Genentech
A Member of the Roche Group

March 2025

Subject: ITOVEBI™ (inavolisib): Cases of serious life-threatening ketoacidosis

Dear Health Care Provider:

The purpose of this letter is to inform you of important safety information for ITOVEBI, 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.

Serious Risk With Use of ITOVEBI

- Two cases of life-threatening ketoacidosis have been reported in diabetic patients treated with ITOVEBI in the post-market setting.
- Ketoacidosis is a medical emergency characterized by hyperglycemia, electrolyte derangements, metabolic acidosis, and ketonemia. The mainstays of treatment include restoration of circulating volume, insulin therapy, electrolyte replacement, and treatment of any underlying precipitating event. Without optimal treatment, ketoacidosis could result in morbidity and mortality.

Prescriber Action

- Hyperglycemia is a known risk associated with ITOVEBI. ITOVEBI should not be administered to patients until their blood glucose levels are well controlled and stable. Fasting blood glucose should be frequently monitored as described in the product information. Consider consultation with a health care provider experienced in managing hyperglycemia.
- In patients who experience hyperglycemia including ketoacidosis, the recommended ITOVEBI dose modification guidance for hyperglycemia in the product information should be followed.

- The safety of ITOVEBI in patients with Type 1 diabetes mellitus, or Type 2 diabetes mellitus requiring ongoing anti-hyperglycemic treatment has not been studied in clinical trials.
- All patients should be evaluated for renal impairment and the guidance provided in the renal impairment section of the product information should be followed.

Background on the Safety Concern

Hyperglycemia is a known class effect risk associated with PI3K-AKT inhibitors due to disruption of the insulin signaling pathway. Ketoacidosis is a rare but serious complication of hyperglycemia induced by PI3K and AKT inhibitors.

Hyperglycemia is an identified risk associated with ITOVEBI and is included as a warning and precaution in the product information. In the Phase III trial INAVO120 (WO41554, NCT04191499) no cases of ketoacidosis were reported. However, two cases of life-threatening ketoacidosis have been reported in patients receiving ITOVEBI in the post marketing setting. One patient had both renal impairment and uncontrolled Type 2 diabetes, and another patient was a Type 2 diabetic on insulin.

The corresponding updates to the product information will be forthcoming.

Reporting Adverse Events / Product Complaints and Company Contact

Health Care Providers should report any adverse events suspected to be associated with the use of ITOVEBI to Genentech at 1-888-835-2555. Alternatively, this information may be reported to FDA's MedWatch reporting system by phone (1-800-FDA-1088) or online (www.fda.gov/medwatch).

Please report any product complaint suspected to be associated with the use of ITOVEBI to Genentech at (800) 334-0290.

Should you have any questions about the information in this letter or the safe and effective use of ITOVEBI, please feel free to contact us at: Genentech Medical Communications at (800) 821-8590.

This letter is not intended as a complete description of the benefits and risks related to the use of ITOVEBI. Please refer to the enclosed full prescribing information.

Sincerely,

Dr Toby Patterson, MBBS
Senior Vice President
Head of U.S. Medical