

Gedatolisib (REVTORPYK) Combination Therapy for Locally Advanced or Metastatic Breast Cancer

Description:

- The purpose of this document is to discuss some of the clinical considerations and general management of patients undergoing treatment with gedatolisib in combination with fulvestrant, with or without palbociclib, for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative (HR+/HER2-) locally advanced or metastatic breast cancer.

Background:

- Gedatolisib is a potent multi-target inhibitor of the PI3K/AKT/mTOR (PAM) pathway that inhibits the activity of all four class I PI3K isoforms, mTORC1, and mTORC2, effectively inducing a comprehensive blockade of the PAM pathway and inhibiting downstream targets critical for cancer cell survival and proliferation. This comprehensive inhibition addresses pathway redundancies, limits reactivation with single-target inhibitors, inhibits cross-activation with endocrine therapy (ET) or CDK4/6 inhibitors, and, potentially, restores sensitivity to ET and CDK4/6i therapy in patients with HR+/HER2- advanced breast cancer.^{1,2}
- Gedatolisib is FDA-approved in combination with fulvestrant, with or without palbociclib, for the treatment of HR+/HER2-, PIK3CA wild-type locally advanced or metastatic breast cancer in patients who have progressed on at least one prior endocrine therapy in the metastatic setting.¹
- Most common adverse reactions (≥ 20%):
 - Gedatolisib-triplet (gedatolisib + fulvestrant + palbociclib):** decreased white blood cells, neutrophils, hemoglobin, lymphocytes, platelets and sodium; increased eosinophils, fasting glucose, alanine aminotransferase (ALT) and aspartate aminotransferase (AST); stomatitis, nausea, vomiting, fatigue, rash, constipation, musculoskeletal pain
 - Gedatolisib-doublet (gedatolisib + fulvestrant):** decreased hemoglobin, lymphocytes; increased eosinophils, fasting glucose, ALT and AST; stomatitis, nausea, rash, fatigue, musculoskeletal pain, vomiting, pruritus, and diarrhea

PQI Process: Upon receipt of a new order for treatment with gedatolisib:

- Dosing and Administration:**
 - Starting dose:** Gedatolisib 180 mg as an intravenous infusion over 30 minutes once weekly on Days 1, 8, and 15 of every 28-day cycle
 - Reconstitution and Dilution**
 - DO NOT** use common chloride-containing infusion solutions (for example: normal saline, Ringer's solution, Lactated Ringer's solution)
 - Add 20 mL of Sterile Water for Injection or 5% Dextrose Injection to the gedatolisib vial. Stability of the reconstituted solution in the vial is up to 4 hours at room temperature (20°-25° C; 68°-77° F). Do not refrigerate.

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- Dilute the reconstituted gedatolisib in an infusion bag containing 250 mL of 5% Dextrose Injection. Stability of the diluted gedatolisib infusion solution is up to 24 hours at room temperature (20°-25° C; 68°-77° F). Do not refrigerate.

Table 1. Volume to Withdraw from Reconstituted Vial Based on Dose

Dose	Volume of Reconstituted Gedatolisib
180 mg	20 mL
150 mg	17 mL
130 mg	14 mL

- **Combination agents:**
 - Gedatolisib is given in combination with fulvestrant, with or without palbociclib
 - Fulvestrant (starting dose): 500 mg IM on days 1 and 15 of cycle 1 then day 1 of each subsequent 28-day cycle
 - Palbociclib (starting dose): 125 mg by mouth daily on days 1-21 of each 28-day cycle
- **Adverse effect prophylaxis and management**
 - **Stomatitis/ mucositis**
 - Initiate steroid-containing alcohol-free mouthwash 4 times daily for the first 8 weeks of treatment and longer as needed if stomatitis occurs. Example: dexamethasone 0.5 mg/5 mL alcohol-free solution
 - If stomatitis occurs, increase the frequency of mouthwash and administer other topical treatments as clinically indicated
 - For $\geq$ grade 3 stomatitis: hold gedatolisib until recovery to $\leq$ grade 2. Resume at next lower dose. Permanently discontinue gedatolisib for grade 4 stomatitis (see Table 2 in [PI](#) for full recommended dose adjustments for adverse reactions)
 - **Dermatologic (rash)**
 - Monitor patients for rash and infectious sequelae
 - Consider initiation of a nonsedating oral antihistamine for rash prophylaxis¹⁻³
 - **Hyperglycemia**
 - Check fasting glucose (FG) and hemoglobin A1c (HbA1c) at baseline and optimize FG prior to treatment initiation
 - Evaluate blood glucose and HbA1c at regular intervals during treatment
 - Initiate at-home glucose monitoring for patients with HbA1c level $>6.4\%$
 - Risk factors identified for increased risk of treatment-related hyperglycemia include history of prediabetes, diabetes, or gestational diabetes; baseline FG ≥ 100 or HbA1c $\geq 5.7\%$; BMI ≥ 25 ; Age ≥ 70 years⁶⁻⁸
 - The safety of gedatolisib in patients with type 1 or uncontrolled type 2 diabetes has not been established
 - **Neutropenia**
 - Monitor complete blood cell count prior to treatment initiation and at the beginning of each cycle as well as on Day 15 of first 2 cycles and as clinically indicated^{3,5}
 - Adjust palbociclib dosing per standard recommendations⁵

Table 2. Recommended Dosage Reductions of Gedatolisib for Adverse Reactions

Dose reduction	Recommended dose
First	Reduce to 150 mg
Second	Reduce to 130 mg
Permanently discontinue if unable to tolerate 130 mg	

- **Drug-drug interactions:** Gedatolisib inhibits CYP2C8, BCRP, and MATE1/2-K and is a P-gp substrate. However, no clinically significant differences in pharmacokinetics were observed.¹
 - No dose modifications are needed for the following drugs when used concomitantly with gedatolisib: metformin (MATE1/2-K substrate), rosuvastatin (BCRP substrate), or repaglinide (CYP2C8 sensitive substrate)

Patient-Centered Activities:

- Stomatitis
 - Coordinate prescription for steroid-containing alcohol-free mouthwash ordering and dispense before patient starts treatment with gedatolisib
 - Instruct patients to initiate use of mouthwash prior to first dose of gedatolisib on Cycle 1 Day 1
 - Instruct patients to swish with steroid-containing mouthwash for at least 2 minutes before spitting out and to not eat or drink for at least 1 hour after each administration
 - Encourage patients to maintain good oral hygiene and provide them with [Patient Education Sheet](#) reviewing stomatitis
 - Reinforce importance of stomatitis prevention techniques throughout therapy
- Rash
 - Counsel patients to avoid sun exposure during treatment and use sunscreen or physical block when unable to avoid
 - Provide patient with [Patient Education Sheet](#) reviewing treatment-related rash
- Hyperglycemia
 - Advise patients of the signs/symptoms of hyperglycemia (e.g., increased thirst or frequency of urination, headache, blurred vision, etc.) and counsel patients on lifestyle changes (e.g., recommend a low carbohydrate diet [60-130 g/day])
 - Preventative strategies for development of treatment-induced hyperglycemia have not been studied with gedatolisib, however prophylactic metformin has been studied with PI3K-inhibitor therapy as a strategy to reduce toxicity⁶⁻⁸
- Advise females of reproductive potential (or male patients with a partner of reproductive potential) to use effective contraception during treatment and for at least 2 weeks after last dose

References:

1. REVTORPYK (gedatolisib) [[prescribing information](#)]. Minneapolis, MN: Celcuity Inc; July 2026.
2. Hurvitz SA, Layman RM, Curigliano G, et al. VIKTORIA-1 Trial of Gedatolisib Plus Fulvestrant With or Without Palbociclib in Hormone Receptor-Positive/HER2-/PIK3CA Wild-Type Advanced Breast Cancer. *J Clin Oncol*. 2026;44(12):1108-1119. doi:10.1200/JCO-25-02643
3. Hurvitz SA, Layman RM, Curigliano G, et al. VIKTORIA-1 trial of gedatolisib plus fulvestrant with or without palbociclib in hormone receptor-positive/HER2-negative/PIK3CA wild-type advanced breast cancer: study protocol. *J Clin Oncol*. 2026;44(12):1108-1119. doi:10.1200/JCO-25-02643. Supplementary material.
4. Teysir J, Lloyd MR, Alkassis S, et al. After a CDK4/6 Inhibitor: State of the Art in Hormone Receptor-Positive Metastatic Breast Cancer. *Am Soc Clin Oncol Educ Book*. 2025;45(3):e473372. doi:10.1200/EDBK-25-473372
5. IBRANCE (palbociclib) [[prescribing information](#)]. New York, NY: Pfizer; June 2026.
6. Tankova T, et al. Management Strategies for Hyperglycemia Associated with the α -Selective PI3K Inhibitor Alpelisib for the Treatment of Breast Cancer. *Cancers (Basel)*. 2022 Mar 22;14(7):1598.

7. Llombart-Cussac A, Pérez-García JM, Ruiz Borrego M, et al. Preventing alpelisib-related hyperglycaemia in HR+/HER2-/PIK3CA-mutated advanced breast cancer using metformin (METALLICA): a multicentre, open-label, single-arm, phase 2 trial. *EClinicalMedicine*. 2024 Apr 11;71:102520.
8. Moore HN, Goncalves MD, Johnston AM, Mayer EL, Rugo HS, Gradishar WJ, Zylla DM, Bergenstal RM. Effective Strategies for the Prevention and Mitigation of Phosphatidylinositol-3-Kinase Inhibitor-Associated Hyperglycemia: Optimizing Patient Care. *Clin Breast Cancer*. 2025 Jan;25(1):1-11. doi: 10.1016/j.clbc.2024.09.017. Epub 2024 Sep 28. PMID: 39462728.