VERZENIO CONTINUOUS CARE™

Verzenio® abemaciclib
50|100|150|200 mg tablets

Composing a Letter of Medical Necessity (LMN)

The following information is presented for informational purposes only and is not intended to provide reimbursement or legal advice. Laws, regulations, and policies concerning reimbursement are complex and are updated frequently. While we have made an effort to be current as of the issue date of this document, the information may not be as current or comprehensive when you view it. Providers are encouraged to contact third-party payers for specific information on their coverage policies. For questions, please call Verzenio Continuous Care™ at 1-844-VERZENIO. Verzenio Continuous Care may provide information but not assistance in drafting the letter.

Many health plans require that an LMN accompanies a Coverage Authorization Appeals Letter.* The purpose of an LMN is to explain the prescribing healthcare provider's (HCP's) rationale and clinical decision making when choosing a treatment.

This resource, **Composing a Letter of Medical Necessity (LMN)**, provides information on the process of drafting an LMN. Included on pages 3 through 5 is a list of considerations, which can be followed when creating an LMN.

- **Patients who are continuing therapy:** There are three common scenarios in which this denial of coverage can occur:
  - The patient initiated therapy with a patient assistance program
  - The patient has switched insurance companies
  - The patient's insurance no longer covers Verzenio
- **Patients who are new to therapy:** Some plans have specific Coverage Authorization Forms that must be used to document an LMN

Follow the patient's plan requirements when requesting Verzenio; otherwise, treatment may be delayed.

* For Medicare beneficiaries, specific requirements must be met for the HCP to be considered a legal representative of the patient in an appeal. For additional information, please visit https://www.cms.gov/Medicare/CMS-Forms/CMS-Forms/downloads/cms1696.pdf.

Indications

VERZENIO® is a kinase inhibitor indicated[1]:

- in combination with endocrine therapy (tamoxifen or an aromatase inhibitor) for the adjuvant treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-positive, early breast cancer at high risk of recurrence.
- in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer.
- in combination with fulvestrant for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer with disease progression following endocrine therapy.
- as monotherapy for the treatment of adult patients with HR-positive, HER2−negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting.

Select Important Safety Information

Severe **diarrhea** associated with dehydration and infection occurred in patients treated with Verzenio. Across four clinical trials in 3691 patients, diarrhea occurred in 81 to 90% of patients who received Verzenio. Grade 3 diarrhea occurred in 8 to 20% of patients receiving Verzenio. Most patients experienced diarrhea during the first month of Verzenio treatment. The median time to onset of the first diarrhea event ranged from 6 to 8 days; and the median duration of Grade 2 and Grade 3 diarrhea ranged from 6 to 11 days and 5 to 8 days, respectively. Across trials, 19 to 26% of patients with diarrhea required a Verzenio dose interruption and 13 to 23% required a dose reduction.

Instruct patients to start antidiarrheal therapy, such as loperamide, at the first sign of loose stools, increase oral fluids, and notify their healthcare provider for further instructions and appropriate follow-up. For Grade 3 or 4 diarrhea, or diarrhea that requires hospitalization, discontinue Verzenio until toxicity resolves to ≤Grade 1, and then resume Verzenio at the next lower dose.

Please see Important Safety Information on pages 7 and 8 and click to access the full Prescribing Information for Verzenio.

Lilly

VERZENIO CONTINUOUS CARE™

Verzenio® abemaciclib
50 | 100 | 150 | 200 mg tablets

Composing a Letter of Medical Necessity (LMN), cont'd

Recommended components of an LMN

1. Include the patient's full name, date of birth, plan identification number, and case identification number if a decision has already been rendered.
2. Provide a copy of the patient's records with the following details: patient's history, diagnosis with specific International Classification of Diseases (ICD) code, lab results, and condition.
3. Note the severity of the patient's condition.
4. Document prior treatments, the duration of each, and the rationale for discontinuation. It may be beneficial to include CPT-4 and/or J-codes to define prior services/treatments, so that the health plan can conduct research and make a timely determination.
5. Attach clinical documentation that supports your recommendation; this information may be found in the Verzenio prescribing information and/or clinical peer-reviewed literature.

[Date]
[Prior Authorization Department]
[Name of Health Plan]
[Mailing Address]

Re: **[Patient's Name]**
1 **[Plan Identification Number]**
[Date of Birth]

To whom it may concern:

2 We have reviewed and recognize your guidelines for the responsible management of medications within this class. We are requesting that you reassess your recent denial of Verzenio® (abemaciclib) coverage. We understand that the reason for your denial is **[copy reason verbatim from the plan's denial letter]**. However, we believe that Verzenio **[dose, frequency]** is the appropriate treatment for the patient. In support of our recommendation for Verzenio treatment, we have provided an overview of the patient's relevant clinical history below.

3 **Patient's history, diagnosis, condition, and symptoms*:**

Patient must either:

- Use in combination with endocrine therapy (tamoxifen or an aromatase inhibitor) for the adjuvant treatment of adult patients with HR+, HER2–, node-positive, early breast cancer at high risk of recurrence†

OR

- Have a diagnosis of HR-positive, HER2– advanced or metastatic breast cancer and one of the following:†
  - For Verzenio in combination with an aromatase inhibitor, no prior systemic therapy in the advanced or metastatic setting
  - For Verzenio in combination with fulvestrant, disease progression following endocrine therapy
  - For Verzenio taken as a single agent, disease progression following endocrine therapy and prior chemotherapy in the metastatic setting

4

Past Treatments‡	Start/Stop Dates	Reason(s) for Discontinuing

5 **[Provide clinical rationale for this treatment; this information may be found in the Verzenio prescribing information and/or clinical peer-reviewed literature.]**

[Insert your recommendation summary here, including your professional opinion of the patient's likely prognosis or disease progression without treatment with Verzenio.]

Please feel free to contact me, **[HCP's name]**, at **[office phone number]** or **[patient's name]** at **[patient's phone number]** for any additional information you may require. We look forward to receiving your timely response and approval of this claim.

Sincerely,

[Physician's name and signature]
[Physician's medical specialty]
[Physician's NPI]
[Physician's practice name]
[Phone #]
[Fax #]

[Patient's name and signature]

Encl: Medical records
Clinical trial information
Letter of Medical Necessity (LMN)

* Include patient's medical records, applicable lab results, and supporting documentation.
† Hormone receptor-positive (HR+) and human epidermal growth factor receptor 2-negative (HER2-).
‡ Identify drug name, strength, dosage form, and therapeutic outcome.

Please see Important Safety Information on pages 7 and 8 and click to access the full Prescribing Information for Verzenio.

VERZENIO CONTINUOUS CARE™

Verzenio® abemaciclib
50|100|150|200 mg tablets

Considerations for Why Verzenio May Be Medically Necessary

Based on the patient's medical need and history, some considerations may be, but are not limited to the following.

Medical Necessity is based on a specific patient's individual need for treatment of their medical condition. Only include information in the LMN that accurately reflects the particular patient's need and medical history. Based on the patient's medical need and history, the journal articles listed on page 6 may be relevant.

In patients with HR+, HER2–, node-positive EBC at high risk* of recurrence (N=5,120)[1,2]

Verzenio reduced the risk of recurrence by 35% in combination with ET, and absolute differences in IDFS benefit increased over time[2]

At 4 years, 6.9% absolute difference with Verzenio + ET vs ET alone, 2 years post-treatment with Verzenio[1,2]

- 3.1% absolute difference at 2 years and 5.0% at 3 years
- **85.5% of patients** remained recurrence-free with Verzenio + ET vs 78.6% with ET alone[1,2]
- 317 IDFS events were observed with Verzenio + ET vs 474 with ET alone **(HR=0.653 (95% CI: 0.567-0.753))[1,2]**

7.9% absolute IDFS difference at 5 years[3]

At the 5-year analysis, all patients have been off Verzenio treatment for at least a year[2,3]

- **83.2% of patients** remained recurrence-free with Verzenio + ET vs 75.3% with ET alone
- 382 IDFS events were observed with Verzenio + ET vs 553 with ET alone **(HR=0.670 (95% CI:0.588, 0.764))[3]**

At 5 years, absolute difference between treatment arms in distant relapse-free survival was 7.1%[4]
In the Verzenio + ET arm, the risk of distant relapse was reduced by 33.5%[4]

- **7.1% absolute difference in DRFS between the two arms[4]**
  - **85.6% of patients** remained free of distant relapse with Verzenio + ET vs 78.5% with ET alone[4]
    325 DRFS events were observed with Verzenio plus ET vs 477 with ET alone **(HR=0.665 (95% CI: 0.577-0.765))[4]**

Pre-specified efficacy analyses from the original statistical plan were performed at a median follow-up of 42 months (4-year analysis) and 54 months (5-year analysis). **IDFS analysis for this subpopulation and DRFS analysis were not powered or alpha controlled for testing statistical significance.**[1-4] At the time of each analysis, OS was immature. At 4 years, a total of 315 (6%) of patients had died, at 5 years, a total of 420 (8%) of patients had died, across the two treatment arms. Long term follow-ups continue.[1-4.]

*High risk was defined as patients who had 4+ positive nodes or 1-3 positive nodes and at least one of the following: tumors that were ≥5 cm or Grade 3.[1,2]

MONARCH E study design

MonarchE was a Phase III clinical trial that enrolled 5,637 adults with HR+, HER2–, node-positive EBC at high risk of recurrence. To be enrolled in Cohort 1 (n=5,120), which is the FDA-approved population, patients had to have 4+ positive nodes, OR 1-3 positive nodes and at least one of the following: tumors that were ≥5 cm or Grade 3. To be enrolled in Cohort 2 (n=517), patients had to have 1-3 positive nodes and Ki-67 score ≥20%.

Patients in each cohort were randomized 1:1 to receive either Verzenio 150 mg twice daily plus SoC adjuvant ET (Cohort 1, n=2,555; Cohort 2, n=253) or SoC adjuvant ET alone (Cohort 1, n=2,565; Cohort 2, n=264) for 2 years. ET continued for at least 5 years if deemed medically appropriate. The primary endpoint was IDFS.[1,2]

Verzenio is approved for use in the Cohort 1 patient population. A statistically significant difference in IDFS was observed in the ITT population primarily due to patients in Cohort 1 (91% of the study population). While the OS data in Cohort 2 remains immature, more deaths were observed among those receiving Verzenio + ET vs ET alone (n=10/253 vs n=5/264).[1,2]

CI=confidence interval; DRFS=distant relapse-free survival; EBC=early breast cancer; ET=endocrine therapy; HER2–=human epidermal growth factor receptor 2–negative; HR=hazard ratio; HR+=hormone receptor–positive; IDFS=invasive disease-free survival; ITT=intent-to-treat; OS=overall survival; SoC=standard of care.

Select Important Safety Information

Neutropenia, including febrile neutropenia and fatal neutropenic sepsis, occurred in patients treated with Verzenio. Across four clinical trials in 3691 patients, neutropenia occurred in 37 to 46% of patients receiving Verzenio. A Grade ≥3 decrease in neutrophil count (based on laboratory findings) occurred in 19 to 32% of patients receiving Verzenio. Across trials, the median time to first episode of Grade ≥3 neutropenia ranged from 29 to 33 days, and the median duration of Grade ≥3 neutropenia ranged from 11 to 16 days. Febrile neutropenia has been reported in <1% of patients exposed to Verzenio across trials. Two deaths due to neutropenic sepsis were observed in MONARCH 2. Inform patients to promptly report any episodes of fever to their healthcare provider. Monitor complete blood counts prior to the start of Verzenio therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated. Dose interruption, dose reduction, or delay in starting treatment cycles is recommended for patients who develop Grade 3 or 4 neutropenia.

Please see Important Safety Information on pages 7 and 8 and click to access the full Prescribing Information for Verzenio.

VERZENIO CONTINUOUS CARE™

Verzenio® abemaciclib
50|100|150|200 mg tablets

Considerations for Why Verzenio May Be Medically Necessary, cont'd

HR+, HER2– Metastatic or Advanced Breast Cancer

1. **Verzenio + an AI demonstrated >28-month median PFS as initial endocrine-based therapy[1] in postmenopausal women with HR+, HER2– MBC**
   - Median PFS: 28.2 months with Verzenio + an AI (95% CI: 23.5-NR) vs 14.8 months with placebo + an AI (95% CI: 11.2-19.2); (HR=0.540 [95% CI: 0.418-0.698])) *P*<.0001[1]
   - The percentage of PFS events at the time of analysis was 42.1% (n=138/328) and 65.5% (n=108/165) in the Verzenio + an AI and placebo + an AI arms, respectively[1]
   - ORR*† in patients with measurable disease: 55.4% (n=148/267) (95% CI: 49.5-61.4) with Verzenio +AI vs 40.2% (n=53/132) (95% CI: 31.8-48.5) with placebo + an AI[1]
   - At the time of the primary analysis of PFS, overall survival data were not mature (19% of patients had died)[1]

*ORR was defined as the proportion of patients with CR + PR and does not include stable disease. PR was defined as ≥30% reduction in target lesion size per RECIST 1.1.[5,6]
†Based upon confirmed responses.[1]
CR=complete responce; PR=partial response

MONARCH 3 study design

MONARCH 3 was a multicenter trial that enrolled 493 patients with HR+, HER2– locoregionally recurrent or metastatic breast cancer in combination with a nonsteroidal aromatase inhibitor as initial endocrine-based therapy. The median patient age was 63 years (range, 32 to 88 years). Forty-seven percent of patients had received prior endocrine therapy and 39% of patients had received chemotherapy in the adjuvant setting. Patients were randomized 2:1 to Verzenio + an AI or placebo + an AI. Patients received either letrozole (80%) or anastrozole (20%). Verzenio was dosed continuously until disease progression or unacceptable toxicity. The primary endpoint was progression-free survival. Key secondary endpoints were ORR and duration of response.[1,7]

2. **For patients with HR+, HER2– MBC with disease recurrence or progression following ET, Verzenio + fulvestrant provided statistically significant OS improvement with consistent results even in patients likely to do worse*[1,8-12]**
   - **Median PFS in the ITT population[1]:** 16.4 months with Verzenio + fulvestrant (n=446) (95% CI: 14.4-19.3) vs 9.3 months with placebo + fulvestrant (n=223) (95% CI: 7.4-12.7); HR=0.553 (95% CI: 0.449-0.681) *P*<.0001. The percentage of PFS events at the time of analysis was 49.8% (n=222) and 70.4% (n=157) in the Verzenio + fulvestrant and placebo + fulvestrant arms, respectively[1]
   - **Median OS in the ITT population[8,13]:** 46.7 months with Verzenio + fulvestrant (n=446) (95% CI: 39.2-52.2) vs 37.3 months with placebo + fulvestrant (n=223) (95% CI: 34.4-43.2); HR=0.757 (95% CI: 0.606-0.945) *P*=0.0137. Results are based on a preplanned interim analysis and considered to be definitive. The percentage of deaths at the time of analysis was 47.3% (n=211) and 57.0% (n=127) in the Verzenio + fulvestrant and placebo + fulvestrant arms, respectively[8,13]

*Visceral disease and primary ET resistance were studied in the clinical trial and have been associated with a less favorable prognosis. For more information, visit verzenio.com/hcp/efficacy
   - Primary resistance: relapse within 2 years of adjuvant ET or progressive disease within 6 months of first-line ET for MBC[1]
   - Visceral disease: ≥1 lesion on an internal organ or in the third space (eg, lung, liver, pleural, or peritoneal metastatic involvement)[14]

Select Important Safety Information

Severe, life-threatening, or fatal **interstitial lung disease (ILD) or pneumonitis** can occur in patients treated with Verzenio and other CDK4/6 inhibitors. In Verzenio-treated patients in EBC (monarchE), 3% of patients experienced ILD or pneumonitis of any grade: 0.4% were Grade 3 or 4 and there was one fatality (0.1%). In Verzenio-treated patients in MBC (MONARCH 1, MONARCH 2, MONARCH 3), 3.3% of Verzenio-treated patients had ILD or pneumonitis of any grade: 0.6% had Grade 3 or 4, and 0.4% had fatal outcomes. Additional cases of ILD or pneumonitis have been observed in the postmarketing setting, with fatalities reported. Monitor patients for pulmonary symptoms indicative of ILD or pneumonitis. Symptoms may include hypoxia, cough, dyspnea, or interstitial infiltrates on radiologic exams. Infectious, neoplastic, and other causes for such symptoms should be excluded by means of appropriate investigations. Dose interruption or dose reduction is recommended in patients who develop persistent or recurrent Grade 2 ILD or pneumonitis. Permanently discontinue Verzenio in all patients with Grade 3 or 4 ILD or pneumonitis.

Please see Important Safety Information on pages 7 and 8 and click to access the full Prescribing Information for Verzenio.

Considerations for Why Verzenio May Be Medically Necessary, cont'd

HR+, HER2– Metastatic or Advanced Breast Cancer, cont'd

3. Verzenio + fulvestrant delayed time to chemotherapy[8]

- 50.2-month median time to chemotherapy with Verzenio + fulvestrant (n/N=200/446) vs 22.1 months with placebo + fulvestrant (n/N=135/223); HR=0.625 (95% CI: 0.501-0.779)
- Time to chemotherapy is defined as time from randomization to initiation of first post-discontinuation chemotherapy. Patients who died prior to receiving chemotherapy (n=111) did not contribute an event to this analysis
- This exploratory analysis was not controlled for type 1 error, and the study was not powered to test this endpoint

MONARCH 2 study design

MONARCH 2 was a phase III, randomized, double-blind, placebo-controlled trial that enrolled 669 patients with HR+, HER2– MBC who progressed on or after ET. Pre/perimenopausal women (17%) were rendered postmenopausal prior to the study. Patients had received no chemotherapy and no more than 1 prior ET in the metastatic setting. Patients were randomized 2:1 to Verzenio + fulvestrant (n=446) or placebo + fulvestrant (n=223). Verzenio and placebo were dosed PO BID on a continuous dosing schedule until disease progression or unacceptable toxicity. 500 mg fulvestrant was administered by IM injection on days 1, 15, and 29 of the first month and once monthly thereafter. The primary endpoint was PFS. Key secondary endpoints were ORR, OS, and DoR.[1,15]

4. Verzenio is the only CDK4 & 6 inhibitor to receive single-agent approval[1]

- 19.7% ORR (n=26) (95% CI: 13.3-27.5) per investigator assessment[1,16*]
- 17.4% ORR (n=23) (95% CI: 11.4-25.0) per independent review[1,16*]

MONARCH 1 study design

MONARCH 1 was a single-arm, open-label, multicenter study in 132 women with measurable HR+, HER2– MBC whose disease progressed during or after ET, had received a taxane in any setting, and who received 1 or 2 prior chemotherapy regimens in the metastatic setting. Patients had an Eastern Cooperative Oncology Group Performance Status of 0 or 1. Patients took 200 mg of Verzenio orally, twice daily, on a continuous schedule, unless disease progression or unacceptable toxicity occurred. The primary endpoint was ORR. A key secondary endpoint was DoR.[1,16]

- A distinct study population: 100% received ET plus 1-2 chemotherapy regimens in the metastatic setting, 90% had visceral disease at baseline, 71% had liver metastases, 51% had 3 or more metastatic sites[†1,16]

* ORR was defined as the proportion of patients with CR + PR and does not include stable disease. PR defined as ≥30% reduction in target lesion size per RECIST 1.1.[5,6]

† In a study protocol deviation, 1 woman received 3 chemotheraphy regimens in the metastatic setting, first receiving capecitabine, followed by 2 regimens of docetaxel separated by a treatment-free interval of >1 year.[16, 17]

AI=aromatase inhibitor; BID=twice a day; CDK=cyclin-dependent kinase; CR=complete response; DoR=duration of response; PO=orally; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors.

Select Important Safety Information

Grade ≥3 increases in alanine aminotransferase (ALT) (2 to 6%) and **aspartate aminotransferase (AST)** (2 to 3%) were reported in patients receiving Verzenio. Across three clinical trials in 3559 patients (monarchE, MONARCH 2, MONARCH 3), the median time to onset of Grade ≥3 ALT increases ranged from 57 to 87 days and the median time to resolution to Grade <3 was 13 to 14 days. The median time to onset of Grade ≥3 AST increases ranged from 71 to 185 days and the median time to resolution to Grade <3 ranged from 11 to 15 days. Monitor liver function tests (LFTs) prior to the start of Verzenio therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated. Dose interruption, dose reduction, dose discontinuation, or delay in starting treatment cycles is recommended for patients who develop persistent or recurrent Grade 2, or any Grade 3 or 4 hepatic transaminase elevation.

Please see Important Safety Information on pages 7 and 8 and click to access the full Prescribing Information for Verzenio.

VERZENIO CONTINUOUS CARE™

Verzenio® abemaciclib
50|100|150|200 mg tablets

Relevant Journal Articles for Review and Consideration in Support of Verzenio's Use:

- Johnston SRD, Toi M, O'Shaughnessy J, et al; on behalf of monarchE Committee Members. Abemaciclib plus endocrine therapy for hormone receptor-positive, HER2−negative, node-positive, high-risk early breast cancer (monarchE): results from a preplanned interim analysis of a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2023;24(1):77-90. doi:10.1016/S1470-2045(22)00694-5
- Johnston SRD, Harbeck N, Hegg R, et al; monarchE Committee Members and Investigators. Abemaciclib combined with endocrine therapy for the adjuvant treatment of HR+, HER2−, node-positive, high-risk, early breast cancer (monarchE). *J Clin Oncol*. 2020;38(34):3987-3998. doi:10.1200/JCO.20.02514.
- Sledge GW Jr, Toi M, Neven P, et al. The effect of abemaciclib plus fulvestrant on overall survival in hormone receptor-positive, ERBB2-negative breast cancer that progressed on endocrine therapy–MONARCH 2: a randomized clinical trial. *JAMA Oncol*. https://www.jamanetwork.com/journals/jamaoncology/fullarticle/2752266. Published September 29, 2019.
- Di Leo A, O'Shaughnessy J, Sledge GW Jr, et al. Prognostic characteristics in hormone receptor-positive advanced breast cancer and characterization of abemaciclib efficacy. *NPJ Breast Cancer.* 2018;4:41. https://www.nature.com/articles/s41523-018-0094-2. Published December 18, 2018.
- Johnston S, Martin M, Di Leo A, et al. MONARCH 3 final PFS: a randomized study of abemaciclib as initial therapy for advanced breast cancer. *NPJ Breast Cancer* 2019;5:5. Published online January 17, 2019. doi:10.1038/s41523-018-0097-z
- Dickler MN, Tolaney SM, Rugo HS, et al. MONARCH 1, a phase II study of abemaciclib, a CDK4 and CDK6 inhibitor, as a single agent, in patients with refractory HR+/HER2- metastatic breast cancer. *Clin Cancer* Res. 2017;23:5218-5224.

Medical Necessity is based on a specific patient's individual need for treatment of their medical condition. Only include information in the LMN that accurately reflects the particular patient's need and medical history. Based on the patient's medical need and history, the journal articles listed above may be relevant.

References

1. Verzenio (abemaciclib). Prescribing Information. Lilly USA, LLC.
2. Johnston SRD, et al. *Lancet Oncol*. 2023;24(1):77-90. doi:10.1016/S1470-2045(22)00694-5
3. Data on file. Lilly USA, LLC. DOF-AL-US-0109.
4. Data on file. Lilly USA, LLC. DOF-AL-US-0110.
5. Eisenhauer EA, et al. *Eur J Cancer*. 2009;45:228-247
6. Johnston S, et al. *NPJ Breast Cancer*. 2019;5:5.
7. Goetz MP, et al. *J Clin Oncol*. 2017;35:3638-3646.
8. Sledge GW Jr, et al. *JAMA Oncol*. 2020;6:116-124.
9. Imkampe A, et al. *Eur J Surg Oncol*. 2007;33:420-423.
10. Largillier R, et al. *Ann Oncol*. 2008;19:2012-2019.
11. Solomayer EF, et al. *Breast Cancer Res Treat*. 2000;59:271-278.
12. Cardoso F, et al. *Breast*. 2017;31:244-259.
13. Data on file, Lilly USA, LLC. DOF-AL-US-0088.
14. Turner NC, et al. *N Engl J Med*. 2018;379:1926-1936.
15. Sledge GW Jr, et al. *J Clin Oncol*. 2017;35:2875-2884.
16. Dickler MN, et al. *Clin Cancer Res*. 2017;23:5218-5224.
17. Data on file, Lilly USA, LLC. ONC20170111b.

Select Important Safety Information

Venous thromboembolic events (VTE) were reported in 2 to 5% of patients across three clinical trials in 3559 patients treated with Verzenio (monarchE, MONARCH 2, MONARCH 3). VTE included deep vein thrombosis, pulmonary embolism, pelvic venous thrombosis, cerebral venous sinus thrombosis, subclavian and axillary vein thrombosis, and inferior vena cava thrombosis. In clinical trials, deaths due to VTE have been reported in patients treated with Verzenio. Verzenio has not been studied in patients with early breast cancer who had a history of VTE. Monitor patients for signs and symptoms of venous thrombosis and pulmonary embolism and treat as medically appropriate. Dose interruption is recommended for EBC patients with any grade VTE and for MBC patients with a Grade 3 or 4 VTE.

Please see Important Safety Information on pages 7 and 8 and click to access the full Prescribing Information for Verzenio.

Important Safety Information

Severe **diarrhea** associated with dehydration and infection occurred in patients treated with Verzenio. Across four clinical trials in 3691 patients, diarrhea occurred in 81 to 90% of patients who received Verzenio. Grade 3 diarrhea occurred in 8 to 20% of patients receiving Verzenio. Most patients experienced diarrhea during the first month of Verzenio treatment. The median time to onset of the first diarrhea event ranged from 6 to 8 days; and the median duration of Grade 2 and Grade 3 diarrhea ranged from 6 to 11 days and 5 to 8 days, respectively. Across trials, 19 to 26% of patients with diarrhea required a Verzenio dose interruption and 13 to 23% required a dose reduction.

Instruct patients to start antidiarrheal therapy, such as loperamide, at the first sign of loose stools, increase oral fluids, and notify their healthcare provider for further instructions and appropriate follow-up. For Grade 3 or 4 diarrhea, or diarrhea that requires hospitalization, discontinue Verzenio until toxicity resolves to ≤Grade 1, and then resume Verzenio at the next lower dose.

Neutropenia, including febrile neutropenia and fatal neutropenic sepsis, occurred in patients treated with Verzenio. Across four clinical trials in 3691 patients, neutropenia occurred in 37 to 46% of patients receiving Verzenio. A Grade ≥3 decrease in neutrophil count (based on laboratory findings) occurred in 19 to 32% of patients receiving Verzenio. Across trials, the median time to first episode of Grade ≥3 neutropenia ranged from 29 to 33 days, and the median duration of Grade ≥3 neutropenia ranged from 11 to 16 days. Febrile neutropenia has been reported in <1% of patients exposed to Verzenio across trials. Two deaths due to neutropenic sepsis were observed in MONARCH 2. Inform patients to promptly report any episodes of fever to their healthcare provider.

Monitor complete blood counts prior to the start of Verzenio therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated. Dose interruption, dose reduction, or delay in starting treatment cycles is recommended for patients who develop Grade 3 or 4 neutropenia.

Severe, life-threatening, or fatal **interstitial lung disease (ILD) or pneumonitis** can occur in patients treated with Verzenio and other CDK4/6 inhibitors. In Verzenio-treated patients in EBC (monarchE), 3% of patients experienced ILD or pneumonitis of any grade: 0.4% were Grade 3 or 4 and there was one fatality (0.1%). In Verzenio-treated patients in MBC (MONARCH 1, MONARCH 2, MONARCH 3), 3.3% of Verzenio-treated patients had ILD or pneumonitis of any grade: 0.6% had Grade 3 or 4, and 0.4% had fatal outcomes. Additional cases of ILD or pneumonitis have been observed in the postmarketing setting, with fatalities reported.

Monitor patients for pulmonary symptoms indicative of ILD or pneumonitis. Symptoms may include hypoxia, cough, dyspnea, or interstitial infiltrates on radiologic exams. Infectious, neoplastic, and other causes for such symptoms should be excluded by means of appropriate investigations. Dose interruption or dose reduction is recommended in patients who develop persistent or recurrent Grade 2 ILD or pneumonitis. Permanently discontinue Verzenio in all patients with Grade 3 or 4 ILD or pneumonitis.

Grade ≥3 increases in alanine aminotransferase (ALT) (2 to 6%) and **aspartate aminotransferase (AST)** (2 to 3%) were reported in patients receiving Verzenio. Across three clinical trials in 3559 patients (monarchE, MONARCH 2, MONARCH 3), the median time to onset of Grade ≥3 ALT increases ranged from 57 to 87 days and the median time to resolution to Grade <3 was 13 to 14 days. The median time to onset of Grade ≥3 AST increases ranged from 71 to 185 days and the median time to resolution to Grade <3 ranged from 11 to 15 days.

Monitor liver function tests (LFTs) prior to the start of Verzenio therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated. Dose interruption, dose reduction, dose discontinuation, or delay in starting treatment cycles is recommended for patients who develop persistent or recurrent Grade 2, or any Grade 3 or 4 hepatic transaminase elevation.

Venous thromboembolic events (VTE) were reported in 2 to 5% of patients across three clinical trials in 3559 patients treated with Verzenio (monarchE, MONARCH 2, MONARCH 3). VTE included deep vein thrombosis, pulmonary embolism, pelvic venous thrombosis, cerebral venous sinus thrombosis, subclavian and axillary vein thrombosis, and inferior vena cava thrombosis. In clinical trials, deaths due to VTE have been reported in patients treated with Verzenio.

Verzenio has not been studied in patients with early breast cancer who had a history of VTE. Monitor patients for signs and symptoms of venous thrombosis and pulmonary embolism and treat as medically appropriate. Dose interruption is recommended for EBC patients with any grade VTE and for MBC patients with a Grade 3 or 4 VTE.

Verzenio can cause **fetal harm** when administered to a pregnant woman, based on findings from animal studies and the mechanism of action. In animal reproduction studies, administration of abemaciclib to pregnant rats during the period of organogenesis caused teratogenicity and decreased fetal weight at maternal exposures that were similar to the human clinical exposure based on area under the curve (AUC) at the maximum recommended human dose. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with Verzenio and for 3 weeks after the last dose. Based on findings in animals, Verzenio may impair fertility in males of reproductive potential. There are no data on the presence of Verzenio in human milk or its effects on the breastfed child or on milk production. Advise lactating women not to breastfeed during Verzenio treatment and for at least 3 weeks after the last dose because of the potential for serious adverse reactions in breastfed infants.

The **most common adverse reactions (all grades, ≥10%)** observed in **monarchE for Verzenio plus tamoxifen or an aromatase inhibitor vs tamoxifen or an aromatase inhibitor, with a difference between arms of ≥2%**, were diarrhea (84% vs 9%), infections (51% vs 39%), neutropenia (46% vs 6%), fatigue (41% vs 18%), leukopenia (38% vs 7%), nausea (30% vs 9%), anemia (24% vs 4%), headache (20% vs 15%), vomiting (18% vs 4.6%), stomatitis (14% vs 5%), lymphopenia (14% vs 3%), thrombocytopenia (13% vs 2%), decreased appetite (12% vs 2.4%), ALT increased (12% vs 6%), AST increased (12% vs 5%), dizziness (11% vs 7%), rash (11% vs 4.5%), and alopecia (11% vs 2.7 %).

The **most frequently reported ≥5% Grade 3 or 4 adverse reaction** that occurred in the Verzenio arm vs the tamoxifen or an aromatase inhibitor arm of monarchE were neutropenia (19.6% vs 1%), leukopenia (11% vs <1%), diarrhea (8% vs 0.2%), and lymphopenia (5% vs <1%).

Verzenio®
abemaciclib
50 | 100 | 150 | 200 mg tablets

Please see additional Important Safety Information on page 8 and click to access the full Prescribing Information for Verzenio.

Important Safety Information, cont'd

Lab abnormalities (all grades; Grade 3 or 4) for monarchE in ≥10% for Verzenio plus tamoxifen or an aromatase inhibitor with a difference between arms of ≥2% were increased serum creatinine (99% vs 91%; .5% vs <.1%), decreased white blood cells (89% vs 28%; 19.1% vs 1.1%), decreased neutrophil count (84% vs 23%; 18.7% vs 1.9%), anemia (68% vs 17%; 1% vs .1%), decreased lymphocyte count (59% vs 24%; 13.2 % vs 2.5%), decreased platelet count (37% vs 10%; .9% vs .2%), increased ALT (37% vs 24%; 2.6% vs 1.2%), increased AST (31% vs 18%; 1.6% vs .9%), and hypokalemia (11% vs 3.8%; 1.3% vs 0.2%).

The **most common adverse reactions (all grades, ≥10%)** observed in **MONARCH 3 for Verzenio plus anastrozole or letrozole vs anastrozole or letrozole, with a difference between arms of ≥2%**, were diarrhea (81% vs 30%), fatigue (40% vs 32%), neutropenia (41% vs 2%), infections (39% vs 29%), nausea (39% vs 20%), abdominal pain (29% vs 12%), vomiting (28% vs 12%), anemia (28% vs 5%), alopecia (27% vs 11%), decreased appetite (24% vs 9%), leukopenia (21% vs 2%), creatinine increased (19% vs 4%), constipation (16% vs 12%), ALT increased (16% vs 7%), AST increased (15% vs 7%), rash (14% vs 5%), pruritus (13% vs 9%), cough (13% vs 9%), dyspnea (12% vs 6%), dizziness (11% vs 9%), weight decreased (10% vs 3.1%), influenza-like illness (10% vs 8%), and thrombocytopenia (10% vs 2%).

The **most frequently reported ≥5% Grade 3 or 4 adverse reactions** that occurred in the Verzenio arm vs the placebo arm of **MONARCH 3** were neutropenia (22% vs 1%), diarrhea (9% vs 1.2%), leukopenia (7% vs <1%)), increased ALT (6% vs 2%), and anemia (6% vs 1%).

Lab abnormalities (all grades; Grade 3 or 4) for **MONARCH 3 in ≥10% for Verzenio plus anastrozole or letrozole with a difference between arms of ≥2%** were increased serum creatinine (98% vs 84%; 2.2% vs 0%), decreased white blood cells (82% vs 27%; 13% vs 0.6%), anemia (82% vs 28%; 1.6% vs 0%), decreased neutrophil count (80% vs 21%; 21.9% vs 2.6%), decreased lymphocyte count (53% vs 26%; 7.6% vs 1.9%), decreased platelet count (36% vs 12%; 1.9% vs 0.6%), increased ALT (48% vs 25%; 6.6% vs 1.9%), and increased AST (37% vs 23%; 3.8% vs 0.6%).

The **most common adverse reactions (all grades, ≥10%)** observed in **MONARCH 2 for Verzenio plus fulvestrant vs fulvestrant, with a difference between arms of ≥2%**, were diarrhea (86% vs 25%), neutropenia (46% vs 4%), fatigue (46% vs 32%), nausea (45% vs 23%), infections (43% vs 25%), abdominal pain (35% vs 16%), anemia (29% vs 4%), leukopenia (28% vs 2%), decreased appetite (27% vs 12%), vomiting (26% vs 10%), headache (20% vs 15%), dysgeusia (18% vs 2.7%), thrombocytopenia (16% vs 3%), alopecia (16% vs 1.8%), stomatitis (15% vs 10%), ALT increased (13% vs 5%), pruritus (13% vs 6%), cough (13% vs 11%), dizziness (12% vs 6%), AST increased (12% vs 7%), peripheral edema (12% vs 7%), creatinine increased (12% vs <1%), rash (11% vs 4.5%), pyrexia (11% vs 6%), and weight decreased (10% vs 2.2%).

The **most frequently reported ≥5% Grade 3 or 4 adverse reactions** that occurred in the Verzenio arm vs the placebo arm of **MONARCH 2** were neutropenia (25% vs 1%), diarrhea (13% vs 0.4%), leukopenia (9% vs 0%), anemia (7% vs 1%), and infections (5.7% vs 3.5%).

Lab abnormalities (all grades; Grade 3 or 4) for MONARCH 2 in ≥10% for Verzenio plus fulvestrant with a difference between arms of ≥2% were increased serum creatinine (98% vs 74%; 1.2% vs 0%), decreased white blood cells (90% vs 33%; 23.7% vs .9%), decreased neutrophil count (87% vs 30%; 32.5% vs 4.2%), anemia (84% vs 34%; 2.6% vs .5%), decreased lymphocyte count (63% vs 32%; 12.2% vs 1.8%), decreased platelet count (53% vs 15%; 2.1% vs 0%), increased ALT (41% vs 32%; 4.6% vs 1.4%), and increased AST (37% vs 25%; 3.9% vs 4.2%).

The **most common adverse reactions (all grades, ≥10%)** observed in **MONARCH 1** with Verzenio were diarrhea (90%), fatigue (65%), nausea (64%), decreased appetite (45%), abdominal pain (39%), neutropenia (37%), vomiting (35%), infections (31%), anemia (25%), thrombocytopenia (20%), headache (20%), cough (19%), constipation (17%), leukopenia (17%), arthralgia (15%), dry mouth (14%), weight decreased (14%), stomatitis (14%), creatinine increased (13%), alopecia (12%), dysgeusia (12%), pyrexia (11%), dizziness (11%), and dehydration (10%).

The **most frequently reported ≥5% Grade 3 or 4 adverse reactions** from **MONARCH 1** with Verzenio were diarrhea (20%), neutropenia (24%), fatigue (13%), and leukopenia (5%).

Lab abnormalities (all grades; Grade 3 or 4) for MONARCH 1 with Verzenio were increased serum creatinine (99%; .8%), decreased white blood cells (91%; 28%), decreased neutrophil count (88%; 26.6%), anemia (69%; 0%), decreased lymphocyte count (42%; 13.8%), decreased platelet count (41%; 2.3%), increased ALT (31%; 3.1%), and increased AST (30%; 3.8%).

Strong and moderate CYP3A inhibitors increased the exposure of abemaciclib plus its active metabolites to a clinically meaningful extent and may lead to increased toxicity. Avoid concomitant use of ketoconazole. Ketoconazole is predicted to increase the AUC of abemaciclib by up to 16-fold. In patients with recommended starting doses of 200 mg twice daily or 150 mg twice daily, reduce the Verzenio dose to 100 mg twice daily with concomitant use of strong CYP3A inhibitors other than ketoconazole. In patients who have had a dose reduction to 100 mg twice daily due to adverse reactions, further reduce the Verzenio dose to 50 mg twice daily with concomitant use of strong CYP3A inhibitors. If a patient taking Verzenio discontinues a strong CYP3A inhibitor, increase the Verzenio dose (after 3 to 5 half-lives of the inhibitor) to the dose that was used before starting the inhibitor. With concomitant use of moderate CYP3A inhibitors, monitor for adverse reactions and consider reducing the Verzenio dose in 50 mg decrements. Patients should avoid grapefruit products.

Avoid concomitant use of strong or moderate CYP3A inducers and consider alternative agents. Coadministration of strong or moderate CYP3A inducers decreased the plasma concentrations of abemaciclib plus its active metabolites and may lead to reduced activity.

With severe hepatic impairment (Child-Pugh C), reduce the Verzenio dosing frequency to once daily. The pharmacokinetics of Verzenio in patients with **severe renal impairment** (CLcr <30 mL/min), end stage renal disease, or in patients on dialysis is unknown. No dosage adjustments are necessary in patients with mild or moderate hepatic (Child-Pugh A or B) and/or renal impairment (CLcr ≥30-89 mL/min).

Please see full Prescribing Information for Verzenio.

AL HCP ISI 12OCT2021

Verzenio®
abemaciclib
50 | 100 | 150 | 200 mg tablets

Lilly