9 mg QD. In the dose-expansion phase, patients with PIK3CA-mutated, HR-positive, HER2-negative BC were enrolled in three different combination treatment arms, among a total of seven arms. The efficacy results of these three arms confirm the activity of inavolisib. Dose finding is suboptimal as it is derived from a very small sample size and based on an MTD approach, which might be not the appropriate choice for targeted therapies. As there is not an ER relationship for efficacy, it remains unclear whether a lower dosage could have had the same efficacy. However, although suboptimal, the dose finding can be accepted.

6.3 Efficacy

Study INAVO120 study was a pivotal Phase III, randomised, double-blind, placebo-controlled, multi-centre trial designed to evaluate the efficacy and safety of the addition of inavolisib to palbociclib and fulvestrant in patients with PIK3CA-mutated, HR-positive, HER2-negative, locally advanced or metastatic BC. Eligible patients had disease progression during treatment or within 12 months of completing adjuvant endocrine therapy and had not received prior systemic therapy for locally advanced or metastatic disease.
A total of 325 patients were randomised: 161 to the inavolisib + palbociclib + fulvestrant (Inavo+Palbo+Fulv) arm and 164 to the placebo + palbociclib + fulvestrant (Pbo+Palbo+Fulv) arm.
The demographic and disease-related baseline characteristics were as follows: median age of 54 years; 98.2% female, of whom 38.2% were pre-/perimenopausal; 58.8% white, 38.2% Asian, 2.5% unknown, and 0.6% black or African American; 6.2% of patients were of Hispanic or Latin American origin. The Eastern Cooperative Oncology Group (ECOG) performance status was 0 in 63.4% of patients and 1 in 36.3%. Secondary endocrine resistance was observed in 64.3% of patients. A total of 82.8% of patients

had received prior chemotherapy. Three patients (0.9%) had previously been treated with a CDK4/6 inhibitor. At study entry, 0.9% of patients had locally advanced BC.

The primary endpoint was investigator-assessed progression-free survival (PFS); type I controlled secondary endpoints included overall survival (OS). Given the double-blind placebo controlled design, investigator-assessed PFS is acceptable.

As of the clinical cutoff date (CCOD) on 29 September 2023, 64.6% of patients in the Inavo+Palbo+Fulv arm and 59.1% in the Pbo+Palbo+Fulv arm were continuing the study. At the time, 41.6% were still on treatment in the inavolisib arm compared to 29.9% in the placebo arm.

INAVO120 met its primary endpoint, demonstrating a statistically significant and clinically meaningful improvement in investigator-assessed PFS. At CCOD, the median follow-up was 21.3 months in the Inavo+Palbo+Fulv arm and 21.5 months in the placebo arm. A total of 195 PFS events had occurred: 82 (50.9%) in the inavolisib arm and 113 (68.9%) in the placebo arm. The PFS hazard ratio was 0.43 (95% CI: 0.32, 0.59; p-value <0.0001). The median PFS was 15.0 months in the Inavo+Palbo+Fulv arm versus 7.3 months in the Pbo+Palbo+Fulv arm. The Kaplan-Meier curves began to separate at around 2.5 months and remained separated throughout follow-up.

At CCOD, 97 OS events had occurred (63% of the planned total), with a median follow-up of 21.3 months. At the 1st Interim Analysis for OS the hazard ratio was 0.64 (95% CI: 0.43, 0.97; p = 0.0338), with 42 deaths (26.1% of the intent-to-treat population) in the Inavo+Palbo+Fulv arm and 55 deaths (33.5%) in the Pbo+Palbo+Fulv arm. A statistical significance was not met, as the interim analysis stopping boundary (p < 0.0098) was not crossed. The median OS was not estimable (NE) in the Inavo+Palbo+Fulv arm (95% CI: 27.3-NE) and 31.1 months (95% CI: 22.3-NE) in the Pbo+Palbo+Fulv arm. The Kaplan-Meier curves started to separate around month 2 in favour of the Inavo+Palbo+Fulv arm and remained separated throughout follow-up. The OS results are currently immature, with high censoring beyond 12 months of follow-up; however, a detriment was not observed. The final OS analysis is planned at 153 OS events, expected in Q2 2025.

6.4 Safety

Overall, the addition of inavolisib to palbociclib and fulvestrant led to an increased incidence of the following treatment-emergent adverse events (TEAEs) occurring in at least 20% of patients in the Inavo+Palbo+Fulv arm: hyperglycaemia (53.7% in the Inavo+Palbo+Fulv vs. 7.4% in the Inavo+Palbo+Fulv arm), diarrhoea (48.1% vs. 16.0%), stomatitis (32.7% vs. 16.7%), nausea (27.8% vs. 16.7%), fatigue (23.5% vs. 13.0%), decreased appetite (23.5% vs. 8.6%), COVID-19 (22.8% vs. 10.5%), and headache (21.0% vs. 13.6%).

The incidence of Grade 3-4 TEAEs was comparable between the two arms, occurring in 85.8% of patients in the Inavo+Palbo+Fulv arm and 82.1% in the Pbo+Palbo+Fulv arm.

Serious adverse events (SAEs) were reported in 24.1% of patients in the Inavo+Palbo+Fulv arm compared to 10.5% in the Pbo+Palbo+Fulv arm. The most frequently occurring SAEs in the Inavo+Palbo+Fulv arm (reported in ≥2 patients) included COVID-19, pneumonia, anaemia, and febrile neutropenia.

Fatal adverse events were reported in six patients (3.7%) in the Inavo+Palbo+Fulv arm and two patients (1.2%) in the Pbo+Palbo+Fulv arm. In the Inavo+Palbo+Fulv arm the causes of death were the following: acute coronary syndrome, COVID-19, cerebral haemorrhage, cerebrovascular accident, gastrointestinal haemorrhage, death.

6.5 Final clinical benefit risk assessment

The INAVO120 study met its primary endpoint, demonstrating a statistically significant and clinically meaningful improvement in PFS. However, the results must be interpreted alongside OS outcomes, a key secondary endpoint of the study. At the time of the current analysis, OS results were immature, as shown by the high censoring rate in the Kaplan-Meier curves starting from 12 months of follow-up. Nevertheless, with the data currently available no OS detriment is observed. Updated OS data will be required as a post-authorisation requirement.
The toxicity is higher in the experimental arm compared to the control arm but can be managed by physicians experienced with these agents. The relevant risks are adequately addressed in the Information for healthcare professionals.
In conclusion, the benefit-risk is positive for the addition of inavolisib to palbociclib and fulvestrant.

7 Risk management plan summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Itovebi was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼ 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 new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

Itovebi®

Composition

Active substances

Inavolisibum.

Excipients

Cellulosum microcristallinum, Lactosum monohydricum, Carboxymethylamylum natricum A, Magnesii stearas.
One 3 mg film-coated tablet contains max. 0.17mg sodium.
One 9 mg film-coated tablet contains max. 0.51mg sodium.
Tablet coating:
Poly (alcohol vinylicus) partim hydrolysatum, Titanii dioxidum (E 171), Macrogolum 3350, Talcum, Ferrum oxydatum rubrum (E 172), Ferrum oxydatum flavum (E 172, only in 9 mg film-coated tablet).

Pharmaceutical form and active substance quantity per unit

Film-coated tablets containing 3 mg inavolisib and 9 mg inavolisib.
3 mg film-coated tablet:
Each 3 mg film-coated tablet contains 3 mg inavolisib. Itovebi 3 mg film-coated tablets are red and round convex-shaped with “INA 3” embossed on one side.
9 mg film-coated tablet:
Each 9 mg film-coated tablet contains 9 mg inavolisib. Itovebi 9 mg film-coated tablets are pink and oval-shaped with “INA 9” embossed on one side.

Indications/Uses

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

Dosage/Administration

General information

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

Recommended dosage

The recommended dose of Itovebi is 9 mg taken orally once daily independently of meals.
Itovebi should be administered in combination with palbociclib and fulvestrant. The recommended dose of palbociclib is 125 mg taken orally once daily for 21 consecutive days, followed by a 7-day break in treatment, to comprise a complete cycle of 28 days. Please refer to the Information for Healthcare Professionals for palbociclib and fulvestrant (500 mg) for the complete dosing information.
Treatment of pre/perimenopausal women with Itovebi should also include a luteinizing hormone-releasing hormone (LHRH) agonist in accordance with local clinical practice.

Duration of treatment

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

Missed/delayed administration

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

Dose adjustment following undesirable effects/interactions

Management of adverse reactions may require temporary interruption, a dose reduction, or discontinuation of treatment with Itovebi. Itovebi treatment should be permanently discontinued if patients are unable to tolerate the 3 mg daily dose (see Table 1). The recommended dose reduction guidelines for adverse reactions are listed in Table 1.

Table 1: Dose Reduction Guidelines for Adverse Reactions

Dose Reduction Schedule	Modified Dose
Starting dose	9 mg/day
First dose reduction	6 mg/day
Second dose reduction	3 mg/day

Hyperglycaemia

Before initiating treatment with Itovebi, fasting plasma glucose (FPG)/fasting blood glucose (FBG) and HbA_{1C} levels should be measured, and plasma/blood glucose levels should be optimised in all patients. After initiating treatment with Itovebi, fasting glucose (FPG or FBG) levels in the patient should be monitored or self-monitored based on the recommended schedule (see "Warnings and precautions").

Table 2: Dose Adjustment and Management for Hyperglycaemia

Fasting Glucose Levels[a]	**Recommendation[b]**
> ULN to 160 mg/dL (8.9 mmol/L)	● No dose adjustment of Itovebi required. ● Consider dietary modifications (e.g., low carbohydrate diet) and ensure adequate hydration. ● Consider initiating or intensifying oral anti-hyperglycaemic medication[c] for patients with risk factors for hyperglycaemia[d].
> 160 to 250 mg/dL (> 8.9 – 13.9 mmol/L)	● Interrupt Itovebi until fasting glucose level decreases to ≤ 160 mg/dL (≤ 8.9 mmol/L). ● Initiate or intensify anti-hyperglycaemic medication[c,e]. ● Resume Itovebi at the same dose level. ● If fasting glucose level persists at > 200 – 250 mg/dL (> 11.1 – 13.9 mmol/L) for 7 days under appropriate anti-hyperglycaemic treatment, consultation with a healthcare professional experienced in the treatment of hyperglycaemia is recommended
> 250 to 500 mg/dL (> 13.9 – 27.8 mmol/L)	● Interrupt Itovebi. ● Initiate or intensify anti-hyperglycaemic medication[c,e]. ● Administer appropriate hydration if required. ● If fasting glucose level decreases to ≤ 160 mg/dL (≤ 8.9 mmol/L) within 7 days, resume Itovebi at the same dose level. ● If fasting glucose level decreases to ≤ 160 mg/dL (≤ 8.9 mmol/L) within ≥ 8 days, resume Itovebi at the next dose level down (see Table 1). ● If fasting glucose level of > 250 to 500 mg/dL (> 13.9 – 27.8 mmol/L) recurs within 30 days, interrupt Itovebi until fasting glucose level decreases to ≤ 160 mg/dL (≤ 8.9 mmol/L). Resume Itovebi at the next dose level down (see Table 1).
> 500 mg/dL (> 27.8 mmol/L)	● Interrupt Itovebi. ● Initiate or intensify anti-hyperglycaemic medication[c,e]. ● Assess for volume depletion and ketosis and administer appropriate hydration.

Fasting Glucose Levels[a]	Recommendation[b]
	● If fasting glucose level decreases to ≤ 160 mg/dL (≤ 8.9 mmol/L), resume Itovebi at the next dose level down (see Table 1). ● If fasting glucose level of > 500 mg/dL (> 27.8 mmol/L) recurs within 30 days, permanently discontinue Itovebi.

ULN = upper limit of normal

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

[b] Metformin prophylaxis was recommended for patients with risk factors in the INAVO120 study (see "Warnings and precautions").

[c] Initiate suitable anti-hyperglycaemic medication, such as metformin, sodium-glucose cotransporter-2 (SGLT2) inhibitors or insulin sensitisers (such as thiazolidinediones or dipeptidyl peptidase-4 [DPP-4] inhibitors), and review the respective Information for Healthcare Professionals for recommendations on dosing and dose titration, including local hyperglycaemia treatment guidelines. Metformin was recommended in the INAVO120 study as the preferred initial agent (see "Undesirable effects").

[d] Risk factors for hyperglycaemia include, but are not limited to, (pre)diabetes, HbA_{1C} ≥ 5.7% to < 6.5%, BMI ≥ 30 kg/m^2, an age of ≥ 45 years, a medical history of gestational diabetes, and a family history of diabetes mellitus (see "Warnings and precautions").

[e] In the INAVO120 study, short-term insulin was permitted to control blood glucose levels, with the aim of only maintaining blood glucose levels on oral agents once the acute episode has resolved.

Other Adverse Reactions

Table 3: Dose Adjustment and Management for Other Adverse Reactions

Grade[a]	Recommendation
For all grades: Initiate supportive therapy and monitor as clinically indicated.	
Grade 1	● No dose adjustment of Itovebi required.
Grade 2	● Consider interruption of Itovebi, if clinically indicated, until recovery to Grade ≤ 1. ● Resume Itovebi at the same dose level.
Grade 3, first event	● Interrupt Itovebi until recovery to Grade ≤ 1. ● Resume Itovebi at the same dose level or at the next dose level down based on the clinical evaluation (see Table 1).
Grade 3, recurrent OR Grade 4, non-life-threatening	● Interrupt Itovebi until recovery to Grade ≤ 1. ● Resume Itovebi at the next dose level down (see Table 1).

Grade[a]	Recommendation
For all grades: Initiate supportive therapy and monitor as clinically indicated.	
Grade 4, life-threatening	● Permanently discontinue Itovebi.
[a] Based on CTCAE version 5.0.	

Special dosage instructions

Children and adolescents

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

Elderly patients

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

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

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

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

Patients with renal disorders

No dose adjustment is required in patients with mild renal disorders (CrCl ≥ 60 to < 90 mL/min) based on the population pharmacokinetic analysis. The recommended dose for Itovebi in patients with moderate renal insufficiency (CrCl 30 to 59 ml/min) is 6 mg once daily. The safety and efficacy of Itovebi have not been established in patients with severe renal disorders based on the population pharmacokinetic analysis. For details on data on renal disorders, see section "Pharmacokinetics”. Itovebi is known to be excreted via the kidneys, and the risk of adverse reactions may be greater in patients with impaired renal function.

Patients with hepatic disorders

No dose adjustment is required in patients with mild hepatic disorders (total bilirubin > ULN to ≤ 1.5 x ULN or AST > ULN and total bilirubin ≤ ULN). The safety and efficacy of Itovebi have not been studied in patients with moderate to severe hepatic disorders. For details on data on hepatic disorders, see “Warnings and precautions”.

Contraindications

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

Warnings and precautions

Hyperglycaemia

Cases of hyperglycaemia have been reported in patients treated with Itovebi. Such cases were frequently observed and severe hyperglycaemia may occur.

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

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

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

In patients with risk factors for hyperglycaemia including, but not limited to, (pre)diabetes, HbA_{1C} ≥ 5.7% to < 6.5%, BMI ≥ 30 kg/m^2, an age of ≥ 45 years, a medical history of gestational diabetes, and a family history of diabetes mellitus, fasting glucose levels should be monitored or self-monitored daily as clinically indicated. Anti-hyperglycaemic treatment should be initiated or adjusted as required (see " Dosage/Administration"). Metformin prophylaxis was recommended for patients with risk factors for hyperglycaemia in the INAVO120 study.

Patients with a medical history of well-controlled type 2 diabetes mellitus may require intensified anti-hyperglycaemic treatment and close monitoring of fasting glucose levels, as clinically indicated. The safety of Itovebi in patients with type 1 diabetes mellitus or type 2 diabetes mellitus requiring ongoing

systemic therapy, including patients with baseline HbA_{1c} ≥ 7% and fasting blood glucose > 140mg/dL FPG, has not been studied. Only limited data are available for patients with fasting blood glucose levels of 126-140 mg/dL and an HbA_{1c} value of between 6-7%.

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

Consultation with a healthcare professional experienced in the treatment of hyperglycaemia, and initiation of fasting blood glucose monitoring at home should be considered for patients who have risk factors for hyperglycaemia or who experience hyperglycaemia more often than clinically indicated.

Based on the severity of the hyperglycaemia, Itovebi may require a dose interruption, reduction of the dose, or discontinuation, as described in Table 2 (see “Dosage/Administration”). All patients should be instructed to make lifestyle changes (e.g., change in diet, exercise programme).

Embryo-foetal toxicity

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

Lactose

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

Sodium

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

Stomatitis

Cases of stomatitis have been frequently reported in patients being treated with Itovebi. Based on the severity of the stomatitis, Itovebi may require a dose interruption, reduction of the dose or discontinuation, as described in Table 3.

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

Diarrhoea

Cases of diarrhoea have been reported in patients being treated with Itovebi. Such cases were frequently observed and severe diarrhoea may occur. Based on the severity of the diarrhoea, Itovebi may require a dose interruption, a reduction of the dose or discontinuation, as described in

Table 3. Patients should be advised to start anti-diarrhoeal treatment, increase oral fluids, and notify their healthcare professionals if diarrhoea occurs while taking Itovebi (see "Undesirable effects: Description of specific adverse reactions and additional information").

Infections and infestations

Infections have been reported in patients being treated with Itovebi, including Covid-19, urinary tract infections and pneumonia. Patients should be monitored for signs and symptoms of infections and, based on severity, dosing of Itovebi may be interrupted or reduced, or discontinued permanently (see Table 3)

Patients previously treated with CDK46i (adjuvant)

No conclusive efficacy data are available for patients who have received prior CDK4/6 inhibitors due to the small sample size.

Interactions

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

Effects of inavolisib on the pharmacokinetics of other agents

CYP substrates

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

Transporters

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

Effects of other agents on the pharmacokinetics of inavolisib

CYP inhibitors/inducers

Clinical study results show that the predominant metabolites of inavolisib are not mediated by CYP enzymes, suggesting a low likelihood of interaction between inavolisib and CYP inhibitors or inducers.

Transporters

In vitro studies have shown that inavolisib is not a substrate of OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT2, MATE1, or MATE2K, but is a substrate of P-gp and BCRP. However, based on the pharmacokinetic profile of inavolisib, no clinically relevant drug-drug interactions are to be expected between inhibitors or inducers of P-gp and/or BCRP and inavolisib.

Antacids

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

Pregnancy, lactation

Women of child-bearing age

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

Contraception in women and men

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

Pregnancy

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

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

Lactation

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

Fertility

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

Effects on ability to drive and use machines

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

Undesirable effects

Summary of the safety profile

The overall safety profile of Itovebi is based on pooled data from 335 patients with locally advanced or metastatic breast cancer who received 9 mg Itovebi once daily as monotherapy or combination therapy in the Phase 3, randomised INAVO120 study and non-randomised Phase 1 GO39374 study.
The most common adverse reactions (reported at a frequency of ≥ 20%) were hyperglycaemia (63.3%), diarrhoea (57.6%), stomatitis (52.5%), nausea (44.2%), fatigue (42.4%), anaemia (33.7%), thrombocytopenia (33.7%), decreased appetite (29.9%), vomiting (29%), rash (27.2%), headache (26.9%), abdominal pain (21.5%) and alopecia (20.3%).
The most common grade 3 or 4 adverse reactions (reported at frequency of ≥ 2%) were hyperglycaemia (15.8%), thrombocytopenia (9.3%), anaemia (6.6%), stomatitis (4.2%), alanine aminotransferase increased (3.9%), hypokalaemia (3.9%), fatigue (3.3%), diarrhoea (3.3%) and weight loss (2.7%). Serious adverse drug reactions reported in > 1% of patients receiving treatment with inavolisib plus palbociclib plus fulvestrant included urinary tract infections (1.5%).
Regardless of the causal relationship, Grade 5 adverse reactions were reported in 9 (2.7%) patients in the pooled population. These included acute coronary syndrome, hypertrophic cardiomyopathy, gastrointestinal haemorrhage, death, Covid-19, peritonitis, cerebral haemorrhage, cerebrovascular accident and pleural effusion. None of the Grade 5 adverse reactions were reported in more than 1 patient.
In the same pooled population, dose reductions of Itovebi due to adverse reactions were reported in 51 (15.2%) patients. The most common adverse reactions (reported at frequency of ≥ 2%) leading to a dose reduction of inavolisib were hyperglycaemia (5.4%) and stomatitis (3.9%).
Discontinuation of treatment due to adverse reactions occurred in 17 (5.1%) patients. The most common adverse reaction (reported in >1 patient) leading to discontinuation of treatment was hyperglycaemia (0.6%).

List of adverse reactions

The adverse reactions observed during treatment with Itovebi are classified according to MedDRA system organ class and conventional frequencies as follows: "very common" (≥ 1/10), "common" (≥ 1/100, < 1/10), "uncommon" (≥ 1/1,000, < 1/100), "rare" (≥ 1/10,000, < 1/1,000), "very rare" (< 1/10,000), "not known" (cannot be estimated from the available data), see Table 4:

Table 4: Adverse Drug Reactions

System Organ Class Adverse Reaction	Itovebi Monotherapy or Combination therapy N=335			Placebo + Palbociclib + Fulvestrant N=162	
	Frequency Category (All Grades)	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Infections and Infestations					
Urinary Tract Infection	Very Common	14.6	1.5*	7.4	0
Covid-19	Very Common	14.9	0.9	10	0.6
Blood and Lymphatic System Disorders					
Thrombocytopenia[a]	Very Common	33.7	9.3*	45.1	4.3
Anaemia[b]	Very Common	33.7	6.6*	36.4	1.9*
Neutrophils (total, absolute) decreased**	Very Common	95.1	82	97	78.8
Haemoglobin decreased**	Very Common	87.5	7.5	85.1	2.5*
Platelets decreased**	Very Common	83.8	15.6	71.4	3.7
Lymphocytes (absolute) decreased**	Very Common	72.1	9	68.2	14.4
Metabolism and Nutrition Disorders					
Hyperglycaemia[c]	Very Common	63.3	15.8*	9.9	0
Decreased appetite	Very Common	29.9	0.9	8.6	0
Hypokalaemia	Very Common	14.6	3.9*	6.2	0
Hypocalcaemia	Common	7.5	1.2*	2.5	0.6*
Glucose (fasting) increased**[i]	Very Common	85.4	12.1	42.9	0
Calcium decreased**	Very Common	41.9	3.1	31.7	3.7
Potassium decreased**	Very Common	37.5	6.2	20.5	0.6*
Sodium decreased**	Very Common	27.5	2.5	18.6	2.5
Magnesium decreased**	Very Common	26.9	0.6	20.5	0

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

Pooled dataset includes INAVO120 (n=162, grading according to CTCAE version 5.0) and GO39374 (N=173, grading according to CTCAE version 4.0).

* Grade 4 events were observed.

**Only based on INAVO120 study; the denominator used to calculate the incidence in the Itovebi arm varied between 122 and 160 based on the number of patients with a baseline value and at least one post-treatment value, whereas the denominator used to calculate the incidence in the placebo arm varied between 131 and 161 based on the number of patients with a baseline value and at least one post-treatment value.

[a] Includes platelet count decreased and thrombocytopenia.

[b] Includes anaemia and haemoglobin decreased.

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

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

e Includes abdominal pain, upper abdominal pain, and lower abdominal pain

f Includes dysgeusia, ageusia, and hypogeusia

[g] Includes dermatitis, dermatitis acneiform, dermatitis bullous, erythema, folliculitis, rash, rash erythematous, rash maculo-papular, rash papular, rash pruritic, and rash pustular.

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

Description of specific adverse reactions and additional information

Hyperglycaemia

In the INAVO120 study, hyperglycaemia of any grade was reported in 59.9% of patients treated with Itovebi in combination with palbociclib and fulvestrant; Grade 2 and Grade 3 events were reported in 38.3% and 5.6% of patients, respectively, and no Grade 4 events were reported (based on CTCAE version 5.0). Among the patients who experienced hyperglycaemia, the incidence of new-onset hyperglycaemia events was highest during the first two months of treatment (range: 1 to 32 months), with a median time to first onset of 7 days (range: 2 to 955 days).

In patients who received Itovebi in combination with palbociclib and fulvestrant, 43.8% were managed with anti-hyperglycaemic medication, including metformin as a single agent or in combination with other anti-hyperglycaemic medication (i.e., insulin, DPP-4 inhibitors, and sulphonylureas), SGLT2 inhibitors, thiazolidinediones, and DPP-4 inhibitors. In patients with fasting glucose levels > 160 mg/dL (> 8.9 mmol/L), with improvement in fasting glucose levels by at least one level (see Table 2) (n=52), the median time to improvement from the first event was 8 days (range: 2 to 43 days).

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

Stomatitis and oral mucositis

Stomatitis was reported in 51.2% of patients treated with Itovebi in combination with palbociclib and fulvestrant; Grade 1 events were reported in 32.1% of patients, Grade 2 events in 13.6% of patients,

and Grade 3 events in 5.6% of patients. No Grade 4 stomatitis events were reported. The median time to first onset was 13 days (range: 1 to 610 days).
Stomatitis led to an interruption of treatment with Itovebi in 9.9%, to a dose reduction of Itovebi in 3.7%, and to discontinuation of Itovebi in 0.6% of patients.
In patients who received Itovebi in combination with palbociclib and fulvestrant, 24.1% used a mouthwash containing dexamethasone for the management of stomatitis.
Corticosteroid mouthwash was recommended for prophylaxis against stomatitis in the INAVO120 study. Among patients who received Itovebi in combination with palbociclib and fulvestrant, prophylaxis containing dexamethasone or triamcinolone was used in 19.1% and 1.2% of patients, respectively.
Diarrhoea
Diarrhoea was reported in 48.1% of patients treated with Itovebi in combination with palbociclib and fulvestrant; Grade 1 events were reported in 27.8% of patients, Grade 2 events in 16.7% of patients, and Grade 3 events in 3.7% of patients. No Grade 4 diarrhoea events were reported. The median time to first onset was 15 days (range: 2 to 602 days).
Diarrhoea led to an interruption of treatment with Itovebi in 6.8%, to a dose reduction of Itovebi in 1.2%, and did not result in the discontinuation of Itovebi in any patients.
Anti-diarrhoeal medicines (e.g., loperamide) were used to manage symptoms in 28.4% of patients who were treated with Itovebi in combination with palbociclib and fulvestrant.

Undesirable effects from the post-marketing phase
Not applicable.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

There are limited data on overdoses with Itovebi in clinical studies. Itovebi was administered at doses of up to 12 mg once daily in clinical studies.
The highest dose administered in the INAVO120 study was 18 mg in one patient. This case of an accidental overdose was resolved in one day and did not require either treatment or a dose adjustment of any study drugs.
Treatment
Patients who experience an overdose should be closely monitored and supportive care instituted. There are no known antidotes for Itovebi.

Properties/Effects

ATC code

Not yet assigned.

Mechanism of action

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

Clinical efficacy

Locally advanced or metastatic breast cancer

INAVO120

The efficacy of Itovebi in combination with palbociclib and fulvestrant was evaluated in a Phase III, randomised, double-blind, placebo-controlled study in adult patients with *PIK3CA*-mutated, HR-positive, HER2-negative, locally advanced or metastatic breast cancer, whose disease had progressed during or within 12 months of completing adjuvant endocrine therapy and who had not received prior systemic therapy for locally advanced or metastatic disease. The study excluded patients with fasting blood glucose levels ≥ 126 mg/dL (≥ 7.0 mmol/L) and HbA_{1c} values ≥ 6.0% (≥ 42 mmol/mol), and patients on chronic corticosteroid therapy of ≥ 10 mg of prednisone per day or an equivalent dose of other anti-inflammatory corticosteroids or immunosuppressants for a chronic disease. Moreover, patients with type 1 diabetes mellitus or type 2 diabetes mellitus requiring ongoing systemic therapy at the start of study treatment were also excluded.

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

PIK3CA mutation status was prospectively determined through testing of plasma-derived circulating tumour DNA (ctDNA) using a next-generation sequencing (NGS) assay at a central laboratory, or in local laboratories using various validated polymerase chain reaction (PCR) or NGS assays on tumour tissue or plasma. 92.6% of patients were enrolled by ctDNA testing (of these, 94.4% were tested using central ctDNA tests and 5.6% using local ctDNA tests). Central ctDNA tests were performed in all patients with FoundationOne®Liquid CDx (Foundation Medicine), with the exception of the Chinese patient population. 7.4% of patients were enrolled via local tissue testing.

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

A total of 325 patients were randomised 1:1 to receive either 9 mg Itovebi (n=161) or placebo (n=164) orally once daily, in combination with palbociclib and fulvestrant, until disease progression or unacceptable toxicity. In addition, pre/perimenopausal women and men received an LHRH agonist throughout therapy. Randomisation was stratified by presence of visceral disease (yes or no), endocrine resistance (primary or secondary), and geographic region (North America/Western Europe, Asia, other).

The baseline demographic and disease characteristics were: median age 54 years (range: 27 to 79 years); 98.2% female, of whom 38.2% were pre/perimenopausal; 58.8% White, 38.2% Asian, 2.5% unknown, 0.6% Black or African American; 6.2% Hispanic or Latino; and Eastern Cooperative Oncology Group (ECOG) performance status of 0 (63.4%) or 1 (36.3%); secondary endocrine resistance 64.3%. Tamoxifen (56.9%) and aromatase inhibitors (50.2%) were the most commonly used adjuvant endocrine therapies; 82.8% of patients had received prior chemotherapy. Three patients (0.9%) had received prior treatment with a CDK4/6 inhibitor. 0.9% of patients had locally advanced breast cancer at study entry. The demographics and baseline disease characteristics were balanced and comparable between study arms.

The primary efficacy outcome measure was investigator (INV)-assessed progression-free survival (PFS) based on the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. The secondary efficacy outcome measures included overall survival (OS), which is the key secondary endpoint.

Efficacy results are summarised in Table 5, Figure 1, and Figure 2.

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

Table 5: Efficacy Results in Patients with Locally Advanced or Metastatic Breast Cancer in INAVO120 (DCO 29 September 2023)

Efficacy Endpoint	**Itovebi + Palbociclib + Fulvestrant N=161**	**Placebo + Palbociclib + Fulvestrant N=164**
Primary Endpoint		
INV-Assessed Progression-Free Survival[a]		
Patients with event, n (%)*	82 (50.9)	113 (68.9)

Median, months (95% CI)	15 (11.3, 20.5)	7.3 (5.6, 9.3)
Hazard ratio (95% CI)	0.43 (0.32, 0.59)	
p-value	< 0.0001	

CI = confidence interval;

[a] Based on RECIST version 1.1.

Data on overall survival (OS) are still immature. At the DCO date of 29 September 2023, the number of events was as follows:

- 42 OS events in the treatment arm
- 55 OS events in the control arm

Pharmacokinetics

The pharmacokinetics of inavolisib were investigated in patients with locally advanced or metastatic *PIK3CA*-mutated solid tumours, including breast cancer, under an oral dosing regimen ranging from 6 mg to 12 mg daily and in healthy subjects after administration of a single dose of 9 mg.
Inavolisib exhibited dose-proportional pharmacokinetics in patients with locally advanced or metastatic breast cancer over a dose range of 6 mg to 12 mg.
No dose-response relationship was observed for the efficacy of inavolisib. Dose-response relationships were observed for hyperglycaemia (CTCAE Grade ≥ 2) at doses of 3 mg to 12 mg (0.3 to 1.3 times the recommended dosage) and anaemia (CTCAE Grade ≥ 2) at the recommended dosage of 9 mg

Absorption

The time to maximum plasma concentration (T_{max}) was reached after a median of 3 hours (range: 0.5 to 4 hours) at steady state following 9 mg once daily dosing of inavolisib under fasting conditions.
The geometric mean accumulation ratio was 2.04 for 9 mg once daily dosing.
The absolute bioavailability of inavolisib was 76%.
No clinically significant effect of food on the exposure to inavolisib was observed. The geometric mean ratio (GMR) (90% CI) for the AUC_{0-24} after a meal in comparison to the fasting condition was 0.895 (0.737 – 1.09) after a single dose and 0.876 (0.701 – 1.09) at steady state. The GMR (90% CI) for C_{max} after a meal in comparison to the fasting condition was 0.925 (0.748 – 1.14) after a single dose and 0.910 (0.712 – 1.16) at steady state.

Distribution

Plasma protein binding of inavolisib ranged from 27% to 75% (mouse, 75%; rat, 40%; rabbit, 47%; dog, 31%; monkey, 27%; and human, 37%) and did not appear to be concentration-dependent over

the concentration range that was tested (0.1 - 10 µM). In humans, the estimated volume of distribution at steady state after oral administration is 155 L and the blood-to-plasma ratio is approximately 0.794.

Metabolism

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

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

Elimination

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

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

Kinetics in specific patient groups

Children and adolescents

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

Elderly patients

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

Renal impairment

Population pharmacokinetic analyses indicated that mild renal impairment is not a significant covariate of exposure to Itovebi. The pharmacokinetics of inavolisib in patients with mild renal impairment (CrCl 60 to < 90 mL/min) were similar to those in patients with normal renal function.

The pharmacokinetics of inavolisib were investigated in subjects with moderate renal insufficiency (N = 7), corresponding to a CrCl ranging between 30 and 59 ml/min, as well as in 7 control subjects with normal renal function. The AUC and C_{max} for inavolisib were increased by 64% and 11%, respectively, in patients with moderate renal insufficiency in comparison to healthy control subjects after a single administration of an oral dose of 9 mg inavolisib.

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

Hepatic impairment

Population pharmacokinetic analyses indicated that mild hepatic impairment is not a significant covariate of exposure to Itovebi. The pharmacokinetics of inavolisib in patients with mild hepatic impairment (total bilirubin > ULN to ≤ 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 the pharmacokinetics of Itovebi has not been studied.

Preclinical data

Repeated dose toxicity

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

Genotoxicity

Inavolisib was not mutagenic in the bacterial mutagenesis assay.

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

Carcinogenicity

No carcinogenicity studies have been conducted with inavolisib.

Reproductive toxicity

No dedicated fertility studies have been conducted with inavolisib.

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

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

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

Other information

Shelf life

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

Special precautions for storage

Keep out of the reach of children.
Do not store above 30°C.

Disposal of unused/expired medicinal products

The release of medicines into the environment should be minimised. Medicinal products should not be disposed of in wastewater. Avoid disposal in household waste.
Dispose of unused medicinal products and/or waste in accordance with national guidelines.

Authorisation number

69792 (Swissmedic).

Packs

Itovebi 3 mg film-coated tablets: 28 (4 blister packs with 7 film-coated tablets) [A]

Itovebi 9 mg film-coated tablets: 28 (4 blister packs with 7 film-coated tablets) [A]

Marketing authorisation holder

Roche Pharma (Switzerland) Ltd., Basel.

Date of revision of the text

October 2024.