VERZENIO® (abemaciclib) tablets, for oral use

FULL PRESCRIBING INFORMATION

1. NAME OF THE MEDICINAL PRODUCT

VERZENIO 50 mg, (Abemaciclib 50 mg) film-coated tablets for oral use.
VERZENIO 100 mg, (Abemaciclib 100 mg) film-coated tablets for oral use.
VERZENIO 150 mg, (Abemaciclib 150 mg) film-coated tablets for oral use.
VERZENIO 200 mg, (Abemaciclib 200 mg) film-coated tablets for oral use.

2. THERAPEUTIC INDICATIONS

2.1 Early Breast Cancer

- VERZENIO in combination with endocrine therapy is indicated 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 pre- or perimenopausal women and in men, aromatase inhibitor endocrine therapy should be combined with a luteinising hormone-releasing hormone (LHRH) agonist.

2.2 Advanced or Metastatic Breast Cancer

VERZENIO (abemaciclib) is indicated:

- in combination with a non-steroidal 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 in the metastatic setting and prior chemotherapy in the metastatic setting including taxane in adjuvant or metastatic setting.

  VERZENIO should not be used in adult patients after prior treatment with cyclin-dependent kinases 4 and 6 (CDK4 and CDK6) inhibitor.

3. DOSAGE AND ADMINISTRATION

3.1 Recommended Dose and Schedule

- When used in combination with fulvestrant, tamoxifen, or a non-steroidal aromatase inhibitor, the recommended dose of VERZENIO is 150 mg taken orally twice daily. Refer to the Full Prescribing Information for the recommended dose of the fulvestrant, tamoxifen or non-steroidal aromatase inhibitor being used.
- Pre/perimenopausal women and men treated with the combination of VERZENIO plus an aromatase inhibitor should be treated with a gonadotropin-releasing hormone agonist (GnRH) according to current clinical practice standards.
- Pre/perimenopausal women treated with the combination of VERZENIO plus fulvestrant should be treated with a GnRH according to current clinical practice standards.
- When used as monotherapy, the recommended dose of VERZENIO is 200 mg taken orally twice daily.
- For early breast cancer, continue VERZENIO until completion of 2 years of treatment or until disease recurrence, or unacceptable toxicity.
- For advanced or metastatic breast cancer, continue treatment until disease progression or unacceptable toxicity.

VERZENIO may be taken with or without food *[see Clinical Pharmacology (12.3)]*.

Instruct patients to take their doses of VERZENIO at approximately the same times every day.

If the patient vomits or misses a dose of VERZENIO, instruct the patient to take the next dose at its scheduled time. Instruct patients to swallow VERZENIO tablets whole and not to chew, crush, or split tablets before swallowing. Instruct patients not to ingest VERZENIO tablets if broken, cracked, or otherwise not intact.

3.2 Dose Modification

Dose Modifications for Adverse Reactions

The recommended VERZENIO dose modifications for adverse reactions are provided in Tables 1-7. Discontinue VERZENIO for patients unable to tolerate 50 mg twice daily.

Table 1: VERZENIO Dose Modification —Adverse Reactions

Dose Level	**VERZENIO Dose in Combination with Fulvestrant, Tamoxifen or a Non-steroidal Aromatase Inhibitor**	**VERZENIO Dose for Monotherapy**
Recommended starting dose	150 mg twice daily	200 mg twice daily
First dose reduction	100 mg twice daily	150 mg twice daily
Second dose reduction	50 mg twice daily	100 mg twice daily
Third dose reduction	not applicable	50 mg twice daily

Table 2: VERZENIO Dose Modification and Management — Hematologic Toxicities[a]

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.	
CTCAE Grade	**VERZENIO Dose Modifications**
Grade 1 or 2	No dose modification is required.
Grade 3	Suspend dose until toxicity resolves to ≤Grade 2. Dose reduction is not required.
Grade 3 recurrent, or Grade 4	Suspend dose until toxicity resolves to ≤Grade 2. Resume at *next lower dose*.

Abbreviation: CTCAE = Common Terminology Criteria for Adverse Events.

[a] If blood cell growth factors are required, suspend VERZENIO dose for at least 48 hours after the last dose of blood cell growth factor and until toxicity resolves to ≤Grade 2. Resume at *next lower dose* unless already performed for the toxicity that led to the use of the growth factor. Growth factor use as per current treatment guidelines.

Table 3: VERZENIO Dose Modification and Management — Diarrhea

At the first sign of loose stools, start treatment with antidiarrheal agents and increase intake of oral fluids.	
CTCAE Grade	**VERZENIO Dose Modifications**
Grade 1	No dose modification is required.
Grade 2	If toxicity does not resolve within 24 hours to ≤Grade 1, suspend dose until resolution. No dose reduction is required.
Grade 2 that persists or recurs after resuming the same dose despite maximal supportive measures	Suspend dose until toxicity resolves to ≤Grade 1. Resume at *next lower dose*.
Grade 3 or 4 or requires hospitalization	Suspend dose until toxicity resolves to ≤Grade 1. Resume at *next lower dose*.

Table 4: VERZENIO Dose Modification and Management — Hepatotoxicity

Monitor ALT, AST, and serum bilirubin 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.	
CTCAE Grade for ALT and AST	**VERZENIO Dose Modifications**
Grade 1 (>ULN-3.0 x ULN) Grade 2 (>3.0-5.0 x ULN), WITHOUT increase in total bilirubin above 2 x ULN	No dose modification is required.
Persistent or Recurrent Grade 2, or Grade 3 (>5.0-20.0 x ULN), WITHOUT increase in total bilirubin above 2 x ULN	Suspend dose until toxicity resolves to baseline or Grade 1. Resume at next lower dose.
Elevation in AST and/or ALT >3 x ULN WITH total bilirubin >2 x ULN, in the absence of cholestasis	Discontinue VERZENIO.
Grade 4 (>20.0 x ULN)	Discontinue VERZENIO.

Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, ULN = upper limit of normal.

Table 5: VERZENIO Dose Modification and Management — Interstitial Lung Disease/Pneumonitis

CTCAE Grade	VERZENIO Dose Modifications
Grade 1 or 2	No dose modification is required.
Persistent or recurrent Grade 2 toxicity that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1	Suspend dose until toxicity resolves to baseline or ≤Grade 1. Resume at *next lower dose*.
Grade 3 or 4	Discontinue VERZENIO.

Table 6: VERZENIO Dose Modification and Management — Venous Thromboembolic Events (VTEs)

CTCAE Grade	VERZENIO Dose Modifications
Early Breast Cancer	
Any Grade	Suspend dose and treat as clinically indicated. Resume VERZENIO when the patient is clinically stable.
Advanced or Metastatic Breast Cancer	
Grade 1 or 2	No dose modification is required.
Grade 3 or 4	Suspend dose and treat as clinically indicated. Resume VERZENIO when the patient is clinically stable.

Table 7: VERZENIO Dose Modification and Management — Other Toxicities[a]

CTCAE Grade	VERZENIO Dose Modifications
Grade 1 or 2	No dose modification is required.
Persistent or recurrent Grade 2 toxicity that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1	Suspend dose until toxicity resolves to baseline or ≤Grade 1. Resume at *next lower dose*.
Grade 3 or 4	Suspend dose until toxicity resolves to baseline or ≤Grade 1. Resume at *next lower dose*.

[a] Excluding diarrhea, hematologic toxicity, hepatotoxicity ILD/pneumonitis, and VTEs.

Refer to the Full Prescribing Information for coadministered fulvestrant, tamoxifen or a non-steroidal aromatase inhibitor for dose modifications and other relevant safety information.

Dose Modification for Use with Strong and Moderate CYP3A Inhibitors

Avoid concomitant use of the strong CYP3A inhibitor ketoconazole.

With concomitant use of strong CYP3A inhibitors other than ketoconazole, 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. 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. If a patient taking VERZENIO discontinues a CYP3A inhibitor, increase the VERZENIO dose (after 3-5 half-lives of the inhibitor) to the dose that was used before starting the strong inhibitor *[see Drug Interactions (8.1) and Clinical Pharmacology (12.3)]*.

With concomitant use of moderate CYP3A inhibitors, monitor for adverse reactions and consider reducing the VERZENIO dose in 50 mg decrements as demonstrated in Table 1, if necessary.

Dose Modification for Patients with Severe Hepatic Impairment

For patients with severe hepatic impairment (Child Pugh-C), reduce the VERZENIO dosing frequency to once daily *[see Use in Specific Populations (9.7) and Clinical Pharmacology (12.3)]*.

Refer to the Full Prescribing Information for the coadministered fulvestrant, tamoxifen or a non-steroidal aromatase inhibitor for dose modification requirements for severe hepatic impairment.

4 DOSAGE FORMS AND STRENGTHS

50 mg tablets: oval beige tablet with “Lilly” debossed on one side and “50” on the other side.

100 mg tablets: oval white to practically white tablet with “Lilly” debossed on one side and “100” on the other side.

150 mg tablets: oval yellow tablet with “Lilly” debossed on one side and “150” on the other side.

200 mg tablets: oval beige tablet with “Lilly” debossed on one side and “200” on the other side.

5 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in section 11.

6 WARNINGS AND PRECAUTIONS

6.1 Diarrhea

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 *[see Adverse Reactions (7.1)].*

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, withhold VERZENIO until resolution to ≤Grade 1, and then resume VERZENIO at the next lower dose *[see Dosage and Administration (3.2)]*.

6.2 Neutropenia

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 the first episode of Grade ≥3 neutropenia ranged from 29 days to 33 days, and the median duration of Grade ≥3 neutropenia ranged from 11 days to 16 days *[see Adverse Reactions (7.1)]*.

Febrile neutropenia has been reported in <1% of patients receiving 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 *[see Dosage and Administration (3.2)]*.

6.3 Interstitial Lung Disease (ILD) or Pneumonitis

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 early breast cancer (monarchE, N=2791), 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 advanced or metastatic breast cancer (N=900) (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 *[see Adverse Reactions (7.2)]*.

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.

Withhold or reduce dose for 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 [see Dosage and Administration (3.2)].

6.4 Hepatotoxicity

Grade ≥3 ALT (2% to 6%) and 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 Grade 4 hepatic transaminase elevation *[see Dosage and Administration (3.2)]*.

6.5 Venous Thromboembolism

Across three clinical trials in 3559 patients (monarchE, MONARCH 2, MONARCH 3), venous thromboembolic (VTE) events occurred in 2% to 5% of patients treated with VERZENIO. VTE events included deep vein thrombosis, pulmonary embolism, pelvic venous thrombosis, cerebral venous sinus thrombosis, subclavian and axillary vein thrombosis, inferior vena cava thrombosis, jugular vein thrombosis, peripheral vein thrombosis and superficial vein thrombosis. In clinical trials, deaths due to VTE occurred 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 early breast cancer patients with any grade VTE event and for advanced or metastatic breast cancer patients with a Grade 3 or 4 VTE event *[see Dosage and Administration (3.2)]*.

6.6 Embryo-Fetal Toxicity

Based on findings from animal studies and the mechanism of action, VERZENIO can cause fetal harm when administered to a pregnant woman. 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 *[see Use in Specific Populations (9.1, 9.3) and Clinical Pharmacology (12.1)]*.

6.7 Arterial Thromboembolic Events

A potential increased risk for serious arterial thromboembolic events (ATEs), including ischemic stroke and myocardial infarction, has been observed in metastatic breast cancer studies when abemaciclib was administered in combination with endocrine therapies. The benefits and risks of continuing abemaciclib in patients who experience a serious ATE should be considered.

6.8 Increased Serum Creatinine without Affecting Renal Function

VERZENIO can increase serum creatinine. Across four clinical trials in 3691 patients (monarchE, MONARCH 1, MONARCH 2, MONARCH 3), increases in serum creatinine (mean increase, 0.2-0.3 mg/dL) occurred within the first 28-day cycle of VERZENIO treatment, remained elevated through the treatment, and were reversible upon treatment discontinuation. These increases were not associated with changes in glomerular function [see Adverse Reactions (7.1)]. The increases in serum creatinine may be due to inhibition of renal tubular secretion transporters [see Clinical Pharmacology (12.3)]. During VERZENIO treatment, use alternative measures that are not based on serum creatinine to assess renal function such as BUN, cystatin C, or calculated GFR.

6.9 Lactose

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

6.10 Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially “sodium-free”.

7 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Diarrhea *[see Warnings and Precautions (6.1)]*.
- Neutropenia *[see Warnings and Precautions (6.2)]*.
- Interstitial Lung Disease (ILD) or Pneumonitis *[see Warnings and Precautions (6.3)]*.
- Hepatotoxicity *[see Warnings and Precautions (6.4)]*.
- Venous Thromboembolism *[see Warnings and Precautions (6.5)]*.

7.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety population described in the Warnings and Precautions reflect exposure to VERZENIO in 3691 patients from four clinical trials: monarchE, MONARCH 1, MONARCH 2, and MONARCH 3. The safety population includes exposure to VERZENIO as a single agent at 200 mg twice daily in 132 patients in MONARCH 1 and to VERZENIO at 150 mg twice daily in 3559 patients administered in combination with fulvestrant, tamoxifen, or an aromatase inhibitor in monarchE, MONARCH 2, and MONARCH 3. The median duration of exposure ranged from 4.5 months in MONARCH 1 to 24 months in monarchE. The most common adverse reactions (incidence ≥20%) across clinical trials were: diarrhea, neutropenia, nausea, abdominal pain, infections, fatigue, anemia, leukopenia, decreased appetite, vomiting, headache, alopecia, and thrombocytopenia.

Early Breast Cancer

monarchE: VERZENIO in Combination with Tamoxifen or an Aromatase Inhibitor as Adjuvant Treatment

Adult patients with HR-positive, HER2-negative, node-positive early breast cancer at a high risk of recurrence

The safety of VERZENIO was evaluated in monarchE, a study of 5591 adult patients receiving VERZENIO in combination with endocrine therapy (tamoxifen or an aromatase inhibitor) or endocrine therapy (tamoxifen or an aromatase inhibitor) alone *[see Clinical Studies (14.1)].* Patients were randomly assigned to receive 150 mg of VERZENIO orally, twice daily, in combination with tamoxifen or an aromatase inhibitor, or tamoxifen or an aromatase inhibitor, for two years or until discontinuation criteria were met. The median duration of VERZENIO treatment was 24 months (range: 1-28 months).

Serious adverse reactions occurred in 15% of patients who received VERZENIO in combination with endocrine therapy (tamoxifen or an aromatase inhibitor). Serious adverse reactions in ≥1% of patients included venous thromboembolism (VTE) (1.2%) and pneumonia (1%).

Fatal adverse reactions occurred in 0.8% of patients who received VERZENIO plus endocrine therapy (tamoxifen or an aromatase inhibitor), including: cardiac failure (0.1%), cardiac arrest, myocardial infarction, ventricular fibrillation, cerebral hemorrhage, cerebrovascular accident, pneumonitis, hypoxia, diarrhea and mesenteric artery thrombosis (0.03% each).

Permanent discontinuation of VERZENIO due to an adverse reaction occurred in 19% of patients. Adverse reactions which resulted in permanent discontinuation in >1% of patients were diarrhea (5%), and fatigue (2%).

Dosage interruptions of VERZENIO due to an adverse reaction occurred in 62% of patients. Adverse reactions which required dosage interruptions in ≥5% of patients were diarrhea (20%), neutropenia (16%), leukopenia (7%), and fatigue (5%).

Dose reductions of VERZENIO due to an adverse reaction occurred in 44% of patients. Adverse reactions which required dose reductions in ≥5% of patients were diarrhea (17%), neutropenia (8%), and fatigue (5%).

The most common (>20%) adverse reactions, including laboratory abnormalities in the VERZENIO plus tamoxifen or an aromatase inhibitor arm and ≥2% higher than the tamoxifen or an aromatase inhibitor arm were: increased creatinine, decreased neutrophils, diarrhea, decreased hemoglobin, decreased lymphocytes, infections, fatigue, increased alanine aminotransferase (ALT), decreased platelets, increased aspartate aminotransferase (AST), nausea, and headache. Adverse reactions are shown in Table 8 and laboratory abnormalities are shown in Table 9.

Table 8: Adverse Reactions (≥10%) of Patients Receiving VERZENIO Plus Tamoxifen or an Aromatase Inhibitor [with a Difference between Arms of ≥2%] in monarchE

Adverse Reaction[a]	VERZENIO Plus Tamoxifen or an Aromatase Inhibitor N=2791			Tamoxifen or an Aromatase Inhibitor N=2800		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Gastrointestinal Disorders						
Diarrhea	84	8	0	9	0.2	0
Nausea	30	0.5	0	9	<0.1	0
Vomiting	18	0.5	0	4.6	0.1	0
Stomatitis[b]	14	0.1	0	5	0	0
Infections and Infestations						
Infections[b]	51	4.9	0.6	39	2.7	0.1
General Disorders and Administration Site Conditions						
Fatigue[b]	41	2.9	0	18	0.1	0

Nervous System Disorders						
Headache	20	0.3	0	15	0.2	0
Dizziness	11	0.1	0	7	<0.1	0
Metabolism and Nutrition Disorders						
Decreased appetite	12	0.6	0	2.4	<0.1	0
Skin and Subcutaneous Tissue Disorders						
Rash[b]	11	0.4	0	4.5	0	0
Alopecia	11	0	0	2.7	0	0

[a] Adverse reactions were graded using NCI CTCAE version 4.0

[b] Includes other related terms.

Clinically relevant adverse reactions in <10% of patients who received VERZENIO in combination with tamoxifen or an aromatase inhibitor in monarchE include: pruritus (9%), dyspepsia (8%), nail disorder (6%), increased lacrimation (6%), dysgeusia (5%), ILD/pneumonitis (3%), and VTE (3%).

Table 9: Laboratory Abnormalities (≥10%) in Patients Receiving VERZENIO Plus Tamoxifen or an Aromatase Inhibitor [with a Difference between Arms of ≥2%] in monarchE

	VERZENIO Plus Tamoxifen or an Aromatase Inhibitor N=2791			**Tamoxifen or an Aromatase Inhibitor N=2800**		
	All Grades %	**Grade 3 %**	**Grade 4 %**	**All Grades %**	**Grade 3 %**	**Grade 4 %**
Chemistry						
Creatinine increased	99	0.5	0	91	<0.1	0
ALT increased	37	2.5	<0.1	24	1.2	0
AST increased	31	1.5	<0.1	18	0.9	0
Potassium decreased	11	1.2	0.1	3.8	0.1	0.1
Hematology						
Neutrophils decreased	84	18	0.7	23	1.6	0.3
Hemoglobin decreased	68	1	0	17	0.1	0
Lymphocytes decreased	59	13	0.2	24	2.4	0.1
Platelets decreased	37	0.7	0.2	10	0.1	0.1

Advanced or Metastatic Breast Cancer

MONARCH 3: VERZENIO in Combination with a Non-steroidal Aromatase Inhibitor (Anastrozole or Letrozole) as Initial Endocrine-Based Therapy

Postmenopausal Women with HR-positive, HER2-negative locoregionally recurrent or metastatic breast cancer with no prior systemic therapy in this disease setting

The safety of VERZENIO was evaluated in MONARCH 3, a study of 488 women receiving VERZENIO in combination with a non-steroidal aromatase inhibitor or placebo in combination with an aromatase inhibitor *[see Clinical Studies (14.2)]*. Patients were randomly assigned to receive 150 mg of VERZENIO or placebo orally twice daily, in combination with investigator's choice of anastrozole or letrozole once daily until discontinuation criteria were met. The median duration of VERZENIO treatment was 15.1 months (range: 5 days – 27.4 months).

Serious adverse reactions occurred in 28% of patients who received VERZENIO plus a non-steroidal aromatase inhibitor. Serious adverse reactions in ≥1.5% of patients included infections (6%), VTE (2.5%) and diarrhea and anemia (1.5%, each).

Fatal adverse reactions occurred in 3% of patients who received VERZENIO including underlying disease (0.9%), lung infection (0.9%), VTE (0.9%), pneumonitis (0.3%), and cerebral infarction (0.3%).

Permanent discontinuation of VERZENIO due to an adverse reaction occurred in 13% of patients. Adverse reactions which resulted in permanent discontinuation in >1% of patients were diarrhea (2%), ALT increased (2%), infection (1%), and VTE (1%).

Dosage interruptions of VERZENIO due to an adverse reaction occurred in 56% of patients. Adverse reactions which required dosage interruptions in ≥5% of patients were neutropenia (16%) and diarrhea (15%).

Dose reductions of VERZENIO due to an adverse reaction occurred in 43% of patients. Adverse reactions which required dose reductions in ≥5% of patients were diarrhea (13%) and neutropenia (11%).

The most common (≥20%) adverse reactions including laboratory abnormalities in the VERZENIO plus a non-steroidal aromatase inhibitor arm and ≥2% higher than the placebo arm were: increased creatinine, decreased hemoglobin, diarrhea, decreased neutrophils, decreased lymphocytes, increased ALT, fatigue, infections, nausea, increased AST, decreased platelets, abdominal pain, vomiting, alopecia, and decreased appetite. Adverse reactions are shown in Table 10 and laboratory abnormalities in Table 11.

Table 10: Adverse Reactions (≥10%) in Patients Receiving VERZENIO Plus Anastrozole or Letrozole [with a Difference between Arms of ≥2%] in MONARCH 3

Adverse Reaction[a]	VERZENIO plus Anastrozole or Letrozole N=327			Placebo plus Anastrozole or Letrozole N=161		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Gastrointestinal Disorders						
Diarrhea	81	9	0	30	1.2	0
Nausea	39	0.9	0	20	1.2	0
Abdominal pain	29	1.2	0	12	1.2	0
Vomiting	28	1.2	0	12	1.9	0
Constipation	16	0.6	0	12	0	0
Infections and Infestations						
Infections[b]	39	4	0.9	29	2.5	0.6
General Disorders and Administration Site Conditions						
Fatigue	40	1.8	0	32	0	0
Influenza like illness	10	0	0	8	0	0
Skin and Subcutaneous Tissue Disorders						
Alopecia	27	0	0	11	0	0
Rash	14	0.9	0	5	0	0
Pruritus	13	0	0	9	0	0
Metabolism and Nutrition Disorders						
Decreased appetite	24	1.2	0	9	0.6	0
Respiratory, Thoracic, and Mediastinal Disorders						
Cough	13	0	0	9	0	0
Dyspnea	12	0.6	0.3	6	0.6	0
Nervous System Disorders						
Dizziness	11	0.3	0	9	0	0
Investigations						

Decreased weight	10	0.6	0	3.1	0.6	0

[a] Adverse reactions were graded using NCI CTCAE version 4.0
[b] Includes other related terms

Clinically relevant adverse reactions (<10%) in patients who received VERZENIO in combination with a non-steroidal aromatase inhibitor included: VTE (5%).

Table 11: Laboratory Abnormalities (≥10%) in Patients Receiving VERZENIO Plus Anastrozole or Letrozole [with a Difference Between Arms of ≥2%] in MONARCH 3

	VERZENIO plus Anastrozole or Letrozole N=327			**Placebo plus Anastrozole or Letrozole N=161**		
Laboratory Abnormality	**All Grades %**	**Grade 3 %**	**Grade 4 %**	**All Grades %**	**Grade 3 %**	**Grade 4 %**
Chemistry						
Creatinine increased	98	2.2	0	84	0	0
ALT increased	48	6	0.6	25	1.9	0
AST increased	37	3.8	0	23	0.6	0
Hematology						
Hemoglobin decreased	82	1.6	0	28	0	0
Neutrophils decreased	80	19	2.9	21	2.6	0
Lymphocytes decreased	53	7	0.6	26	1.9	0
Platelets decreased	36	1.3	0.6	12	0.6	0

MONARCH 2: VERZENIO in Combination with Fulvestrant

Women with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression on or after prior adjuvant or metastatic endocrine therapy

The safety of VERZENIO in combination with fulvestrant versus placebo was evaluated in 664 patients with HR-positive, HER2-negative advanced breast cancer in MONARCH 2 [see Clinical Studies (14.2)]. Patients were randomized (2:1) to receive VERZENIO 150 mg orally twice daily in combination with fulvestrant (N=441) or placebo in combination with fulvestrant (N=223). Among patients treated with VERZENIO plus fulvestrant, the median duration of exposure was 12 months (range: 1 day – 27.8 months).

Serious adverse reactions occurred in 22% of patients who received VERZENIO in combination with fulvestrant. Serious adverse reactions in >1% of patients included VTE and pneumonia (1.8%, each), diarrhea (1.6%), cough (1.4%), sepsis (1.4%) and nausea and acute kidney injury (1.1% each). Fatal adverse reactions occurred in 4% of patients who received VERZENIO plus fulvestrant including underlying disease (2%), sepsis (0.9%), pneumonitis and hepatotoxicity (0.5% each), and cerebral infarction (0.2%).

Permanent discontinuation of VERZENIO due to an adverse reaction occurred in 9% of patients. Adverse reactions which resulted in permanent discontinuation in >1% of patients were infection (2%), and diarrhea and hepatotoxicity (1%, each).

Dosage interruptions of VERZENIO due to an adverse reaction occurred in 52% of patients. Adverse reactions which required dosage interruptions in ≥5% of patients were diarrhea (19%) and neutropenia (16%).

Dose reductions of VERZENIO due to an adverse reaction occurred in 43% of patients. Adverse reactions which required dose reductions in ≥5% of patients were diarrhea (19%) and neutropenia (10%).

The most common (≥20%) adverse reactions, including laboratory abnormalities, in the VERZENIO plus fulvestrant arm and with a ≥ 2% higher than the placebo plus fulvestrant arm were: increased creatinine, decreased neutrophils, diarrhea, decreased hemoglobin, decreased lymphocytes, decreased platelets, fatigue, nausea, infections, increased ALT, increased AST, abdominal pain, decreased appetite, vomiting, and headache. Adverse reactions are shown in Table 12 and laboratory abnormalities in Table 13.

Table 12: Adverse Reactions (≥10%) in Patients Receiving VERZENIO Plus Fulvestrant [with a Difference Between Arms of ≥2%] in MONARCH 2

Adverse Reaction[a]	VERZENIO plus Fulvestrant N=441			Placebo plus Fulvestrant N=223		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Gastrointestinal Disorders						
Diarrhea	86	13	0	25	0.4	0
Nausea	45	2.7	0	23	0.9	0
Abdominal pain[b]	35	2.5	0	16	0.9	0
Vomiting	26	0.9	0	10	1.8	0
Stomatitis	15	0.5	0	10	0	0
General Disorders and Administration Site Conditions						
Fatigue[b]	46	2.7	0	32	0.4	0
Edema peripheral	12	0	0	7	0	0
Pyrexia	11	0.5	0.2	6	0.4	0
Infections and Infestations						
Infections[b]	43	5	0.7	25	3.1	0.4
Metabolism and Nutrition Disorders						
Decreased appetite	27	1.1	0	12	0.4	0
Nervous System Disorders						
Headache	20	0.7	0	15	0.4	0
Dysgeusia	18	0	0	2.7	0	0
Dizziness	12	0.7	0	6	0	0
Skin and Subcutaneous Tissue Disorders						
Alopecia	16	0	0	1.8	0	0
Pruritus	13	0	0	6	0	0
Rash	11	1.1	0	4.5	0	0
Respiratory, Thoracic and Mediastinal Disorders						
Cough	13	0	0	11	0	0
Investigations						
Weight decreased	10	0.2	0	2.2	0.4	0

[a] Adverse reactions were graded using NCI CTCAE version 4.0

[b] Includes other related terms.

Clinically relevant adverse reactions (<10%) in patients who received VERZENIO in combination with fulvestrant included: VTE (5%)

Table 13: Laboratory Abnormalities (≥10%) in Patients Receiving VERZENIO Plus Fulvestrant [with a Difference Between Arms of ≥2%] in MONARCH 2

	VERZENIO plus Fulvestrant N=441			Placebo plus Fulvestrant N=223		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Chemistry						
Creatinine increased	98	1.2	0	74	0	0
ALT increased	41	3.9	0.7	32	1.4	0
AST increased	37	3.9	0	25	3.7	0.5
Hematology						
Neutrophils decreased	87	29	3.5	30	3.7	0.5
Hemoglobin decreased	84	2.6	0	34	0.5	0
Lymphocytes decreased	63	12	0.2	32	1.8	0
Platelets decreased	53	0.9	1.2	15	0	0

MONARCH 1: VERZENIO Administered as a Monotherapy in Metastatic Breast Cancer

Adult patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy in the metastatic setting and prior 1-2 chemotherapy in the metastatic setting including taxane in adjuvant or metastatic setting.

The safety of VERZENIO was evaluated in 132 women with HR-positive, HER2-negative metastatic breast cancer whose disease progressed during or after endocrine therapy, had received a taxane in any setting, and who had received 1 or 2 prior chemotherapy regimens in the metastatic setting [see Clinical Studies (14.2)]. Patients received VERZENIO 200 mg orally twice daily. The median duration of exposure to VERZENIO was 4.5 months (range: 8 days – 20.4 months).

Serious adverse reactions occurred in 24% of patients who received VERZENIO. Serious adverse reactions in >2% of patients included infections (4.5%), increased creatinine (3%), dehydration, nausea, and abdominal pain (2.3%, each). Fatal adverse reactions occurred in 2.3% of patients who received VERZENIO including infection (1.5%) and pneumonitis (0.8%).

Permanent discontinuation of VERZENIO due to adverse reactions occurred in 8% of patients. Adverse reactions which resulted in permanent discontinuation of VERZENIO included abdominal pain, arterial thrombosis, increased AST, increased creatinine, chronic kidney disease, diarrhea, prolonged QT interval, fatigue, hip fracture, and lymphopenia (0.8% each).

Dosage interruptions of VERZENIO due to an adverse reaction occurred in 58% of patients. Adverse reactions which required dosage interruptions in ≥5% of patients were diarrhea (24%), neutropenia (16%), fatigue (10%), vomiting (6%), and nausea (5%).

Dose reductions of VERZENIO due to an adverse reaction occurred in 49% of patients. Adverse reactions which resulted in dose reductions in ≥5% of patients were diarrhea (20%), neutropenia (11%), and fatigue (9%).

The most common (≥20%) adverse reactions, including laboratory abnormalities, in patients treated with VERZENIO were: increased creatinine, diarrhea, decreased neutrophils, decreased hemoglobin, fatigue, nausea, decreased appetite, decreased lymphocytes, decreased platelets, abdominal pain, vomiting, infections, increased ALT, increased AST and headache. Adverse reactions are shown in Table 14 and laboratory abnormalities in Table 15.

Table 14: Adverse Reactions (≥10%) of Patients in MONARCH 1

Adverse Reaction[a]	VERZENIO N=132

	All Grades %	Grade 3 %	Grade 4 %
Gastrointestinal Disorders			
Diarrhea	90	20	0
Nausea	64	4.5	0
Abdominal pain	39	2.3	0
Vomiting	35	1.5	0
Constipation	17	0.8	0
Dry mouth	14	0	0
Stomatitis	14	0	0
General Disorders and Administration Site Conditions			
Fatigue[b]	65	13	0
Pyrexia	11	0	0
Metabolism and Nutrition Disorders			
Decreased appetite	45	3.0	0
Dehydration	10	2.3	0
Infections and Infestations			
Infections	31	4.5	0
Nervous System Disorders			
Headache	20	0	0
Dysgeusia	12	0	0
Dizziness	11	0	0
Respiratory, Thoracic and Mediastinal Disorders			
Cough	19	0	0
Musculoskeletal and Connective Tissue Disorders			
Arthralgia	15	0	0
Investigations			
Weight decreased	14	0	0
Skin and Subcutaneous Tissue Disorders			
Alopecia	12	0	0

[a] Adverse reactions were graded using NCI CTCAE version 4.0

[b] Includes other related terms

Table 15: Laboratory Abnormalities for Patients Receiving VERZENIO in MONARCH 1

	VERZENIO N=132		
	All Grades %	**Grade 3 %**	**Grade 4 %**
Chemistry			
Creatinine increased	99	0.8	0
ALT increased	31	3.1	0
AST increased	30	3.8	0
Hematology			
Neutrophils decreased	88	22	4.6

Hemoglobin decreased	69	0	0
Lymphocytes decreased	42	13	0.8
Platelets decreased	41	2.3	0

7.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of VERZENIO. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Respiratory disorders: Interstitial lung disease (ILD)/pneumonitis *[see Warnings and Precautions (6.3)]*.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://reportsideffect.health.gov.il/drugs/home

8 DRUG INTERACTIONS

8.1 Effect of Other Drugs on VERZENIO

CYP3A Inhibitors

Strong and moderate CYP3A4 inhibitors increased the exposure of abemaciclib plus its active metabolites to a clinically meaningful extent and may lead to increased toxicity.

Ketoconazole

Avoid concomitant use of ketoconazole. Ketoconazole is predicted to increase the AUC of abemaciclib by up to 16-fold *[see Clinical Pharmacology (12.3)]*.

Other Strong CYP3A Inhibitors

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 3-5 half-lives of the inhibitor) to the dose that was used before starting the inhibitor. Patients should avoid grapefruit products *[see Dosage and Administration (3.2) and Clinical Pharmacology (12.3)]*.

Moderate CYP3A Inhibitors

With concomitant use of moderate CYP3A inhibitors, monitor for adverse reactions and consider reducing the VERZENIO dose in 50 mg decrements as demonstrated in Table 1, if necessary.

Strong and Moderate CYP3A Inducers

Coadministration of strong or moderate CYP3A inducers decreased the plasma concentrations of abemaciclib plus its active metabolites and may lead to reduced activity. Avoid concomitant use of strong or moderate CYP3A inducers and consider alternative agents *[see Clinical Pharmacology (12.3)]*.

9 USE IN SPECIFIC POPULATIONS

9.1 Pregnancy

Refer to the Prescribing Information of the agents administered in combination with VERZENIO for pregnancy information.

Risk Summary

Based on findings in animals and its mechanism of action, VERZENIO can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. There are no available human data informing the drug-associated risk. Advise pregnant women of the potential risk to a fetus. In animal reproduction studies, administration of abemaciclib during organogenesis was teratogenic and caused decreased fetal weight at maternal exposures that were similar to human clinical exposure based on AUC at the maximum recommended human dose (*see* Data). Advise pregnant women of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk in the U.S. general population of major birth defects is 2 to 4% and of miscarriage is 15 to 20% of clinically recognized pregnancies.

Data

Animal Data

In an embryo-fetal development study, pregnant rats received oral doses of abemaciclib up to 15 mg/kg/day during the period of organogenesis. Doses ≥4 mg/kg/day caused decreased fetal body weights and increased incidence of cardiovascular and skeletal malformations and variations. These findings included absent innominate artery and aortic arch, malpositioned subclavian artery, unossified sternebra, bipartite ossification of thoracic centrum, and rudimentary or nodulated ribs. At 4 mg/kg/day in rats, the maternal systemic exposures were approximately equal to the human exposure (AUC) at the recommended dose.

9.2 Lactation

Refer to the Prescribing Information of the agents administered in combination with VERZENIO for lactation information. When used in combination, advise patients to not breastfeed during treatment and for the longest post-treatment duration recommended in the prescribing information of any of the individual products.

Risk Summary

There are no data on the presence of abemaciclib in human milk, or its effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed infants from VERZENIO, advise lactating women not to breastfeed during VERZENIO treatment and for 3 weeks after the last dose.

9.3 Females and Males of Reproductive Potential

Refer to the Prescribing Information of the agents administered in combination with VERZENIO for contraception and infertility information. When used in combination, advise patients to use effective contraception during treatment and for the longest post-treatment duration recommended in the prescribing information of the individual products.

Based on animal studies, VERZENIO can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (9.1)]*.

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating treatment with VERZENIO.

Contraception

Females

Advise females of reproductive potential to use effective contraception during VERZENIO treatment and for 3 weeks after the last dose.

Infertility

Males

Based on findings in animals, VERZENIO may impair fertility in males of reproductive potential *[see Nonclinical Toxicology (13.1)]*.

9.4 Pediatric Use

The safety and effectiveness of VERZENIO have not been established in pediatric patients.

9.5 Geriatric Use

Of the 2791 VERZENIO-treated patients in monarchE, 15% were 65 years of age or older and 2.7% were 75 years of age or older.

Of the 900 patients who received VERZENIO in MONARCH 1, MONARCH 2, and MONARCH 3, 38% were 65 years of age or older and 10% were 75 years of age or older.

No overall differences in safety or effectiveness of VERZENIO as monotherapy or in combination with fulvestrant, tamoxifen, or an aromatase inhibitor have been observed between these patients and younger patients.

9.6 Renal Impairment

No dosage adjustment is required for patients with mild or moderate renal impairment (CLcr ≥30-89 mL/min, estimated by Cockcroft-Gault [C-G]). The pharmacokinetics of abemaciclib in patients with severe renal impairment (CLcr <30 mL/min, C-G), end stage renal disease, or in patients on dialysis is unknown *[see Clinical Pharmacology (12.3)]*.

9.7 Hepatic Impairment

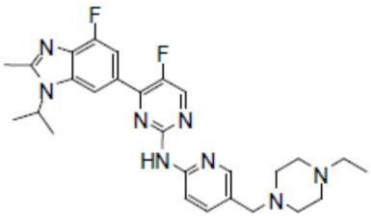
No dosage adjustments are necessary in patients with mild or moderate hepatic impairment (Child-Pugh A or B).

Reduce the dosing frequency when administering VERZENIO to patients with severe hepatic impairment (Child-Pugh C) *[see Dosage and Administration (3.2) and Clinical Pharmacology (12.3)]*.

11 DESCRIPTION

Abemaciclib is a kinase inhibitor for oral administration. It is a white to yellow powder with the empirical formula $C_{27}H_{32}F_2N_8$ and a molecular weight 506.59.

The chemical name for abemaciclib is 2-Pyrimidinamine, *N*-[5-[(4-ethyl-1-piperazinyl)methyl]-2-pyridinyl]-5-fluoro-4-[4-fluoro-2-methyl-1-(1-methylethyl)-1*H*-benzimidazol-6-yl]-. Abemaciclib has the following structure:



VERZENIO (abemaciclib) tablets are provided as immediate-release oval white, beige, or yellow tablets. Inactive ingredients are as follows:

Excipients— microcrystalline cellulose 102, microcrystalline cellulose 101, lactose monohydrate (lactose hydrate), croscarmellose sodium, sodium stearyl fumarate, silicon dioxide (silica, colloidal hydrated; hydrated silicone dioxide).

Color mixture ingredients-

50 mg: polyvinyl alcohol, titanium dioxide, macrogol 4000/PEG MW 3350, talc, iron oxide yellow, iron oxide red.

100 mg: polyvinyl alcohol, titanium dioxide, macrogol 4000/PEG MW 3350, talc.

150 mg: polyvinyl alcohol, titanium dioxide, macrogol 4000/PEG MW 3350, talc, iron oxide yellow.

200 mg: polyvinyl alcohol, titanium dioxide, macrogol 4000/PEG MW 3350, talc, iron oxide yellow, iron oxide red.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Abemaciclib is an inhibitor of cyclin-dependent kinases 4 and 6 (CDK4 and CDK6). These kinases are activated upon binding to D-cyclins. In estrogen receptor-positive (ER+) breast cancer cell lines, cyclin D1 and CDK4/6 promote

phosphorylation of the retinoblastoma protein (Rb), cell cycle progression, and cell proliferation. In vitro, continuous exposure to abemaciclib inhibited Rb phosphorylation and blocked progression from G1 into S phase of the cell cycle, resulting in senescence and apoptosis. In breast cancer xenograft models, abemaciclib dosed daily without interruption as a single agent or in combination with antiestrogens resulted in reduction of tumor size.

12.2 Pharmacodynamics

Cardiac Electrophysiology

Based on evaluation of the QTc interval in patients and in a healthy volunteer study, abemaciclib did not cause large mean increases (i.e., 20 ms) in the QTc interval.

12.3 Pharmacokinetics

The pharmacokinetics of abemaciclib were characterized in patients with solid tumors, including breast cancer, and in healthy subjects.

Following single and repeated twice daily dosing of 50 mg (0.3 times the approved recommended 150 mg dosage) to 200 mg of abemaciclib, the increase in plasma exposure (AUC) and C_{max} was approximately dose proportional. Steady state was achieved within 5 days following repeated twice daily dosing, and the estimated geometric mean accumulation ratio was 2.3 (50% CV) and 3.2 (59% CV) based on C_{max} and AUC, respectively.

Absorption

The absolute bioavailability of abemaciclib after a single oral dose of 200 mg is 45% (19% CV). The median T_{max} of abemaciclib is 8.0 hours (range: 4.1-24.0 hours).

Effect of Food

A high-fat, high-calorie meal (approximately 800 to 1000 calories with 150 calories from protein, 250 calories from carbohydrate, and 500 to 600 calories from fat) administered to healthy subjects increased the AUC of abemaciclib plus its active metabolites by 9% and increased C_{max} by 26%.

Distribution

In vitro, abemaciclib was bound to human plasma proteins, serum albumin, and alpha-1-acid glycoprotein in a concentration independent manner from 152 ng/mL to 5066 ng/mL. In a clinical study, the mean (standard deviation, SD) bound fraction was 96.3% (1.1) for abemaciclib, 93.4% (1.3) for M2, 96.8% (0.8) for M18, and 97.8% (0.6) for M20. The geometric mean systemic volume of distribution is approximately 690.3 L (49% CV).

In patients with advanced cancer, including breast cancer, concentrations of abemaciclib and its active metabolites M2 and M20 in cerebrospinal fluid are comparable to unbound plasma concentrations.

Elimination

The geometric mean hepatic clearance (CL) of abemaciclib in patients was 26.0 L/h (51% CV), and the mean plasma elimination half-life for abemaciclib in patients was 18.3 hours (72% CV).

Metabolism

Hepatic metabolism is the main route of clearance for abemaciclib. Abemaciclib is metabolized to several metabolites primarily by cytochrome P450 (CYP) 3A4, with formation of N-desethylabemaciclib (M2) representing the major metabolism pathway. Additional metabolites include hydroxyabemaciclib (M20), hydroxy-N-desethylabemaciclib (M18), and an oxidative metabolite (M1). M2, M18, and M20 are equipotent to abemaciclib and their AUCs accounted for 25%, 13%, and 26% of the total circulating analytes in plasma, respectively.

Excretion

After a single 150 mg oral dose of radiolabeled abemaciclib, approximately 81% of the dose was recovered in feces and approximately 3% recovered in urine. The majority of the dose eliminated in feces was metabolites.

Specific Populations

Age, Gender, and Body Weight

Based on a population pharmacokinetic analysis in patients with cancer, age (range 24-91 years), gender (134 males and 856 females), and body weight (range 36-175 kg) had no effect on the exposure of abemaciclib.

Patients with Renal Impairment

In a population pharmacokinetic analysis of 990 individuals, in which 381 individuals had mild renal impairment (60 mL/min ≤ CLcr <90 mL/min) and 126 individuals had moderate renal impairment (30 mL/min ≤ CLcr <60 mL/min), mild and moderate renal impairment had no effect on the exposure of abemaciclib *[see Use in Specific Populations (9.6)]*. The effect of severe renal impairment (CLcr <30 mL/min) on pharmacokinetics of abemaciclib is unknown.

Patients with Hepatic Impairment

Following a single 200 mg oral dose of abemaciclib, the relative potency adjusted unbound $AUC_{0\text{-}INF}$ of abemaciclib plus its active metabolites (M2, M18, M20) in plasma increased 1.2-fold in subjects with mild hepatic impairment (Child-Pugh A, n=9), 1.1-fold in subjects with moderate hepatic impairment (Child-Pugh B, n=10), and 2.4-fold in subjects with severe hepatic impairment (Child-Pugh C, n=6) relative to subjects with normal hepatic function (n=10) *[see Use in Specific Populations (9.7)]*. In subjects with severe hepatic impairment, the mean plasma elimination half-life of abemaciclib increased to 55 hours compared to 24 hours in subjects with normal hepatic function.

Drug Interaction Studies

Effects of Other Drugs on Abemaciclib

Strong CYP3A Inhibitors: Ketoconazole (a strong CYP3A inhibitor) is predicted to increase the AUC of abemaciclib by up to 16-fold.

Coadministration of 500 mg twice daily doses of clarithromycin (a strong CYP3A inhibitor) with a single 50 mg dose of VERZENIO (0.3 times the approved recommended 150 mg dosage) increased the relative potency adjusted unbound $AUC_{0\text{-}INF}$ of abemaciclib plus its active metabolites (M2, M18, and M20) by 2.5-fold relative to abemaciclib alone in cancer patients.

Moderate CYP3A Inhibitors: Verapamil and diltiazem (moderate CYP3A inhibitors) are predicted to increase the relative potency adjusted unbound AUC of abemaciclib plus its active metabolites (M2, M18, and M20) by approximately 1.6-fold and 2.4-fold, respectively.

Strong CYP3A Inducers: Coadministration of 600 mg daily doses of rifampin (a strong CYP3A inducer) with a single 200 mg dose of VERZENIO decreased the relative potency adjusted unbound $AUC_{0\text{-}INF}$ of abemaciclib plus its active metabolites (M2, M18, and M20) by approximately 70% in healthy subjects.

Moderate CYP3A Inducers: Efavirenz, bosentan, and modafinil (moderate CYP3A inducers) are predicted to decrease the relative potency adjusted unbound AUC of abemaciclib plus its active metabolites (M2, M18, and M20) by 53%, 41%, and 29%, respectively.

Loperamide: Co-administration of a single 8-mg dose of loperamide with a single 400-mg dose of abemaciclib in healthy subjects increased the relative potency adjusted unbound $AUC_{0\text{-}INF}$ of abemaciclib plus its active metabolites (M2 and M20) by 12%, which is not considered clinically relevant.

Endocrine Therapies: In clinical studies in patients with breast cancer, there was no clinically relevant effect of fulvestrant, anastrozole, letrozole, exemestane or tamoxifen on abemaciclib pharmacokinetics.

Effects of Abemaciclib on Other Drugs

Loperamide: In a clinical drug interaction study in healthy subjects, coadministration of a single 8 mg dose of loperamide with a single 400 mg abemaciclib (2.7 times the approved recommended 150 mg dosage) increased loperamide $AUC_{0\text{-}INF}$ by 9% and C_{max} by 35% relative to loperamide alone. These increases in loperamide exposure are not considered clinically relevant.

Metformin: In a clinical drug interaction study in healthy subjects, coadministration of a single 1000 mg dose of metformin, a clinically relevant substrate of renal OCT2, MATE1, and MATE2-K transporters, with a single 400 mg dose of abemaciclib (2.7 times the approved recommended 150 mg dosage) increased metformin $AUC_{0\text{-}INF}$ by 37% and C_{max} by 22% relative to metformin alone. Abemaciclib reduced the renal clearance and renal secretion of metformin by 45% and 62%, respectively, relative to metformin alone, without any effect on glomerular filtration rate (GFR) as measured by iohexol clearance and serum cystatin C.

Endocrine Therapies: In clinical studies in patients with breast cancer, there was no clinically relevant effect of abemaciclib on the pharmacokinetics of fulvestrant, anastrozole, letrozole, exemestane or tamoxifen.

CYP Metabolic Pathways: In a clinical drug interaction study in patients with cancer, multiple doses of abemaciclib (200 mg twice daily for 7 days) did not result in clinically meaningful changes in the pharmacokinetics of CYP1A2, CYP2C9, CYP2D6 and CYP3A4 substrates. Abemaciclib is a substrate of CYP3A4, and time-dependent changes in pharmacokinetics of abemaciclib as a result of autoinhibition of its metabolism were not observed.

In Vitro Studies

Transporter Systems: Abemaciclib and its major active metabolites inhibit the renal transporters OCT2, MATE1, and MATE2-K at concentrations achievable at the approved recommended dosage. The observed serum creatinine increase in clinical studies with abemaciclib is likely due to inhibition of tubular secretion of creatinine via OCT2, MATE1, and MATE2-K [see Adverse Effects (7.1)]. Abemaciclib and its major metabolites at clinically relevant concentrations do not inhibit the hepatic uptake transporters OCT1, OATP1B1, and OATP1B3 or the renal uptake transporters OAT1 and OAT3.

Abemaciclib is a substrate of P-gp and BCRP. Abemaciclib and its major active metabolites, M2 and M20, are not substrates of hepatic uptake transporters OCT1, organic anion transporting polypeptide 1B1 (OATP1B1), or OATP1B3.

Abemaciclib inhibits P-gp and BCRP. The clinical consequences of this finding on sensitive P-gp and BCRP substrates are unknown.

P-gp and BCRP Inhibitors: In vitro, abemaciclib is a substrate of P-gp and BCRP. The effect of P-gp or BCRP inhibitors on the pharmacokinetics of abemaciclib has not been studied.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Abemaciclib was assessed for carcinogenicity in a 2-year rat study. Abemaciclib was not carcinogenic in male and female rats at oral doses up to 3 mg/kg/day (approximately 1 time the exposure at the maximum recommended human dose based on AUC).

Abemaciclib and its active human metabolites M2 and M20 were not mutagenic in a bacterial reverse mutation (Ames) assay or clastogenic in an in vitro chromosomal aberration assay in Chinese hamster ovary cells or human peripheral blood lymphocytes. Abemaciclib M2 and M20 were not clastogenic in an in vivo rat bone marrow micronucleus assay.

Abemaciclib may impair fertility in males of reproductive potential. In repeat-dose toxicity studies up to 3-months duration, abemaciclib-related findings in the testis, epididymis, prostate, and seminal vesicle at doses ≥10 mg/kg/day in rats and ≥0.3 mg/kg/day in dogs included decreased organ weights, intratubular cellular debris, hypospermia, tubular dilatation, atrophy, and degeneration/necrosis. These doses in rats and dogs resulted in approximately 2 and 0.02 times, respectively, the exposure (AUC) in humans at the maximum recommended human dose. In a rat male fertility study, abemaciclib had

no effects on mating and fertility at oral doses up to 10 mg/kg/day (approximately 2 times the exposure at the maximum recommended human dose based on AUC).

In a rat female fertility and early embryonic development study, abemaciclib did not affect mating and fertility at doses up to 20 mg/kg/day (approximately 3 times the exposure at the maximum recommended human dose based on AUC).

13.2 Animal Toxicology and/or Pharmacology

In repeat-dose toxicity studies up to 6-months duration, oral administration of abemaciclib resulted in retinal atrophy of the eyes in mice at a dose of 150 mg/kg/day (approximately 10 times the exposure at the maximum recommended human dose based on AUC) and in rats at a dose of 30 mg/kg/day (approximately 5 times the exposure at the maximum recommended human dose based on AUC). In a 2-year rat carcinogenicity study, oral administration of abemaciclib resulted in retinal atrophy in the eyes at doses ≥0.3 mg/kg/day (approximately 0.05 times the exposure at the maximum recommended human dose based on AUC).

14 CLINICAL STUDIES

14.1 Early Breast Cancer

VERZENIO in Combination with Endocrine Therapy (monarchE)

Patients with HR-positive, HER2-negative, node-positive early breast cancer at high risk of recurrence

The efficacy of VERZENIO in combination with endocrine therapy (tamoxifen or an aromatase inhibitor) was evaluated in monarchE (NCT03155997), a randomized, open-label, two cohort, multicenter study in 5637 adults with HR-positive, HER2-negative, node-positive, resected, early breast cancer with clinical and pathological features consistent with a high risk of disease recurrence of which 5120 (91%) were randomized in cohort 1. To be enrolled, patients had to have HR-positive HER2-negative early breast cancer with tumor involvement in at least 1 axillary lymph node (pALN) and to be enrolled in cohort 1 had to have either:

- ≥4 pALN or
- 1-3 pALN and at least one of:
  - tumor grade 3 or
  - tumor size ≥50 mm

Patients enrolled in cohort 2 could not have met the eligibility criteria for cohort 1. To be enrolled in cohort 2, patients had to have 1-3 pALN and Ki-67 score ≥20%. Breast tumor samples were tested at central sites using the Ki-67 IHC MIB-1 pharmDx (Dako Omnis) assay to establish if the Ki-67 score was ≥20%.

Patients were randomized 1:1 to receive VERZENIO 150 mg orally twice daily for 2 years in combination with endocrine therapy (tamoxifen or an aromatase inhibitor); or endocrine therapy alone. Randomization was stratified by prior treatment (neoadjuvant chemotherapy versus adjuvant chemotherapy versus no chemotherapy); menopausal status (premenopausal versus postmenopausal); and region (North America/Europe versus Asia versus other). Men were stratified as postmenopausal. After the end of the study treatment period, standard adjuvant endocrine therapy was continued for a duration of at least 5 years if deemed medically appropriate.

The major efficacy outcome for VERZENIO in combination with endocrine therapy (tamoxifen or an aromatase inhibitor) was invasive disease–free survival (IDFS). IDFS was defined as the time from randomization to the first occurrence of: ipsilateral invasive breast tumor recurrence, regional invasive breast cancer recurrence, distant recurrence, contralateral invasive breast cancer, second primary non-breast invasive cancer, or death attributable to any cause. Overall survival (OS) was an additional outcome measure.

A statistically significant difference in IDFS was observed in the intent-to-treat (ITT) population which was primarily attributed to the patients treated in cohort 1.

Of the 5120 patients randomized in cohort 1, the median age was 51 years (range, 22-89 years), 99% were women, 70% were White, 24% were Asian, 1.7% were Black or African American, 2.1% were American Indian or Alaska Native, and 0.1% were Native Hawaiian or Other Pacific Islander; 8% were Hispanic/Latino and 92% were not Hispanic/Latino and 0.2% were not reported/missing. Forty-three percent of patients were premenopausal. Most patients received prior chemotherapy (37% neoadjuvant, 59% adjuvant) and prior radiotherapy (96%). Sixty-five percent of the patients had 4 or more positive lymph nodes with 22% having ≥10 positive lymph nodes, 41% had Grade 3 tumor, and 24% had pathological tumor size ≥50 mm. The majority of patients (99%) had estrogen receptor positive disease and 87% had progesterone receptor positive

disease. Initial endocrine therapy received by patients included letrozole (39%), tamoxifen (31%), anastrozole (22%), or exemestane (8%).

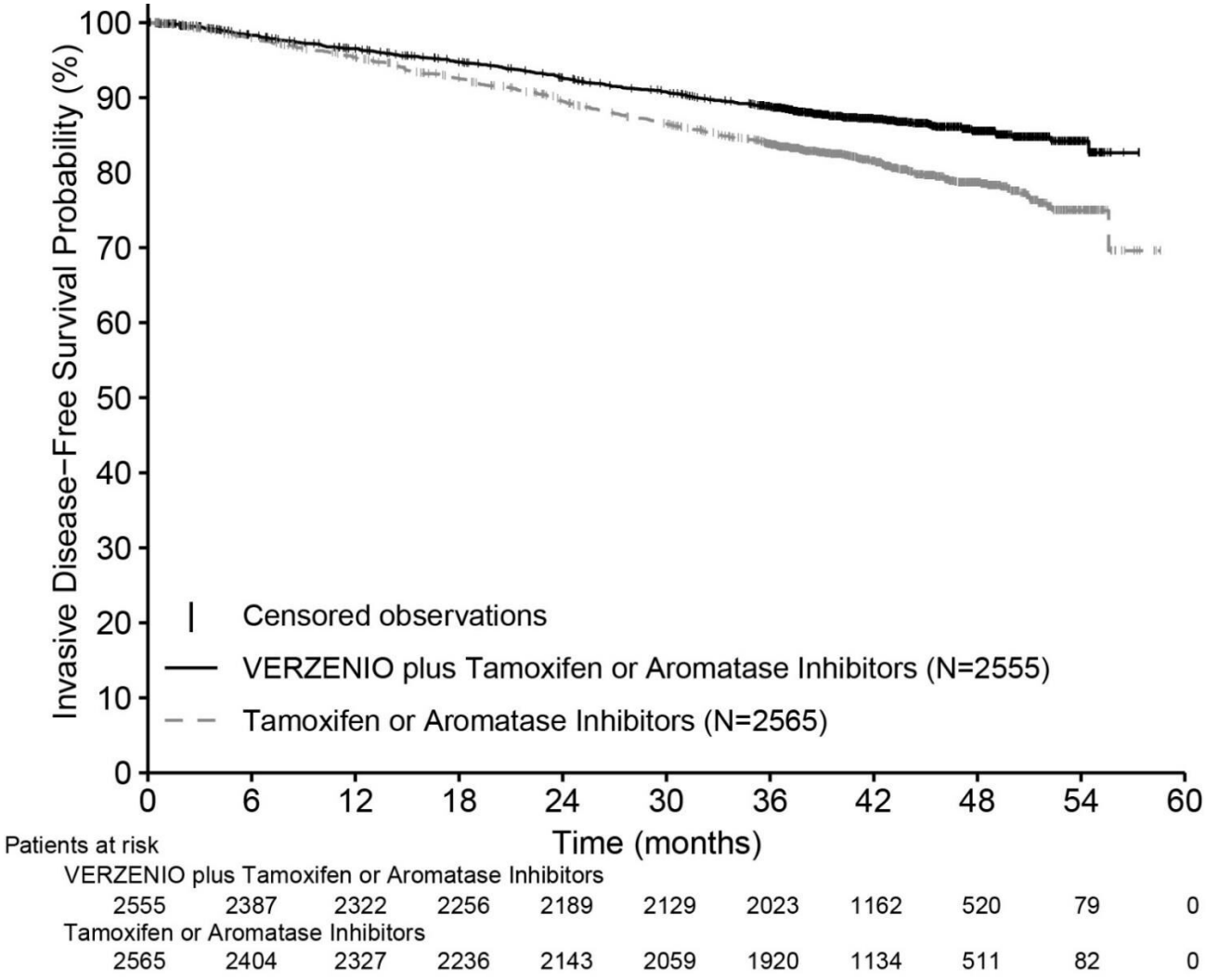
Efficacy results for cohort 1 are summarized in Table 16 and Figure 1.

Table 16: Efficacy Results in monarchE in Cohort 1

	VERZENIO Plus Tamoxifen or an Aromatase Inhibitor N=2555	**Tamoxifen or an Aromatase Inhibitor N=2565**
Invasive Disease–Free Survival (IDFS)		
Number of patients with an event, n (%)	317 (12)	474 (18)
Hazard ratio (95% CI)	0.65 (0.57, 0.75)	
IDFS at 48 months, % (95% CI)	85.5 (83.8, 87.0)	78.6 (76.7, 80.4)

Abbreviations: CI = confidence interval.

Figure 1: Kaplan-Meier Curves of Invasive Disease–Free Survival VERZENIO plus Tamoxifen or an Aromatase Inhibitor versus Tamoxifen or an Aromatase Inhibitor in Cohort 1 (monarchE)



A final OS analysis was conducted after 630 death events were observed in cohort 1. Exploratory OS results showed a HR of 0.84 (95% CI: 0.71, 0.98) for patients treated with VERZENIO plus Tamoxifen or an Aromatase Inhibitor compared with patients treated with Tamoxifen or an Aromatase Inhibitor in cohort 1.

14.2 Advanced or Metastatic Breast Cancer

VERZENIO in Combination with a Non-steroidal Aromatase Inhibitor (Anastrozole or Letrozole) (MONARCH 3)
Postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer with no prior systemic therapy in this disease setting

The efficacy of VERZENIO in combination with a non-steroidal aromatase inhibitor was evaluated in MONARCH 3 (NCT02246621), a randomized, double-blinded, placebo-controlled, multicenter study in 493 postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer in combination with a nonsteroidal aromatase inhibitor as initial endocrine-based therapy, including patients not previously treated with systemic therapy for breast cancer. Patients were randomized 2:1 to VERZENIO 150 mg orally twice daily in combination with a non-steroidal aromatase inhibitor or placebo in combination with an aromatase inhibitor.

Randomization was stratified by disease site (visceral, bone only, or other) and by prior (neo)adjuvant endocrine therapy (aromatase inhibitor versus other versus no prior endocrine therapy). Patients were treated until disease progression or unacceptable toxicity.

The major efficacy outcome for VERZENIO in combination with a non-steroidal aromatase inhibitor was progression free survival (PFS) by investigator assessment using Response Evaluation Criteria (RECIST) v1.1. Other efficacy measures included OS and objective response rate (ORR).

The median age was 63 years (range, 32-88 years), 45% age 65 or older; 58% White, 30% Asian, 1.6% Black or African American, 1.4% American Indian or Alaska Native, 0.2% Native Hawaiian or Other Pacific Islander, and 0.4% multiple races, and race was not reported for 7.9%; 8.9% were Hispanic/Latino and 72% were not Hispanic/Latino and 19% not reported/missing; and baseline ECOG performance status was 0 (60%), or 1 (40%). Most patients had visceral metastasis (53%) at baseline and 22% had bone-only disease. Of the patients enrolled, 51% had received prior systemic therapy and 39% of patients had received chemotherapy. Overall, 80% of patients received letrozole as investigator's choice aromatase inhibitor and 20% received anastrozole.

Efficacy results are summarized in Table 17 and Figure 2. PFS assessment based on a blinded independent radiologic review was consistent with the investigator assessment. Consistent PFS results were observed across patient stratification subgroups of disease site and prior (neo)adjuvant endocrine therapy.

Table 17: Efficacy Results in MONARCH 3 (Investigator Assessment, Intent-to-Treat Population)

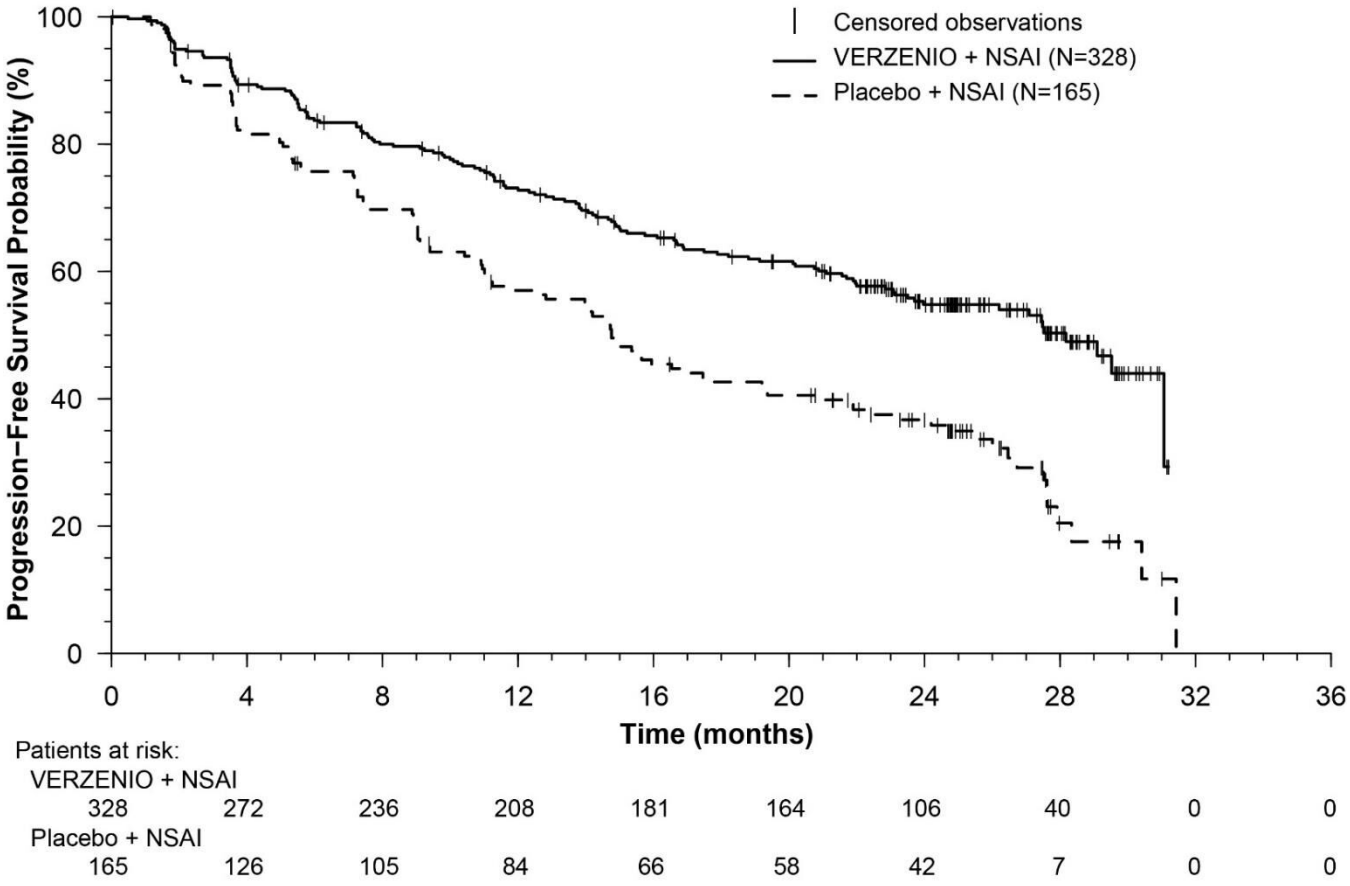
	VERZENIO plus Anastrozole or Letrozole	**Placebo plus Anastrozole or Letrozole**
Progression-Free Survival	**N=328**	**N=165**
Number of patients with an event, n, (%)	138 (42)	108 (65)
Median in months (95% CI)	28.2 (23.5, NR)	14.8 (11.2, 19.2)
Hazard ratio (95% CI)	0.54 (0.42, 0.70)	
p-value	<0.0001	
Overall Survival	**N=328**	**N=165**
Number of patients with an event, n (%)	198 (60)	116 (70)
Median in months (95% CI)	66.8 (59.2, 74.8)	53.7 (44.7, 59.3)
Hazard ratio (95% CI)	0.80 (0.64, 1.02)	
p-value	NS	
Objective Response for Patients with Measurable Disease [a]	**N=267**	**N=132**
Objective response rate, n (%)[a,b]	148 (55)	53 (40)

95% CI	49, 61	32, 49

Abbreviations: CI = confidence interval; OS = overall survival; NR = not reached; NS = not statistically significant.
[a] Complete response + partial response.

[b] Based upon confirmed responses.

Figure 2: Kaplan-Meier Curves of Progression-Free Survival: VERZENIO plus Anastrozole or Letrozole versus Placebo plus Anastrozole or Letrozole in Intent-to-Treat Population (MONARCH 3)



VERZENIO in Combination with Fulvestrant (MONARCH 2)

Patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression on or after prior adjuvant or metastatic endocrine therapy

The efficacy of VERZENIO in combination with fulvestrant was evaluated in MONARCH 2 (NCT02107703), a randomized, placebo-controlled, multicenter study in 669 women with HR-positive, HER2-negative metastatic breast cancer with disease progression following endocrine therapy who had not received chemotherapy in the metastatic setting. Patients were randomized 2:1 to VERZENIO 150 mg orally twice daily or placebo orally twice daily in combination with fulvestrant 500 mg intramuscularly on days 1 and 15 of cycle 1 and then on day 1 of cycle 2 and beyond (28-day cycles). Randomization was stratified by disease site (visceral, bone only, or other) and by sensitivity to prior endocrine therapy (primary or secondary resistance). Primary endocrine therapy resistance was defined as relapse while on the first 2 years of adjuvant endocrine therapy or progressive disease within the first 6 months of first line endocrine therapy for metastatic breast cancer. Pre/perimenopausal women were enrolled in the study and received the gonadotropin-releasing hormone agonist goserelin for at least 4 weeks prior to and for the duration of MONARCH 2. Patients remained on continuous treatment until development of progressive disease or unmanageable toxicity.

The major efficacy outcome for VERZENIO in combination with fulvestrant was PFS by investigator assessment using RECIST v1.1. Other efficacy measures included OS and ORR.

The median age was 60 years (range, 32-91 years), 37% age 65 or older, 56% White, 32% Asian, 3.9% American Indian or Alaska Native, 2.1% Black or African American, and race was not reported for 6.3%; 12% were Hispanic/Latino and 70% were not Hispanic/Latino, 18% not reported/missing; ECOG performance status was 0 (60%), 1 (39%) or 2 (0.1%). Most patients had visceral disease (56%), 27% had bone-only disease, and 20% had de novo metastatic disease. Twenty-five percent (25%) of patients had primary endocrine therapy resistance. Seventeen percent (17%) of patients were pre- or perimenopausal.

Efficacy results are summarized in Table 18, Figure 3, and Figure 4. PFS assessment based on a blinded independent radiologic review was consistent with the investigator assessment. Consistent results were observed across patient stratification subgroups of disease site and endocrine therapy resistance for PFS and OS.

Table 18: Efficacy Results in MONARCH 2 (Intent-to-Treat Population)

	VERZENIO plus Fulvestrant	**Placebo plus Fulvestrant**
Progression-Free Survival (Investigator Assessment)	**N=446**	**N=223**
Number of patients with an event, n (%)	222 (50)	157 (70)
Median in months (95% CI)	16.4 (14.4, 19.3)	9.3 (7.4, 12.7)
Hazard ratio (95% CI) [a]	0.55 (0.45, 0.68)	
p-value[a]	p<.0001	
Overall Survival[b]		
Number of deaths n, (%)	211 (47)	127 (57)
Median OS in months (95% CI)	46.7 (39.2, 52.2)	37.3 (34.4, 43.2)
Hazard ratio (95% CI)[a]	0.76 (0.61, 0.95)	
p-value[a]	p=.0137	
Objective Response for Patients with Measurable Disease	**N=318**	**N=164**
Objective response rate, n (%)[c]	153 (48)	35 (21)
95% CI	43, 54	15, 28

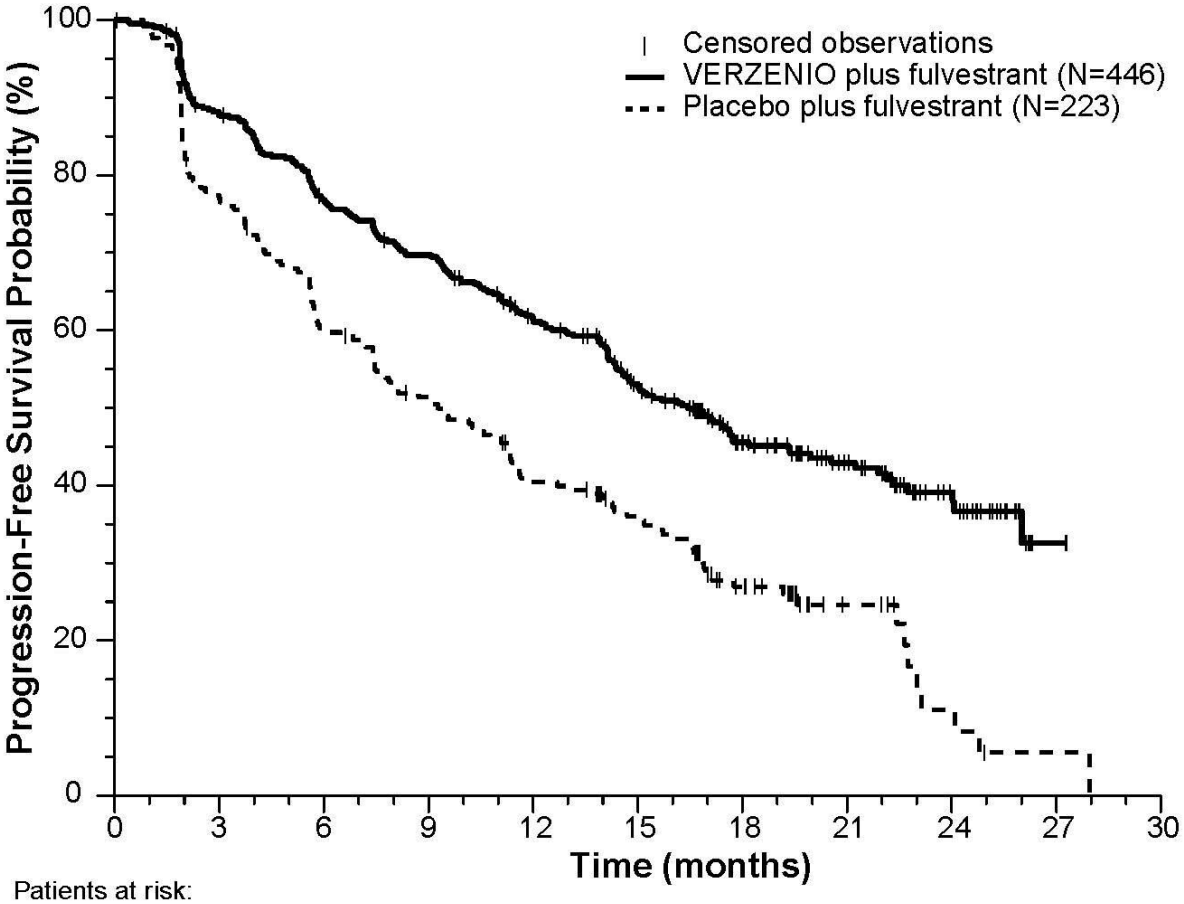
Abbreviation: CI = confidence interval, OS = overall survival.

[a] Stratified by disease site (visceral metastases vs. bone-only metastases vs. other) and endocrine therapy resistance (primary resistance vs. secondary resistance)

[b] Data from a pre-specified interim analysis (77% of the number of events needed for the planned final analysis) with the p-value compared with the allocated alpha of 0.021.

[c] Complete response + partial response.

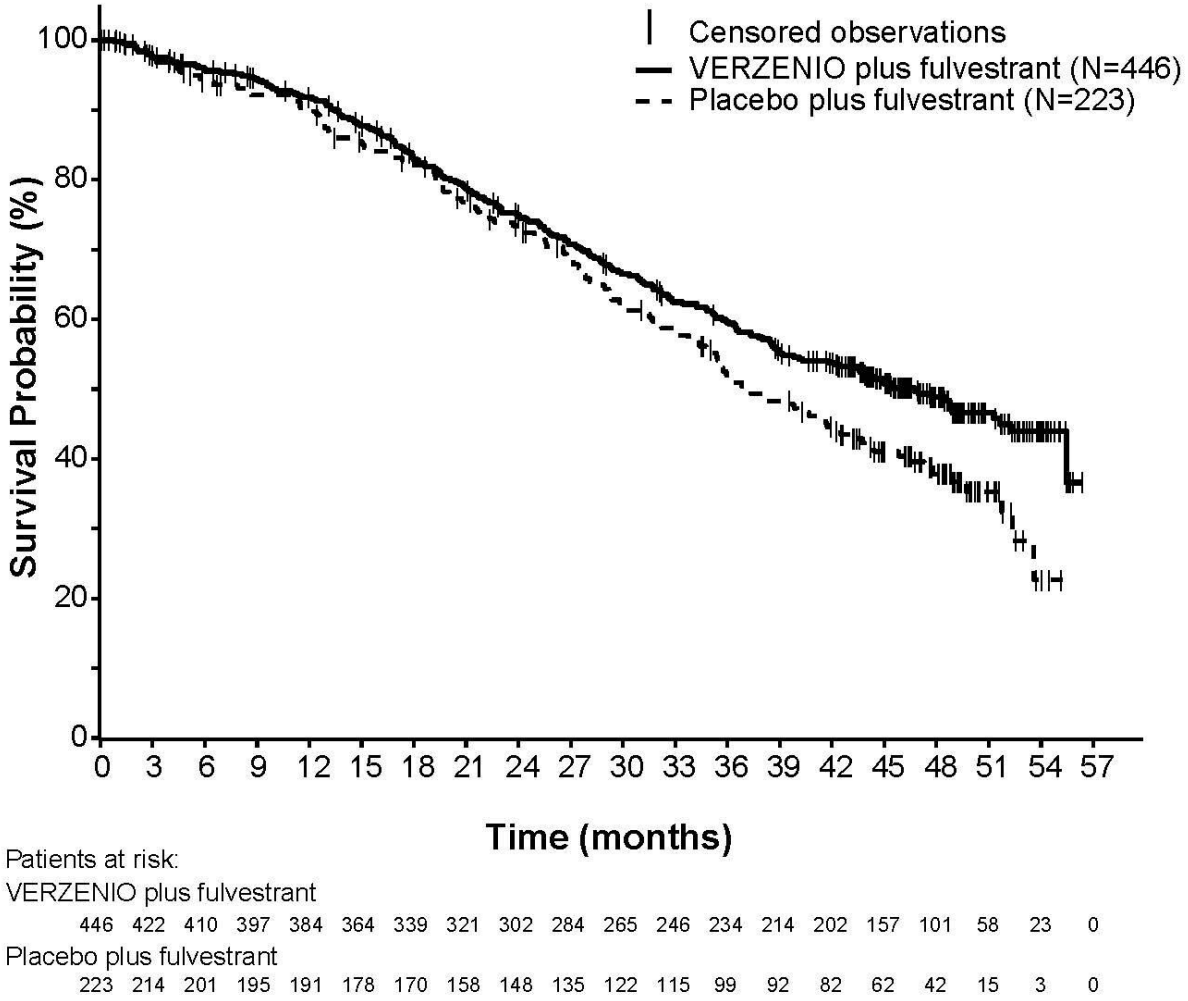
Figure 3: Kaplan-Meier Curves of Progression-Free Survival: VERZENIO plus Fulvestrant versus Placebo plus Fulvestrant (MONARCH 2)



Patients at risk:

VERZENIO plus fulvestrant	446	367	314	281	234	171	101	65	32	2	0
Placebo plus fulvestrant	223	165	123	103	80	61	32	13	4	1	0

Figure 4: Kaplan-Meier Curves of Overall Survival: VERZENIO plus Fulvestrant versus Placebo plus Fulvestrant (MONARCH 2)



VERZENIO Administered as a Monotherapy in Metastatic Breast Cancer (MONARCH 1)

Adult patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy in the metastatic setting and prior 1-2 chemotherapy in the metastatic setting including taxane in adjuvant or metastatic setting.

The efficacy of VERZENIO monotherapy was evaluated in MONARCH 1 (NCT02102490), a single-arm, open-label, multicenter study in 132 women with measurable HR-positive, HER2-negative metastatic breast cancer whose disease progressed during or after endocrine therapy, had received a taxane in any setting, and who received 1 or 2 prior chemotherapy regimens in the metastatic setting. Patients received VERZENIO 200 mg orally twice daily on a continuous schedule until development of progressive disease or unmanageable toxicity.

The major efficacy outcome was ORR. Duration of response (DoR) was another efficacy measure.

The median age was 58 years (range, 36-89 years), 32% age 65 or older; 85% White, 4.5% Black or African American, 1.5% Asian, and race was not reported for 9.1%; 6.1% were Hispanic/Latino and 85% were not Hispanic/Latino, and 9.1% not reported/missing; ECOG performance status was 0 (55%) or 1 (45%). The median duration of metastatic disease was 27.6 months. Ninety percent (90%) of patients had visceral metastases, and 51% of patients had 3 or more sites of metastatic disease. Fifty-one percent (51%) of patients had one line of chemotherapy in the metastatic setting. Sixty-nine

percent (69%) of patients had received a taxane-based regimen in the metastatic setting and 55% had received capecitabine in the metastatic setting. Efficacy results are summarized in Table 19.

Table 19: Efficacy Results in MONARCH 1 (Intent-to-Treat Population)

	VERZENIO 200 mg N=132	
	Investigator Assessed	**Independent Review**
Objective Response Rate[a,b], n (%)	26 (20)	23 (17)
95% CI	13, 28	11, 25
Median Duration of Response in months	8.6	7.2
95% CI	5.8, 10.2	5.6, NR

Abbreviations: CI = confidence interval, NR = not reached.

[a] All responses were partial responses.

[b] Based upon confirmed responses.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

VERZENIO 50 mg tablets are oval beige tablet with “Lilly” debossed on one side and “50” on the other side.

VERZENIO 100 mg tablet are oval white to practically white tablet with “Lilly” debossed on one side and “100” on the other side.

VERZENIO 150 mg tablets are oval yellow tablet with “Lilly” debossed on one side and “150” on the other side.

VERZENIO 200 mg tablets are oval beige tablet with “Lilly” debossed on one side and “200” on the other side.

VERZENIO tablets are supplied in 7-day dose pack configurations as follows:

- 200 mg dose pack (14 tablets) – each blister pack contains 14 tablets (200 mg per tablet) (200 mg twice daily)
- 150 mg dose pack (14 tablets) – each blister pack contains 14 tablets (150 mg per tablet) (150 mg twice daily)
- 100 mg dose pack (14 tablets) – each blister pack contains 14 tablets (100 mg per tablet) (100 mg twice daily)
- 50 mg dose pack (14 tablets) – each blister pack contains 14 tablets (50 mg per tablet) (50 mg twice daily)

16.2 Storage and Handling

Store below 30°C.

The expiry date of the product is indicated on the packaging materials.

17. Manufacturer: Eli Lilly and Company, Lilly Corporate Center, Indianapolis, Indiana (IN) 46285, USA

18. License Holder: Eli Lilly Israel Ltd., 4 HaSheizaf St., P.O.Box 4246, Ra’anana 4366411

19. License Number:

VERZENIO 50 mg: 161-43-35390-00

VERZENIO 100 mg: 161-44-35391-00

VERZENIO 150 mg: 161-45-35392-00

VERZENIO 200 mg: 161-46-35393-00

Revised in October 2026.