Iowa PDL New Drug Review

Proprietary Name: Itovebi®
Common Name: inavolisib
PDL Category: Antineoplastic Agents

Pharmacology/Usage: Inavolisib, the active ingredient of Itovebi®, is a kinase inhibitor. It is an inhibitor of phosphatidylinositol 3-kinase (PI3K) with inhibitory activity mainly against PI3Kα. In vitro, inavolisib induced the degradation of mutated PI3K catalytic alpha subunit p110α (encoded by the *PIK3CA* gene), inhibited phosphorylation of the downstream target AKT, reduced cellular proliferation, and induced apoptosis in *PIK3CA*-mutated breast cancer cell lines. The combination of inavolisib with palbociclib and fulvestrant increased tumor growth inhibition compared to each treatment alone or the doublet combinations.

Indication: In combination with palbociclib and fulvestrant, for the treatment of adults with endocrine-resistant, *PIK3CA*-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer, as detected by an FDA-approved test, following recurrence on or after completing adjuvant endocrine therapy.

There is no pregnancy category for this medication; but the risk summary indicates that based on animal data and its mechanism of action, Itovebi® can cause fetal harm when administered to a pregnant woman. There are no available data on the use of Itovebi® in pregnant women to inform a drug-associated risk. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. In addition, verify pregnancy status in females of reproductive potential prior to starting Itovebi® treatment. Advise females of reproductive potential to use effective non-hormonal contraception during treatment and for 1 week after the last dose and advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 1 week after the last dose. The safety and efficacy of use in the pediatric population have not been established.

Dosage Form: Tablets: 3mg, 9mg.

Recommended Dosage: Select patients for the treatment of HR-positive, HER2-negative, locally advanced or metastatic breast cancer with Itovebi® based on the presence of one or more *PIK3CA* mutations in plasma specimens. Information on FDA-approved tests for the detection of *PIK3CA* mutations in breast cancer is available at http://www.fda.gov/companiondiagnostics.

Assess fasting plasma glucose (FPG)/blood glucose (FBG) and hemoglobin A1c (HbA1c) and optimize blood glucose prior to starting Itovebi® and at regular intervals during treatment.

The recommended dosage is 9mg PO QD, with or without food, until disease progression or unacceptable toxicity. Take at about the same time each day, while swallowing whole. Do not chew, crush, or split prior to swallowing.

If a patient misses a dose, instruct the patient to take the missed dose as soon as possible within 9 hours. After more than 9 hours, instruct the patient to skip the dose and take the next dose at the scheduled time. If a patient vomits a dose, instruct patients not to take an additional dose on that day and resume the usual dosing schedule the next day.

Administer Itovebi® in combination with palbociclib and fulvestrant. The recommended dosage of palbociclib is 125mg PO QD for 21 consecutive days followed by 7 days off treatment to comprise a cycle of 28 days. Refer to the prescribing information for palbociclib and fulvestrant for dosing information.

For premenopausal and perimenopausal women, administer a luteinizing hormone-releasing hormone (LHRH) agonist per local clinical practice. For men, consider administering a LHRH agonist per local clinical practice.

Dosage modifications are recommended for adverse reactions with Itovebi®. Refer to the prescribing information for additional information.

Dosage modification is not recommended in patients with mild renal impairment. Reduce the dosage in patients with moderate renal impairment (eGFR 30 to <60ml/min). The recommended starting dosage for patients with moderate renal impairment is 6mg PO QD. Itovebi® has not been evaluated in patients with severe renal impairment (eGFR <30ml/min).

Drug Interactions: There are no drug interactions listed with this product.

Box Warning: There is no box warning listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Itovebi® plus palbociclib plus fulvestrant) minus reported % incidence for placebo plus palbociclib plus fulvestrant for all grades. Please note that an incidence of 0% means the incidence was the same as or less than placebo.* The most frequently reported adverse events included stomatitis (24%), diarrhea (32%), nausea (11%), vomiting (10%), fatigue (13%), rash (7%), alopecia (13%), dry skin (8.7%), decreased appetite (15%), COVID-19 infection (13%), urinary tract infection (6%), headache (8%), and decreased weight (16.4%).

Laboratory abnormalities included neutrophils decreased (0%), hemoglobin decreased (3%), platelets decreased (13%), lymphocytes (absolute) decreased (4%), glucose (fasting) increased (42%), calcium decreased (10%), potassium decreased (17%), creatinine increased (8%), ALT increased (5%), sodium decreased (9%), magnesium decreased (6%), and lipase (fasting) increased (9%).

Severe hyperglycemia may occur in patients treated with Itovebi®. Increased fasting glucose occurred in 85% of patients treated with Itovebi®. Among patients with hyperglycemia, the median time to first onset was 7 days. The safety of Itovebi® in patients with Type 1 DM, or Type 2 DM requiring ongoing anti-hyperglycemic therapy have not been studied. Before starting Itovebi®, test fasting glucose levels (FPG or FBG), HbA1c levels, and optimize fasting glucose. After starting treatment with Itovebi®, or in patients who experience hyperglycemia after starting Itovebi® treatment, monitor or self-monitor fasting glucose levels once every 3 days for the first week, then once every week for the next 3 weeks, then once every 2 weeks for the next 8 weeks, then once every 4 weeks thereafter, and as clinically indicated. Monitor HbA1c every 3 months and as clinically indicated. Refer to the prescribing information for additional information.

Severe stomatitis can occur in patients treated with Itovebi®. Monitor patients for signs and symptoms of stomatitis.

Severe diarrhea including dehydration and acute kidney injury, can occur in patients treated with Itovebi®. Monitor patients for signs and symptoms of diarrhea. Advise patients to increase oral fluids and start anti-diarrheal treatment at the first sign of diarrhea while taking Itovebi®.

Contraindications: There are no contraindications listed with this product.

Manufacturer: Genentech, Inc.

Analysis: Itovebi® was assessed in a randomized, double-blind, placebo-controlled trial (INAV0120) and was used in combination with palbociclib and fulvestrant in adult patients with endocrine-resistant *PIK3CA*-mutated, HR-positive, HER2-negative, locally advanced or metastatic breast cancer whose disease progressed during or within 12 months of completing adjuvant endocrine therapy and who have not received prior systemic therapy for locally

advanced or metastatic disease. Randomization was stratified by the presence of visceral disease, endocrine resistance (primary or secondary), and geographic region. Primary endocrine resistance was defined as relapse while on the first 2 years of adjuvant endocrine therapy (ET) and secondary endocrine resistance was defined as relapse while on adjuvant ET after at least 2 years or relapse within 12 months of completing adjuvant ET.

Patients received either Itovebi® 9mg (N=161) or placebo (N=164) once daily, in combination with palbociclib and fulvestrant, until disease progression or unacceptable toxicity. In addition, all pre/perimenopausal women and men received an LHRH agonist throughout therapy.

Patients were required to have an HbA1c <6% and fasting blood glucose <126mg/dL, and the study excluded patients with Type 1 DM or Type 2 DM requiring ongoing anti-hyperglycemic treatment at the start of study treatment. Baseline characteristics included patients with a median age of 54 years (range 27 to 79), while 98% were female (of which 39% were pre/perimenopausal), 59% were white, 63% had an Eastern Cooperative Oncology Group (ECOG) performance status of 0, and 36% had an ECOG performance status of 1. Tamoxifen (57%) and aromatase inhibitors (50%) were the most commonly used adjuvant endocrine therapies. In addition, 64% were considered to have secondary endocrine resistance, and 83% had received prior chemotherapy.

The main efficacy outcome measure was investigator (INV)-assessed progression-free survival (PFS) per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Additional efficacy outcome measures included overall survival (OS), INV-assessed objective response rate (ORR) and INV-assessed duration of response (DOR). Efficacy results are presented in the table below, which was adapted from the prescribing information. Note that INV-assessed PFS results were supported by consistent results from a blinded independent central review (BICR) assessment. At the time of the PFS analysis, OS data were not mature with 30% deaths in the overall population.

	Itovebi® + palbociclib + fulvestrant (N=161)	**Placebo + palbociclib + fulvestrant (N=164)**
Progression-Free Survival		
Patients with event, n (%)	82 (51%)	113 (69%)
Median, months	15.0	7.3
Hazard Ratio (HR); p-value	0.43; <0.0001	
Objective Response Rate		
Patients with Complete Response (CR) or Partial Response (PR), n (%)	94 (58%)	41 (25%)
95% Confidence Interval (CI)	(50, 66)	(19, 32)
Duration of Response (DOR)		
Median DOR, months	18.4	9.6

Place in Therapy: Itovebi® is a kinase inhibitor indicated in combination with palbociclib and fulvestrant for the treatment of adults with endocrine-resistant, *PIK3CA*-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer, as detected by an FDA-approved test, following recurrence on or after completing adjuvant endocrine therapy. Select patients for the treatment of HR-positive, HER2-negative, locally advanced or metastatic breast cancer with Itovebi® based on the presence of one or more *PIK3CA* mutations in plasma specimens. Assess FPG/FBG and HbA1c and optimize blood glucose prior to starting Itovebi® and at regular intervals during treatment. The safety and efficacy of Itovebi® were assessed in a double-blind, placebo-controlled study that included adult patients with endocrine-resistant *PIK3CA*-

mutated, HR-positive, HER2 negative, locally advanced or metastatic breast cancer whose disease progressed during or within 12 months of completing adjuvant endocrine therapy and who have not received prior systemic therapy for locally advanced or metastatic disease. The main efficacy endpoint was INV-assessed PFS per RECIST version 1.1, and there were significantly fewer patients with event in the Itovebi® (plus palbociclib and fulvestrant) group as compared with the placebo (plus palbociclib and fulvestrant) group ($p<0.0001$).

Summary

It is recommended that Itovebi® should be non-recommended in order to confirm the appropriate diagnosis and clinical parameters for use.

PDL Placement: ☐ **Recommended**
☒ **Non-Recommended with Conditions**

References

[1] Itovebi® [package insert]. South San Francisco, CA: Genentech USA, Inc; 2025.

Prepared By: Iowa Medicaid Date: 06/23/2025