PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrVERZENIO™

Abemaciclib tablets

50 mg, 100 mg, 150 mg, 200 mg

Protein Kinase Inhibitor

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

VERZENIO™ (abemaciclib) is indicated for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer

- in combination with an aromatase inhibitor in postmenopausal women as initial endocrine-based therapy.
- in combination with fulvestrant in women with disease progression following endocrine therapy. Pre- or perimenopausal women must also be treated with a gonadotropin-releasing hormone (GnRH) agonist.
- as a single agent in women with disease progression following endocrine therapy and at least 2 prior chemotherapy regimens. At least one chemotherapy regimen should have been administered in the metastatic setting, and at least one should have contained a taxane.

Clinical effectiveness of VERZENIO in combination with an aromatase inhibitor is based on the benefit observed in patients treated with VERZENIO in combination with letrozole or anastrozole for the treatment of postmenopausal women with advanced breast cancer.

1.1 Pediatrics

Pediatrics (<18 years of age): The safety and efficacy of VERZENIO in children and adolescents less than 18 years have not been established.

1.2 Geriatrics

Geriatrics (≥65 years of age): Of the 900 patients who received VERZENIO in MONARCH 1, MONARCH 2, and MONARCH 3, 38% were 65 years of age or older. No overall differences in safety or effectiveness of VERZENIO were observed between these patients and younger patients; however, subgroup analyses from clinical studies demonstrated that patients ≥65 years of age reported more hematologic adverse events, hypokalemia (including Grade 3), hypocalcemia, Grade ≥3 infections, decreased appetite, and increased blood creatinine compared to younger patients.

2 CONTRAINDICATIONS

VERZENIO is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see Dosage Forms, Strengths, Composition and Packaging.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

VERZENIO (abemaciclib) should be prescribed and managed by a qualified health professional who is experienced in the use of anti-cancer agents.

The following are significant adverse drug reactions identified in clinical trials conducted with VERZENIO:

- Venous thromboembolism, including deaths (see **Hematologic** section)

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Pre/perimenopausal women treated with the combination of VERZENIO plus fulvestrant therapy should be treated with a gonadotropin releasing hormone (GnRH) agonist according to local clinical practice.

Patients with severe hepatic impairment require dose adjustment (see Recommended Dose and Dosage Adjustment, and ACTION AND CLINICAL PHARMACOLOGY).

Health Canada has not authorized an indication for pediatric use (see INDICATIONS).

4.2 Recommended Dose and Dosage Adjustment

VERZENIO in Combination with Endocrine Therapy:
When used in combination with endocrine (aromatase inhibitor or fulvestrant) therapy, the recommended dose of VERZENIO is 150 mg taken orally, twice daily.

VERZENIO is used in combination with an aromatase inhibitor or fulvestrant. For full dosing instructions of the selected aromatase inhibitor or fulvestrant, refer to the corresponding Product Monograph.

VERZENIO as a Single Agent:
When used as a single agent, the recommended dose of VERZENIO is 200 mg taken orally twice daily.

For All Indications:
Continue treatment until disease progression or unacceptable toxicity.

Management of some adverse reactions may require dose interruptions, dose reductions and/or permanent discontinuation of VERZENIO. The recommended VERZENIO dose modifications for adverse reactions are provided in Tables 1-5.

Discontinue VERZENIO for patients unable to tolerate 50 mg twice daily.

Table 1: VERZENIO Dose Modifications for Adverse Reactions

Dose Level	VERZENIO Dose Combination with Endocrine Therapy	VERZENIO Dose for Single Agent
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 for Hematologic Toxicities[a]

Monitor complete blood counts prior to the start of VERZENIO therapy, every two 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 dose already reduced for the toxicity that led to the use of the growth factor. Use growth factor as per current treatment guidelines.

Table 3: VERZENIO Dose Modification and Management for Diarrhea

At the first sign of loose stools, start treatment with antidiarrheal agents, such as loperamide, 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	

Table 4: VERZENIO Dose Modification and Management for 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 for Other Nonhematologic 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 and hepatotoxicity

CYP3A inhibitors

Avoid concomitant use of strong CYP3A inhibitors (for example, voriconazole) and use caution with co-administered moderate (for example, ciprofloxacin) or weak (for example, ranitidine) CYP3A inhibitors. If co-administration with a CYP3A inhibitor is unavoidable, adjust the abemaciclib dose as described in Table 16 (see DRUG INTERACTIONS).

If a CYP3A inhibitor is discontinued, increase the abemaciclib dose (after 3-5 half-lives of the inhibitor) to the dose that was used before starting the inhibitor (see DRUG INTERACTIONS, and ACTION AND CLINICAL PHARMACOLOGY).

Avoid grapefruit, grapefruit juice, or grapefruit products.

Severe hepatic impairment (Child-Pugh Class C)

Decrease the dosing frequency to once daily (see WARNINGS AND PRECAUTIONS, and ACTION AND CLINICAL PHARMACOLOGY).

CYP3A inducers

Avoid concomitant use of strong CYP3A inducers (for example, rifampin). Consider alternative agents with less CYP3A induction (see ACTION AND CLINICAL PHARMACOLOGY).

4.3 Administration

VERZENIO tablets should be swallowed whole (do not to chew, crush, or split tablets before swallowing). No tablet should be ingested if it is not intact.

VERZENIO may be taken with or without food (see ACTION AND CLINICAL PHARMACOLOGY). Patients should be instructed to take their doses of VERZENIO at approximately the same times every day.

4.4 Missed Dose

If the patient vomits or misses a dose of VERZENIO, the patient should take the prescribed dose at the next scheduled time. The patient should not take 2 doses at the same time to make up for the missed dose.

5 OVERDOSAGE

There is no known antidote for VERZENIO. The treatment of overdose of VERZENIO should consist of general supportive measures.

For management of a suspected drug overdose, contact your regional poison control center.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 6: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength	Non-medicinal Ingredients (Tablet Core)	Non-medicinal Ingredients (Tablet Film Coating)
Oral	Tablet / 50 mg	croscarmellose sodium, lactose monohydrate, microcrystalline cellulose 101, microcrystalline cellulose 102, silicon dioxide, sodium stearyl fumarate	Beige: iron oxide red, iron oxide yellow, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide
Oral	Tablet / 100 mg		White: polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide
Oral	Tablet / 150 mg		Yellow: iron oxide yellow, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide
Oral	Tablet / 200 mg		Beige: iron oxide red, iron oxide yellow, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide

VERZENIO is supplied in packages of 28 tablets (two blister packs of 14 tablets) in dose strengths of 50 mg, 100 mg, 150 mg, or 200 mg.

VERZENIO 50 mg tablets are a modified oval beige tablet with “Lilly” debossed on one side and “50” on the other side.
VERZENIO 100 mg tablets are a modified oval white to practically white tablet with “Lilly” debossed on one side and “100” on the other side.
VERZENIO 150 mg tablets are a modified oval yellow tablet with “Lilly” debossed on one side and “150” on the other side.
VERZENIO 200 mg tablets are a modified oval beige tablet with “Lilly” debossed on one side and “200” on the other side.

7 WARNINGS AND PRECAUTIONS

Please see the Serious Warnings and Precautions Box at the beginning of Part I: Health Professional Information.

General

Patients enrolled in VERZENIO clinical trials did not have prior therapy with any cyclin dependent kinase (CDK) 4/6 inhibitors. Therefore, there are no data regarding VERZENIO safety or efficacy in patients with prior exposure to other CDK 4/6 inhibitors.

Driving and Operating Machinery

No studies on the effects of VERZENIO (abemaciclib) on the ability to drive or operate machinery have been conducted. However, since fatigue and dizziness have been reported with

the use of VERZENIO, patients should exercise caution when driving or operating machinery while taking VERZENIO.

Gastrointestinal
Diarrhea
Diarrhea was the most frequently reported adverse reaction in patients treated with VERZENIO plus letrozole or anastrozole (All Grade: 82%, Grade 3: 10%), VERZENIO plus fulvestrant (All Grade: 86%, Grade 3: 13%), or VERZENIO as a single agent (All Grade: 90%, Grade 3: 20%). There were no reports of Grade 4 diarrhea.

Diarrhea incidence was greatest during the first month of VERZENIO dosing. The time to onset and resolution for diarrhea were similar across MONARCH 3, MONARCH 2, and MONARCH 1 (see ADVERSE REACTIONS). In MONARCH 3, 19% of patients with diarrhea required a dose omission and 17% required a dose reduction. In MONARCH 2, 22% of patients with diarrhea required a dose omission and 22% required a dose reduction. In MONARCH 1, 26% of patients with diarrhea required a dose omission and 23% required a dose reduction.

At the first sign of loose stools, patients should start antidiarrheal therapy such as loperamide, increase oral fluids, and notify their healthcare professional 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 (see DOSAGE AND ADMINISTRATION).

Hematologic
Neutropenia
Grade ≥3 neutropenia was reported in patients receiving abemaciclib in breast cancer studies.

In patients receiving VERZENIO plus letrozole or anastrozole (MONARCH 3), 23% experienced Grade ≥3 neutropenia (based on laboratory findings); median time to first episode was 37 days and median duration was 12 days. In patients receiving VERZENIO plus fulvestrant (MONARCH 2), 32% experienced Grade ≥3 neutropenia; median time to first episode was 29 days and median duration was 15 days. In patients receiving VERZENIO alone (MONARCH 1), 27% experienced Grade ≥3 neutropenia; median time to first episode was 29 days and median duration was 15 days (see ADVERSE REACTIONS).

Febrile neutropenia was reported in ≤1% of patients exposed to VERZENIO in the MONARCH studies. Two deaths due to neutropenic sepsis were observed in MONARCH 2. Inform patients to promptly report any episodes of fever to their healthcare professional (see PATIENT MEDICATION INFORMATION).

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 modification is recommended for patients who develop Grade 3 or 4 neutropenia (see DOSAGE AND ADMINISTRATION, and WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

Venous Thromboembolism
In MONARCH 3, venous thromboembolic events were reported in 6% of patients treated with VERZENIO plus letrozole or anastrozole compared to 0.6% of patients treated with placebo plus letrozole or anastrozole. In MONARCH 2, venous thromboembolic events were reported in 5% of patients treated with VERZENIO plus fulvestrant compared to 0.9% of patients treated with placebo plus fulvestrant. Venous thromboembolic events included deep vein thrombosis (DVT),

pulmonary embolism, pelvic venous thrombosis, cerebral venous thrombosis, subclavian and axillary vein thrombosis, and inferior vena cava thrombosis. Across the clinical development program, deaths due to venous thromboembolism have been reported.

Monitor patents for signs and symptoms of venous thrombosis and pulmonary embolism and treat as medically appropriate (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

Hepatic/Biliary/Pancreatic
Hepatotoxicity
Grade ≥3 increased ALT and AST was reported in patients receiving abemaciclib in breast cancer studies.

In patients receiving VERZENIO plus letrozole or anastrozole (MONARCH 3), adverse reactions of Grade ≥3 increases in ALT were reported more frequently in the VERZENIO treatment arm compared to the placebo arm (6% versus 2%, respectively). The median time to onset was 64 days and median time to resolution to Grade <3 was 14 days. In patients receiving VERZENIO plus fulvestrant (MONARCH 2), adverse reactions of Grade ≥3 increases in ALT were reported more frequently in the VERZENIO treatment arm than the placebo arm (4% versus 2%, respectively). The median time to onset was 57 days and median time to resolution to Grade <3 was 14 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 Grade 3 or 4, hepatic transaminase elevation (see DOSAGE AND ADMINISTRATION, and WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

Immune
Infections
Infections were reported in patients receiving abemaciclib plus endocrine therapy at a higher rate than in patients treated with placebo plus endocrine therapy and were also reported in patients treated with single-agent abemaciclib. Fatal events of infection occurred in approximately 1% of patients across the MONARCH 1, MONARCH 2 and MONARCH 3 studies. Patients should be monitored for signs and symptoms of infection and treated as medically appropriate.

Monitoring and Laboratory Tests
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 modification is recommended for patients who develop Grade 3 or 4 neutropenia (see DOSAGE AND ADMINISTRATION, and WARNINGS AND PRECAUTIONS).

Monitor 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 (see DOSAGE AND ADMINISTRATION, and WARNINGS AND PRECAUTIONS).

Monitor patients for signs and symptoms of venous thrombosis and pulmonary embolism and treat as medically appropriate.

Monitor patients for signs and symptoms of infection and treat as medically appropriate.

Sexual Health
Reproduction
Women with reproductive potential should be advised to use highly effective contraception during treatment with VERZENIO and for at least 3 weeks after the last dose (see NON-CLINICAL TOXICOLOGY).

Pregnancy testing is recommended for women of reproductive potential prior to initiating treatment with VERZENIO.

Fertility
Studies to assess the effects of abemaciclib on fertility have not been performed. Cytotoxic effects to the male reproductive tract in rats and dogs indicate that abemaciclib may impair fertility in males (see NON-CLINICAL TOXICOLOGY).

7.1 Special Populations

7.1.1 Pregnant Women

There are no available human data on VERZENIO use in pregnant women to inform any drug–associated risks. In animal studies, abemaciclib was teratogenic and caused decreased fetal weight at maternal exposures similar to the exposure in humans at the recommended clinical dose (see NON-CLINICAL TOXICOLOGY). Based on findings in animals and its mechanism of action, VERZENIO can cause fetal harm when administered to a pregnant woman.

Pregnant women or women who become pregnant while taking the drug should be apprised of the potential hazard to the fetus (see NON-CLINICAL TOXICOLOGY).

7.1.2 Breast-feeding

It is unknown if abemaciclib or its metabolites are excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in breastfed infants from VERZENIO, advise lactating women not to breastfeed during VERZENIO treatment and for at least 3 weeks after the last dose.

7.1.3 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorised an indication for pediatric use.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety of VERZENIO has been assessed in patients from two randomized Phase 3 studies and one single-arm Phase 2 study of patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer.

The most common adverse reactions reported in ≥20% of patients in any study receiving abemaciclib in combination with endocrine treatment or as a single agent were diarrhea,

neutropenia, fatigue, infections, nausea, vomiting, abdominal pain, decreased appetite, anemia, alopecia, leukopenia, headache, and thrombocytopenia.

Special Populations

Asian Population

Population pharmacokinetic analyses of combined data from MONARCH 2 and MONARCH 3 demonstrated that Japanese patients do not have significantly different abemaciclib exposure compared to patients of other races; however, higher frequencies of adverse events (any grade and Grade ≥3) of ALT increased, AST increased, and neutropenia were reported in East Asian patients compared to Caucasian patients in subgroup analyses of combined data for MONARCH 2 and MONARCH 3. No dose adjustment based on race is required for abemaciclib.

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Metastatic Breast Cancer – Combination with an Aromatase Inhibitor

MONARCH 3 – VERZENIO in combination with a non-steroidal aromatase inhibitor (NSAI: anastrozole or letrozole) as initial endocrine-based therapy in postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer with no prior systemic therapy in this disease setting

The safety of VERZENIO (150 mg twice daily) plus anastrozole (1 mg/day) or letrozole (2.5 mg/day) was evaluated in MONARCH 3, a Phase 3 randomized (2:1), double-blinded, placebo-controlled trial (see CLINICAL TRIALS). The data described below reflect exposure to VERZENIO in 327 out of 488 patients with HR-positive, HER2-negative metastatic breast cancer who received at least 1 dose of VERZENIO plus anastrozole or letrozole. Patients were randomized 2:1 to receive the combination of VERZENIO plus anastrozole or letrozole versus placebo plus anastrozole or letrozole. The median duration of treatment was 15.3 months for the VERZENIO arm and 13.9 months for the placebo arm.

Dose reductions due to an adverse reaction occurred in 47% of patients receiving VERZENIO plus a non-steroidal aromatase inhibitor (NSAI), most commonly due to diarrhea (14%) and neutropenia (13%), compared to 2% and 0.6%, respectively, for patients treated with placebo plus an NSAI.

Permanent study treatment discontinuation due to an adverse event was reported in 17% of patients receiving VERZENIO plus an aromatase inhibitor and in 3% of the patients receiving placebo plus an aromatase inhibitor. Adverse reactions leading to permanent discontinuation for patients receiving VERZENIO plus an aromatase inhibitor included alanine aminotransferase (ALT) increased (1.8%), lung infection (1.8%), diarrhea (1.2%), and venous thromboembolic events (VTEs) (1.2%).

Deaths on therapy or within 30 days of treatment discontinuation were reported for 15 patients (4.6%) treated with VERZENIO plus NSAI (including 11 [3.4%] due to adverse events and 4 [1.2%] due to study disease) and 3 patients (2%) treated with placebo plus NSAI (including 2 [1.2%] due to adverse events and 1 [0.6%] due to study disease). Causes of death for patients

receiving VERZENIO plus an aromatase inhibitor included: 4 (1.2%) due to underlying disease, 4 (1.2%) due to lung infection, 2 (0.6%) due to VTE, 2 (0.6%) due to respiratory failure, 1 (0.3%) due to cerebral ischemia, 1 (0.3%) due to cerebrovascular accident, and 1 (0.3%) due to pneumonitis.

Treatment-emergent adverse events reported in ≥5% and at a higher frequency in patients who received VERZENIO plus anastrozole or letrozole than in patients who received placebo plus anastrozole or letrozole in MONARCH 3 are listed in Table 7.

Table 7: Treatment-Emergent Adverse Events (≥5% and at a Higher Frequency in Patients Receiving VERZENIO Plus Anastrozole or Letrozole Versus Patients Receiving Placebo Plus Anastrozole or Letrozole) in MONARCH 3

	VERZENIO + anastrozole or letrozole N=327			Placebo + anastrozole or letrozole N=161		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Blood and Lymphatic System Disorders						
Neutropenia	44	22	2	2	<1	<1
Anemia	32	7	0	8	1	0
Leukopenia	22	8	<1	3	0	<1
Thrombocytopenia	13	2	<1	3	<1	0
Lymphopenia	7	3	0	4	0	0
Eye Disorders						
Lacrimation increased	7	0	0	<1	0	0
Dry eye	5	0	0	<1	0	0
Gastrointestinal Disorders						
Diarrhea	82	10	0	32	1	0
Nausea	41	1	0	21	1	0
Abdominal pain	31	2	0	13	1	0
Vomiting	30	2	0	13	3	0
Constipation	17	<1	0	14	0	0
Stomatitis	13	0	0	11	0	0
Dyspepsia	8	0	0	3	0	0
Dry mouth	5	0	0	3	0	0
General Disorders and Administration Site Conditions						
Fatigue	41	2	0	34	0	0
Influenza like illness	12	0	0	9	0	0
Peripheral edema	10	0	0	6	0	0
Pain	8	<1	0	7	0	0
Infections and Infestations						
Upper respiratory tract infection	10	0	0	6	0	0
Lung infection	7	2	<1	3	0	0
Injury, Poisoning and Procedural Complications						

Fall	6	<1	0	3	<1	0
Investigations						
Blood creatinine increased	21	2	<1	4	0	0
Alanine aminotransferase increased	17	6	<1	8	2	0
Aspartate aminotransferase increased	17	4	0	8	1	0
Weight decreased	11	<1	0	3	<1	0
Blood alkaline phosphatase increased	6	<1	0	4	<1	0
Metabolism and Nutrition Disorders						
Decreased appetite	26	2	0	11	<1	0
Hypokalemia	9	3	<1	1	0	0
Musculoskeletal and Connective Tissue Disorders						
Bone pain	10	0	0	9	0	0
Muscular weakness	5	0	0	4	<1	0
Nervous System Disorders						
Headache	20	<1	0	16	0	0
Dizziness	14	<1	0	11	0	0
Neuropathy	11	<1	0	10	0	0
Dysgeusia	10	0	0	3	0	0
Respiratory, Thoracic and Mediastinal Disorders						
Cough	15	0	0	12	0	0
Dyspnea	12	<1	<1	7	<1	0
Skin and Subcutaneous Tissue Disorders						
Alopecia	28	0	0	11	0	0
Rash	15	<1	0	5	0	0
Pruritus	14	0	0	9	0	0
Dry skin	10	0	0	3	0	0
Nail ridging	5	0	0	1	0	0
Vascular Disorders						
Hypertension	7	3	0	6	<1	0
Venous thromboembolic events[a]	6	2	<1	<1	0	<1

[a] Venous thromboembolic events included deep vein thrombosis (DVT), pulmonary embolism, and pelvic venous thrombosis.

The most frequently reported (≥5%) Grade 3 or 4 adverse reactions were neutropenia, diarrhea, leukopenia, increased ALT, and anemia.

Diarrhea incidence was greatest during the first month of VERZENIO dosing and was lower during subsequent months. The median time to onset of the first diarrhea event was 8 days, and the median durations of diarrhea for Grade 2 and Grade 3 were 12 days and 8 days, respectively. Most diarrhea events recovered or resolved (89%) with supportive treatment

and/or dose reductions (see DOSAGE AND ADMINISTRATION, and PATIENT MEDICATION INFORMATION). The median time to the first dose reduction due to diarrhea was 41 days. Nineteen percent (19%) of patients with diarrhea required a dose omission.

Table 8: Laboratory Findings – Hematologic Abnormalities in MONARCH 3

	VERZENIO + AI N=327			Placebo + AI N=161		
Laboratory Abnormality	**All Grades %**	**Grade 3 %**	**Grade 4 %**	**All Grades %**	**Grade 3 %**	**Grade 4 %**
White blood cell decreased	83	15	0	31	<1	0
Anemia	84	2	0	33	0	0
Neutrophil count decreased	81	20	3	22	3	0
Lymphocyte count decreased	58	9	<1	27	2	0
Platelet count decreased	40	1	<1	14	<1	0

Table 9: Laboratory Findings – Clinical Chemistry Abnormalities in MONARCH 3

	VERZENIO + AI N=327			Placebo + AI N=161		
Laboratory Abnormality	**All Grades %**	**Grade 3 %**	**Grade 4 %**	**All Grades %**	**Grade 3 %**	**Grade 4 %**
Creatinine increased	98	3	0	85	0	0
Alanine aminotransferase increased	53	7	<1	28	2	0
Aspartate aminotransferase increased	44	5	0	26	<1	0

Metastatic Breast Cancer – Combination with Fulvestrant

MONARCH 2 – VERZENIO in combination with fulvestrant in women with HR-positive, HER2-negative advanced breast cancer with disease progression on or after prior (neo)adjuvant or metastatic endocrine therapy, or as initial endocrine-based therapy

The safety of VERZENIO (150 mg twice daily) plus fulvestrant (500 mg) was evaluated in a Phase 3 randomized, double-blinded, placebo-controlled trial (MONARCH 2). The data described below reflect exposure to VERZENIO in 441 out of 664 patients with HR-positive, HER2-negative metastatic breast cancer who received at least 1 dose of VERZENIO plus fulvestrant in MONARCH 2. Patients were randomized 2:1 to receive the combination VERZENIO plus fulvestrant, versus placebo plus fulvestrant.

Median duration of treatment was 12 months for patients receiving VERZENIO plus fulvestrant and 8 months for patients receiving placebo plus fulvestrant.

Dose reductions due to an adverse reaction occurred in 43% of patients receiving VERZENIO plus fulvestrant. The most frequently reported adverse events that led to dose reduction were diarrhea (19%) and neutropenia (10%).

Permanent study treatment discontinuation due to an adverse event was reported in 9% of patients receiving VERZENIO plus fulvestrant and in 3% of patients receiving placebo plus fulvestrant. Adverse reactions leading to permanent discontinuation for patients receiving VERZENIO plus fulvestrant which occurred at ≥1% were infection (1.6%), diarrhea (1.4%), and hepatotoxicity (0.9%).

Deaths on therapy or within 30 days of treatment discontinuation were reported for 14 patients (3.2%) treated with VERZENIO plus fulvestrant and for 10 patients (4.5%) treated with placebo plus fulvestrant. Causes of death for patients receiving VERZENIO plus fulvestrant included: 5 (1.1%) due to underlying disease, 3 (0.7%) due to sepsis, 1 (0.2%) due to cerebral infarction, 1 (0.2%) due to hepatic failure, 1 (0.2%) due to hepatotoxicity, 1 (0.2%) due to lung infection, 1 (0.2%) due to multiple organ dysfunction syndrome, and 1 (0.2%) due to pneumonitis.

Treatment-emergent adverse events reported in ≥5% and at a higher frequency in patients who received VERZENIO plus fulvestrant than in patients who received placebo plus fulvestrant in MONARCH 2 are listed in Table 10.

Table 10: Treatment-Emergent Adverse Events (≥5% and at a Higher Frequency in Patients Receiving VERZENIO Plus Fulvestrant Versus Patients Receiving Placebo Plus Fulvestrant) in MONARCH 2

	VERZENIO + Fulvestrant N=441			Placebo + Fulvestrant N=223		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Blood and Lymphatic System Disorders						
Neutropenia	46	24	3	4	1	<1
Anemia	29	7	<1	4	<1	0
Leukopenia	28	9	<1	2	0	0
Thrombocytopenia	16	2	1	3	0	<1
Lymphopenia	7	3	<1	<1	0	0
Eye Disorders						
Lacrimation increased	7	<1	0	1	0	0
Gastrointestinal Disorders						
Diarrhea	86	13	0	25	<1	0
Nausea	45	3	0	23	<1	0
Abdominal pain	35	3	0	16	<1	0
Vomiting	26	<1	0	10	2	0
Stomatitis	15	<1	0	10	0	0
Dry mouth	7	0	0	6	0	0

Dyspepsia	6	0	0	5	0	0
General Disorders and Administration Site Conditions						
Fatigue	40	3	0	27	<1	0
Peripheral edema	12	0	0	7	0	0
Pyrexia	11	<1	<1	6	<1	0
Influenza like illness	8	0	0	7	0	0
Chills	6	0	0	<1	0	0
Pain	5	0	0	4	0	0
Infections and Infestations						
Upper respiratory tract infection	11	0	0	8	<1	0
Urinary tract infection	9	<1	0	3	0	0
Investigations						
Alanine aminotransferase increased	13	4	<1	5	2	0
Aspartate aminotransferase increased	12	2	0	7	3	0
Blood creatinine increased	12	<1	0	<1	0	0
Weight decreased	10	<1	0	2	<1	0
Blood alkaline phosphatase increased	5	1	0	3	0	0
Metabolism and Nutrition Disorders						
Decreased appetite	27	1	0	12	<1	0
Hypokalemia	7	3	<1	2	<1	0
Musculoskeletal and Connective Tissue Disorders						
Muscular weakness	11	<1	0	6	0	0
Pain in extremity	8	<1	0	3	<1	0
Myalgia	8	0	0	6	0	0
Nervous System Disorders						
Headache	20	<1	0	15	<1	0
Dysgeusia	18	0	0	3	0	0
Dizziness	13	<1	0	6	0	0
Psychiatric Disorders						
Depression	5	0	0	4	<1	0
Respiratory, Thoracic and Mediastinal Disorders						
Cough	13	0	0	11	0	0
Skin and Subcutaneous Tissue Disorders						
Alopecia	16	0	0	2	0	0
Pruritus	13	0	0	6	0	0
Rash	11	1	0	5	0	0
Dry Skin	9	0	0	1	0	0
Dermatitis acneiform	5	<1	0	2	0	0
Nail ridging	5	0	0	0	0	0

Vascular Disorders						
Venous thromboembolic events[a]	5	2	<1	<1	<1	0

[a] Venous thromboembolic events include deep vein thrombosis (DVT), pulmonary embolism, cerebral venous sinus thrombosis, subclavian and axillary vein thrombosis, and DVT inferior vena cava.

The most frequently reported (≥5%) Grade 3 or 4 adverse reactions were neutropenia, diarrhea, leukopenia, anemia, and infections.

Diarrhea incidence was greatest during the first month of VERZENIO dosing and was lower during subsequent months. The median time to onset of the first diarrhea event was 6 days, and the median durations of diarrhea for Grade 2 and Grade 3 were 9 days and 6 days, respectively. Most diarrhea events recovered or resolved (85%) with supportive treatment and/or dose reductions (see DOSAGE AND ADMINISTRATION, and PATIENT MEDICATION INFORMATION). The median time to the first dose reduction due to diarrhea was 29 days. Twenty-two percent (22%) of patients with diarrhea required a dose omission.

Table 11: Laboratory Findings – Hematologic Abnormalities in MONARCH 2

	VERZENIO + Fulvestrant N=441			**Placebo + Fulvestrant N=223**		
Laboratory Abnormality	**All Grades %**	**Grade 3 %**	**Grade 4 %**	**All Grades %**	**Grade 3 %**	**Grade 4 %**
White blood cell decreased	90	23	<1	33	<1	0
Neutrophil count decreased	87	29	4	30	4	<1
Anemia	84	3	0	34	<1	0
Lymphocyte count decreased	63	12	<1	32	2	0
Platelet count decreased	53	<1	1	15	0	0

Table 12: Laboratory Findings – Clinical Chemistry Abnormalities in MONARCH 2

	VERZENIO + Fulvestrant N=441			Placebo + Fulvestrant N=223		
Laboratory Abnormality	**All Grades %**	**Grade 3 %**	**Grade 4 %**	**All Grades %**	**Grade 3 %**	**Grade 4 %**
Creatinine increased	98	1	0	74	0	0
Alanine aminotransferase increased	41	4	<1	32	1	0
Aspartate aminotransferase increased	37	4	0	25	4	<1

Metastatic Breast Cancer – Used as a Single Agent

MONARCH 1 – VERZENIO administered as a single agent in patients with HR-positive, HER2-negative metastatic breast cancer whose disease progressed after endocrine therapy and who received 1 or 2 chemotherapy regimens in the metastatic setting

The safety of VERZENIO (200 mg) was evaluated in MONARCH 1, a Phase 2 single-arm, open-label, multicenter trial. The data described below reflect exposure to VERZENIO in 132 patients with measurable HR-positive, HER2-negative metastatic breast cancer. The median duration of treatment was 4.6 months.

Dose reductions due to an adverse reaction occurred in 49% of patients receiving VERZENIO as a single agent. The most frequent adverse reactions resulting in a dose reduction were diarrhea (20%), neutropenia (11%), and fatigue (9%).

Deaths during treatment or within 30 days of treatment discontinuation due to adverse events were reported in 3 patients (2%). The cause of death in these patients was due to pneumonitis, sepsis, and lung infection.

Treatment-emergent adverse events (≥5%) reported in patients who received VERZENIO as a single agent in MONARCH 1 are listed in Table 13.

Table 13: Treatment-Emergent Adverse Events (with a Frequency of ≥5% in Patients Receiving VERZENIO as a Single Agent) in MONARCH 1

	Single Agent VERZENIO N=132				
	All Grades[a] %	**Grade 1 %**	**Grade 2 %**	**Grade 3 %**	**Grade 4 %**
Blood and Lymphatic System Disorders					
Neutropenia	37	2	11	19	5
Anemia	25	8	12	5	0
Thrombocytopenia	21	10	7	4	0
Leukopenia	17	2	9	5	<1

Eye Disorders					
Lacrimation increased	8	7	<1	0	0
Dry eye	5	5	0	0	0
Gastrointestinal Disorders					
Diarrhea	90	42	29	20	0
Nausea	64	39	21	5	0
Abdominal pain	39	22	14	2	0
Vomiting	35	23	11	2	0
Constipation	17	13	4	<1	0
Dry mouth	14	12	2	0	0
Stomatitis	14	11	2	0	0
Dyspepsia	8	7	2	0	0
Flatulence	5	5	<1	0	0
Gastroesophageal reflux disease	5	5	0	0	0
General Disorders and Administration Site Conditions					
Fatigue	65	21	31	13	0
Pain	20	11	7	2	0
Pyrexia	11	10	<1	0	0
Peripheral edema	8	5	2	0	0
Chills	6	5	<1	0	0
Infections and Infestations					
Upper respiratory tract infection	8	<1	6	<1	0
Urinary tract infection	8	0	8	0	0
Investigations					
Weight decreased	14	10	4	0	0
Blood creatinine increased	13	5	8	<1	0
Aspartate aminotransferase increased	8	5	<1	2	0
Alanine aminotransferase increased	7	4	2	<1	0
Metabolism and Nutrition Disorders					
Decreased appetite	46	28	14	3	0
Dehydration	10	2	5	2	0
Hypokalemia	5	2	2	2	0
Musculoskeletal and Connective Tissue Disorders					
Back pain	11	7	4	<1	0
Arthralgia	8	6	2	0	0
Bone pain	7	5	<1	<1	0
Muscular weakness	7	2	3	2	0
Myalgia	5	4	2	0	0
Pain in extremity	5	4	<1	0	0

Nervous System Disorders					
Headache	21	14	7	0	0
Dysgeusia	12	11	2	0	0
Dizziness	11	10	2	0	0
Neuropathy	8	5	2	0	0
Psychiatric Disorders					
Anxiety	5	4	2	0	0
Insomnia	5	3	2	0	0
Respiratory, Thoracic and Mediastinal Disorders					
Cough	19	15	4	0	0
Dyspnea	14	5	5	3	<1
Oropharyngeal pain	6	5	<1	0	0
Upper-airway cough syndrome	5	5	0	0	0
Rhinitis allergic	5	5	0	0	0
Skin and Subcutaneous Tissue Disorders					
Alopecia	12	10	2	0	0
Dry skin	9	8	<1	0	0
Rash	8	7	0	2	0
Pruritus	8	6	<1	<1	0

[a] Refer to NCI CTCAE Criteria Version 4.03 for each Grade of toxicity.

The most frequently reported (≥5%) Grade 3 or 4 adverse reactions were neutropenia, diarrhea, fatigue, leukopenia, anemia and nausea (see DOSAGE AND ADMINISTRATION).

Diarrhea incidence was greatest during the first month of VERZENIO dosing and was lower during subsequent months. The median time to onset of the first diarrhea event was 7 days, and the median durations of diarrhea for Grade 2 and Grade 3 were 8 days and 5 days, respectively. Most diarrhea events recovered or resolved (93%) with supportive treatment and/or dose reductions (see DOSAGE AND ADMINISTRATION, and PATIENT MEDICATION INFORMATION). Twenty-six percent (26%) of patients with diarrhea required a dose omission and 23% required a dose reduction. The median time to the first dose reduction due to diarrhea was 28 days.

Table 14: Laboratory Findings – Hematologic Abnormalities for Patients Receiving VERZENIO as a Single Agent in MONARCH 1

	Single Agent VERZENIO N=132				
Laboratory Abnormality	**All Grades %**	**Grade 1 %**	**Grade 2 %**	**Grade 3 %**	**Grade 4 %**
White blood cell decreased	91	19	45	28	0
Neutrophil count decreased	88	18	43	22	5
Anemia	69	30	39	0	0
Lymphocyte	42	5	24	13	<1

count decreased					
Platelet count decreased	41	29	10	2	0

Table 15: Laboratory Findings – Clinical Chemistry Abnormalities for Patients Receiving VERZENIO as a Single Agent in MONARCH 1

	Single Agent VERZENIO N=132				
Laboratory Abnormality	**All Grades %**	**Grade 1 %**	**Grade 2 %**	**Grade 3 %**	**Grade 4 %**
Creatinine increased	99	47	51	<1	0

8.3 Less Common Clinical Trial Adverse Reactions

Additional less common adverse events (all grades) included:

Blood and lymphatic system disorders: febrile neutropenia.
Cardiac disorders: atrial fibrillation, cardiac failure, palpitations, sinus tachycardia.
Eye disorders: eye pain, vision blurred.
Gastrointestinal disorders: abdominal distension, anal hemorrhage, colitis, dental caries, dysphagia, enterocolitis, gastritis, gastroesophageal reflux disease, gingival pain, hemorrhoids, oral pain, periodontal disease.
General disorders and administration site conditions: chills, face edema, localized edema, malaise.
Immune system disorders: hypersensitivity.
Infections and infestations: bronchitis, conjunctivitis, gastroenteritis, gingivitis, pharyngitis, rash pustular, sepsis, skin infection, tooth infection, vaginal infection, wound infection.
Injury, poisoning and procedural complications: fracture.
Investigations: blood bilirubin increased, gamma-glutamyltransferase increased.
Metabolism and nutrition disorders: dehydration, hypercholesterolemia, hyperkalemia, hypoalbuminemia, hypocalcemia, hypomagnesemia, hyponatremia, hypophosphatemia.
Musculoskeletal and connective tissue disorders: arthritis, flank pain, osteonecrosis of jaw.
Nervous system disorders: amnesia, cerebrovascular accident, lethargy, syncope.
Psychiatric disorders: confusional state.
Renal and urinary disorders: acute kidney injury, chronic kidney disease, cystitis noninfective, dysuria, pollakiuria, urinary tract pain.
Reproductive system and breast disorders: pelvis pain, vulvovaginal dryness.
Respiratory, thoracic and mediastinal disorders: dysphonia, epistaxis, nasal dryness, pneumonitis, productive cough, pulmonary fibrosis.
Skin and subcutaneous tissue disorders: eczema, erythema, nail disorder, onychomadesis, pain of skin, palmar-plantar erythrodysesthesia syndrome, skin hyperpigmentation, urticaria.
Vascular disorders: hematoma, hypotension, lymphoedema.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Creatinine Increased

VERZENIO has been shown to increase serum creatinine due to inhibition of renal tubular secretion transporters, without affecting glomerular function (see ACTION AND CLINICAL PHARMACOLOGY). In clinical studies, increases in serum creatinine (mean increase, 0.2-0.3 mg/dL) occurred within the first 28-day cycle of VERZENIO dosing, remained elevated but stable through the treatment period, and were reversible upon treatment discontinuation. Alternative markers such as blood urea nitrogen (BUN), cystatin C, or calculated glomerular filtration rate (GFR), which are not based on creatinine, may be considered to determine whether renal function is impaired.

8.5 Clinical Trial Adverse Reactions (Pediatrics)

Clinical trials have not been conducted in a pediatric population.

9 DRUG INTERACTIONS

9.1 Overview

Abemaciclib is primarily metabolized by CYP3A4 to several active metabolites.

Co-administration of abemaciclib with some CYP3A inhibitors can increase plasma concentrations of abemaciclib and active metabolites. The concomitant use of strong CYP3A inhibitors should be avoided.

Co-administration of abemaciclib with strong CYP3A inducers may decrease the plasma concentrations of abemaciclib and its active metabolites. The concomitant use of strong CYP3A inducers should be avoided.

9.2 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction clinical trials or predicted interactions due to the expected magnitude and seriousness of the interaction.

Table 16: Established or Potential Drug-Drug Interactions – Effect of Other Drugs on Abemaciclib[a]

Concomitant Drug Class: CYP3A Inhibitor	Source of Evidence	Effect on Abemaciclib Concentration[b]	Clinical Comment – Abemaciclib Dose Recommendation
Specific Inhibitors[c]			
Ketoconazole	P	↑	50 mg once daily
Itraconazole	P	↑	50 mg twice daily
Clarithromycin	CT	↑	100 mg twice daily
Diltiazem	P	↑	100 mg twice daily
Verapamil	P	↑	100 mg twice daily
For other inhibitors[c]			
Strong Inhibitor	P	↑	50 mg twice daily
Moderate Inhibitor	P		50 mg twice daily
Weak Inhibitor	T		100 mg twice daily

Legend: CT = Clinical Trial; P = Predicted; T = Theoretical.

[a] Based on a 150 mg or 200 mg twice daily starting dose.

[b] Relative potency adjusted unbound exposure of abemaciclib plus active metabolites.
[c] Based on clinical results and physiologically-based pharmacokinetic (PBPK) simulations. Dose recommendations are based on PBPK simulations.

CYP3A Inhibitors

In a clinical study of 26 patients, co-administration of a CYP3A inhibitor clarithromycin resulted in a 3.4-fold increase in the plasma exposure of abemaciclib and a 2.2-fold increase in the combined plasma exposure of abemaciclib and its active metabolites (see DOSAGE AND ADMINISTRATION, and ACTION AND CLINICAL PHARMACOLOGY).

Avoid concomitant use of strong CYP3A inhibitors (for example, voriconazole) and use caution with co-administered moderate (for example, ciprofloxacin) or weak (for example, ranitidine) CYP3A inhibitors. If co-administration with a CYP3A inhibitor is unavoidable, adjust the abemaciclib dose as described in Table 16. If a CYP3A inhibitor is discontinued, increase the abemaciclib dose (after 3-5 half-lives of the inhibitor) to the dose that was used before starting the inhibitor (see DOSAGE AND ADMINISTRATION).

Avoid grapefruit, grapefruit juice, or grapefruit products.

CYP3A Inducers

Data from a study in 24 healthy subjects indicated that co-administration of abemaciclib with the strong CYP3A inducer rifampin decreased the plasma exposure of abemaciclib plus its active metabolites by 77% based on $AUC_{0\text{-}INF}$ and 45% based on C_{max}. Avoid concomitant use of strong CYP3A inducers (for example, rifampin, phenytoin, carbamazepine, and St. John's wort). Consider alternative agents with less CYP3A induction.

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 52%, 42%, and 29% respectively. No abemaciclib dose adjustment is required for patients who must use concomitant moderate or weak CYP3A inducers.

Loperamide: In a clinical drug interaction study in healthy subjects, co-administration of a single 8 mg dose of loperamide with 400 mg abemaciclib had no statistically significant effect on abemaciclib pharmacokinetics.

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

Effects of Abemaciclib on Other Drugs

Loperamide: In a clinical drug interaction study in healthy subjects, co-administration of a single 8 mg dose of loperamide with a single 400 mg abemaciclib dose 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, co-administration of a single 1000 mg dose of metformin, a clinically relevant substrate of renal organic cation transporter 2 (OCT2), multidrug and toxin extrusion protein 1 (MATE1), and MATE2-K transporters, with a

single 400 mg dose of abemaciclib 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. Concurrent administration of abemaciclib with other clinically relevant substrates of OCT2, MATE1, and MATE2 should be done with caution.

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, or exemestane.

In Vitro Studies

CYP Metabolic Pathways: Abemaciclib and its major active metabolites, M2 and M20, do not induce CYP1A2, CYP2B6, or CYP3A at clinically relevant concentrations. Abemaciclib and its major active metabolites, M2 and M20, down regulate mRNA of CYPs, including CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2D6 and CYP3A4. The mechanism of this down regulation and its clinical relevance are not understood. However, abemaciclib is a substrate of CYP3A4, and time-dependent changes in pharmacokinetics of abemaciclib as a result of autoinhibition of its metabolism was not observed.

Transporters: 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 REACTIONS). 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 and its major active metabolites, M2 and M20, are not substrates of hepatic uptake transporters OCT1, organic anion transporting polypeptide 1B1 (OATP1B1), or OATP1B3.

P-gp and BCRP Transporters: In vitro, abemaciclib is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). The effect of P-gp or BCRP inhibitors on the pharmacokinetics of abemaciclib has not been studied. Based on the in vitro inhibition of P-gp and BCRP observed with abemaciclib, in vivo interactions of abemaciclib with narrow therapeutic index substrates of these transporters, such as digoxin, may occur.

9.3 Drug-Food Interactions

Abemaciclib may be taken with or without food. A food effect study demonstrated a 26% increase in C_{max} of abemaciclib and its active metabolites following a high fat breakfast compared with fasted dosing (see ACTION AND CLINICAL PHARMACOLOGY). Although significant, this increase is within observed variability.

Grapefruit, grapefruit juice, and products containing grapefruit extract may increase abemaciclib plasma concentrations and should be avoided (see DOSAGE AND ADMINISTRATION, and ACTION AND CLINICAL PHARMACOLOGY).

9.4 Drug-Herb Interactions

Interactions with herbal products have not been established. St. John's wort (*Hypericum*

perforatum) is an inducer of CYP3A4/5 that may decrease abemaciclib plasma concentrations and should be avoided (see Drug-Drug Interactions).

9.5 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Abemaciclib is an inhibitor of cyclin D-dependent kinases 4 and 6 (CDK4 and CDK6) and was most active against cyclin D1/CDK4 in enzymatic assays. Abemaciclib prevents retinoblastoma protein (Rb) phosphorylation, blocking progression from G1 into S phase of the cell cycle, leading to suppression of tumor growth in preclinical models following short duration target inhibition. In estrogen receptor–positive breast cancer cell lines, sustained target inhibition by abemaciclib prevents rebound of Rb phosphorylation and cell cycle reentry, resulting in senescence and apoptosis. In breast cancer xenograft models, abemaciclib dosed daily without interruption at clinically relevant concentrations—as a single agent or in combination with antiestrogens—resulted in reduction of tumor size.

10.2 Pharmacodynamics

In cancer patients, abemaciclib inhibits CDK4 and CDK6 as indicated by inhibition of phosphorylation of Rb and topoisomerase II alpha, which results in cell cycle inhibition upstream of the G1 restriction point at doses of 50 mg to 200 mg twice daily. MONARCH 2 and MONARCH 3 exposure-response analyses support the 150 mg twice daily starting dose in combination with endocrine therapy and support dose reductions as needed for tolerability to a dose as low as 50 mg twice daily. MONARCH 1 exposure-response analysis supports the 200 mg twice daily starting dose when used as a single agent.

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.

10.3 Pharmacokinetics

The pharmacokinetics of abemaciclib were characterized in patients with cancer following oral doses ranging from 50 mg to 225 mg once daily and 75 mg to 275 mg twice daily. Healthy subjects received single oral doses ranging from 150 mg to 600 mg.

Table 17: Summary of Abemaciclib Pharmacokinetic Parameters

$C_{max,ss}$ (ng/mL)	T_{max} (hours)	$t_{½}$ (hours)	$AUC_{tau,ss}$ (ng*h/mL)	CL (L/h)	Vd (L)
249 (35%)[a]	8.0 (4.1, 24)	24.8 (52%)	2520 (35%)	21.8 (40%)	747 L (69%)

Abbreviations: $AUC_{tau,ss}$ = area under the concentration versus time curve during one dosing interval at steady state; $C_{max,ss}$ = maximum plasma concentration after multiple dosing at steady-state; CL = hepatic clearance; $t_{1/2}$ = half-life; T_{max} = time of observed maximum plasma concentration after a single dose; Vd = systemic volume of distribution.

Data are presented as geometric mean (CV%) for all parameters except T_{max} which is presented as median (range).

[a] Patients in MONARCH 2 who started at an abemaciclib dose of 150 mg twice daily.

Absorption: The absolute bioavailability of abemaciclib after a single oral dose of 200 mg is 45% (19% CV) (90% confidence interval: 40-51%). In the therapeutic dose range of 50-200 mg, the increase in plasma exposure (AUC) and C_{max} is dose proportional. Steady state was achieved within 5 days following repeated twice daily dosing, and abemaciclib accumulated with a geometric mean accumulation ratio of 3.7 (58% CV) and 5.8 (65% CV) based on C_{max} and AUC, respectively. Abemaciclib absorption is slow, with a median T_{max} of 8.0 hours (range: 4.1-24.0 hours). 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_{0-INF} of abemaciclib plus its active metabolites by 9% and increased C_{max} by 26%.

Distribution: Abemaciclib was highly bound to plasma proteins in humans (mean bound fraction was approximately 96-98%), and the binding was independent of concentration from 152 ng/mL to 5066 ng/mL. Abemaciclib binds to both human serum albumin and alpha-1-acid glycoprotein. The geometric mean systemic volume of distribution is approximately 747 L (68.6% 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.

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.

Elimination: The geometric mean hepatic clearance (CL) of abemaciclib in patients was 21.8 L/h (40% CV), and the mean plasma elimination half-life for abemaciclib in patients was 24.8 hours (52% CV).

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.

Special Populations and Conditions

Pediatrics: Pharmacokinetics of abemaciclib have not been evaluated in children and adolescents <18 years of age.

Geriatrics: Age (range, 24-91 years of age) does not alter abemaciclib pharmacokinetics.

Sex: Gender does not alter abemaciclib pharmacokinetics.

Ethnic Origin: Race was not identified as a significant covariate for abemaciclib pharmacokinetics in patients with cancer.8.1

Hepatic Impairment: Abemaciclib is metabolized in the liver. 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 2.7 in subjects with severe hepatic impairment (Child-Pugh C, n=6) relative to subjects with normal hepatic function (n=10). In addition, 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; therefore, a dose reduction is required in patients with severe hepatic impairment (see DOSAGE AND ADMINISTRATION).

Renal Impairment: Renal clearance of abemaciclib and its metabolites is minor, with appropriately 3.4% of the dose recovered in urine. In a population pharmacokinetic analysis that included baseline Cockcroft-Gault creatinine clearance (CrCl) information for 989 individuals, in which 383 individuals had mild renal impairment (60 mL/min ≤ CrCl <90 mL/min) and 127 individuals had moderate renal impairment (30 mL/min ≤ CrCl <60 mL/min), mild and moderate renal impairment had no effect on the exposure of abemaciclib; therefore, no dose adjustment is needed based on the above-mentioned patient factors for abemaciclib. The effect of severe renal impairment (CrCl <30 mL/min) on pharmacokinetics of abemaciclib is unknown. There are no data in patients with severe renal impairment, end stage renal disease, or in patients on dialysis. Caution should be used in patients with severe renal impairment.

Obesity: Body weight (range 36-175 kg) had no effect on the exposure of abemaciclib.

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature (15°C to 30°C). Keep out of reach and sight of children.

12 SPECIAL HANDLING INSTRUCTIONS

Any unused product or waste material should be disposed of in accordance with local requirements.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

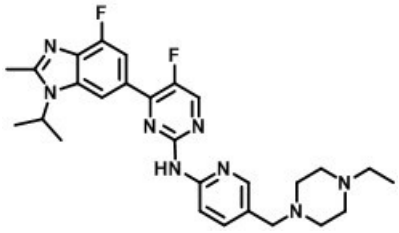
Drug Substance

Proper name: Abemaciclib

Chemical name: 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]-

Molecular formula and molecular mass: The empirical formula is $C_{27}H_{32}F_2N_8$ with a molecular weight of 506.59.

Structural formula:



Physicochemical properties: Abemaciclib is a practically white to yellow powder. Abemaciclib has pH dependent solubility and is considered highly soluble, with solubility ≥5 mg/mL up to pH 6.0 and 1.577 mg/mL at pH 6.8 in aqueous media.

14 CLINICAL TRIALS

14.1 MONARCH 3 – Trial Design and Study Demographics

MONARCH 3 – VERZENIO in combination with a non-steroidal aromatase inhibitor (NSAI: anastrozole or letrozole) in postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer with no prior systemic therapy in this disease setting

Table 18: Summary of Trial Design and Patient Demographics in MONARCH 3

Trial design	Dosage, route of administration and duration	Study subjects (n)	Median age (Range)
Randomized (2:1), Phase III, double-blinded, placebo-controlled, multicenter study	Patients received VERZENIO (150 mg orally twice daily on a continuous schedule) or placebo, plus physician's choice of a NSAI (letrozole 2.5 mg or anastrozole 1 mg, orally once daily) on a 28 day cycle.	VERZENIO + NSAI (N=328) Placebo + NSAI (N=165) (493 total)	VERZENIO + NSAI = 63 (38-87) years Placebo + NSAI = 63 (32-88) years

The efficacy of VERZENIO in combination with a non-steroidal aromatase inhibitor (NSAI) was evaluated in MONARCH 3, a randomized, placebo-controlled multicenter study in postmenopausal women with hormone receptor positive (HR-positive), human epidermal growth factor receptor 2 (HER2)-negative advanced (not amenable to curative therapy) or metastatic breast cancer who had not received prior systemic therapy in this disease setting. Patients could have received (neo)adjuvant endocrine therapy if they were at least 12 months from end of therapy. A total of 493 patients were randomized to receive VERZENIO or placebo orally twice daily in combination with physician's choice of letrozole (80% of patients) or anastrozole (20% of patients). Randomization was stratified by metastatic disease site (visceral, bone only, or other) and by prior (neo)adjuvant endocrine therapy (aromatase inhibitor versus other versus no prior endocrine therapy).

VERZENIO or placebo was given orally, without regard to food, every 12 (±2) hours on Days 1 through 28 of a 28 day cycle. Patients received study treatment until objective disease progression or unacceptable toxicity. Crossover between treatment arms was not allowed.

Demographics and baseline characteristics are outlined in Table 19.

Table 19: Baseline Demographic and Disease Characteristics for the Intent to Treat (ITT) Population – MONARCH 3

	Demographic Parameter	VERZENIO + AI (N=328)	Placebo + AI (N=165)	Total (N = 493)
Age (years)	Median age (range)	63.0 (38.0-87.0)	63.0 (32.0-88.0)	63.0 (32.0-88.0)
Age group n (%)	Age <65 years	180 (54.9)	91 (55.2)	271 (55.0)
	Age ≥65 years	148 (45.1)	74 (44.8)	222 (45.0)
Race, n (%)[a]	White	186 (56.7)	102 (61.8)	288 (58.4)
	Asian	103 (31.4)	45 (27.3)	148 (30.0)
	Black	5 (1.5)	3 (1.8)	8 (1.6)
	Other	6 (1.8)	4 (2.4)	10 (2.0)
ECOG performance status (PS), n (%)	0	192 (58.5)	104 (63.0)	296 (60.0)
	1	136 (41.5)	61 (37.0)	197 (40.0)
Stage of disease at initial diagnosis, n (%)	Stage III	62 (18.9)	24 (14.5)	86 (17.4)
	Stage IV	132 (40.2)	61 (37.0)	193 (39.1)
Disease Setting at Study Entry, n (%)	De novo metastatic	135 (41.2)	61 (37.0)	196 (39.8)
	Metastatic recurrent	182 (55.5)	99 (60.0)	281 (57.0)
	Locoregionally recurrent	11 (3.4)	5 (3.0)	16 (3.2)
Progesterone Receptor (PgR) status, n (%)	Positive	255 (77.7)	127 (77.0)	382 (77.5)
	Negative	70 (21.3)	36 (21.8)	106 (21.5)
Disease site, n (%)	Visceral	172 (52.4)	89 (53.9)	261 (52.9)
	Non-visceral			
	Bone only	70 (21.3)	39 (23.6)	109 (22.1)
	Other	86 (26.2)	37 (22.4)	123 (24.9)
	Number of organ sites			
	1	96 (29.3)	47 (28.5)	143 (29.0)
	2	76 (23.2)	42 (25.5)	118 (23.9)
	≥3	154 (47.0)	75 (45.5)	229 (46.5)
Treatment-free interval, n (%)	Patients with adjuvant therapy, n (%)	137 (97.9)	72 (100.0)	209 (98.6)
	≤24 months	22 (15.7)	19 (26.4)	41 (19.3)
	>24 months	115 (82.1)	53 (73.6)	168 (79.2)
Prior systemic therapy, n (%)	(Neo)adjuvant and/or adjuvant[b]	166 (50.6)	85 (51.5)	251 (50.9)
	Endocrine	141 (43.0)	78 (47.3)	219 (44.4)
	Aromatase inhibitor[c]	85 (25.9)	50 (30.3)	135 (27.4)
	Chemotherapy	125 (38.1)	66 (40.0)	191 (38.7)

Abbreviation: ECOG = Eastern Cooperative Oncology Group.

[a] Race not reported for 8.5%.

[b] Patients may have received treatment in more than 1 setting.

[c] Patient reported.

14.2 MONARCH 3 – Study Results

The primary efficacy objective was investigator-assessed progression-free survival (PFS) evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1. Secondary efficacy endpoints included overall survival (OS) and objective response rate (ORR).

The final analysis, performed at a median follow-up time of 26.7 months for both treatment arms, indicated that patients who received VERZENIO with a NSAI had a statistically significant 46% reduction in the risk of disease progression or death compared to those treated with placebo plus a NSAI. Data from an independent radiographic review was supportive of this treatment effect. Efficacy results from the MONARCH 3 study are summarized in Table 20 and the Kaplan-Meier curve for PFS is shown in Figure 1.

Table 20: Efficacy Results of MONARCH 3 (Investigator Assessment) – Intent-to-Treat (ITT) Population

	VERZENIO + AI	**Placebo + AI**
Progression-Free Survival[a]	**N=328**	**N=165**
Median, months (95% CI)	28.18 (23.51,NR)	14.76 (11.24, 19.20)
Hazard ratio (95% CI)	0.540 (0.418, 0.698)	
p-value (2-sided) log-rank stratified	p<.0001	
Objective Response Rate for Patients with Measurable Disease	**N=267**	**N=132**
Objective response rate[a,b], n (%)	163 (61.0)	60 (45.5)
95% CI	55.2, 66.9	37.0, 53.9
Complete response, n (%)	9 (3.4)	0
Partial response, n (%)	154 (57.7)	60 (45.5)

Abbreviation: CI = confidence interval, RECIST = Response Evaluation Criteria in Solid Tumors.

[a] Evaluated according to RECIST version 1.1.

[b] Complete response + partial response.

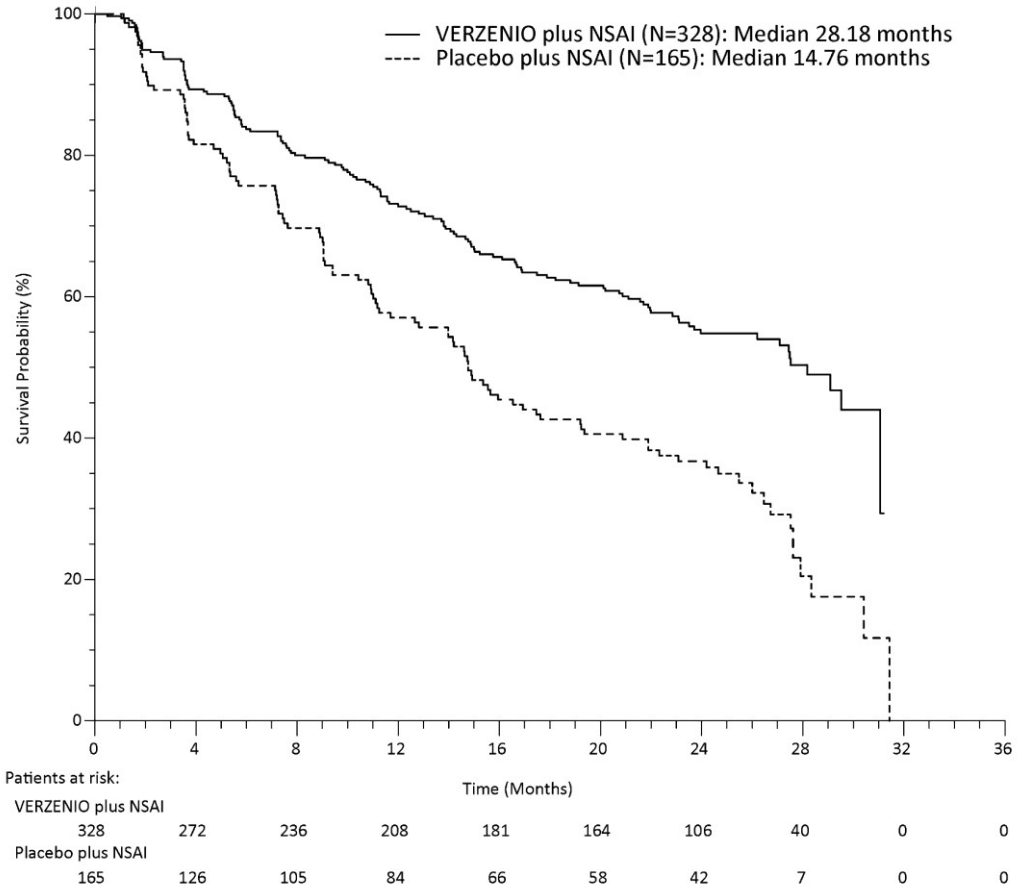


Figure 1. Kaplan-Meier Curves of Progression-Free Survival: VERZENIO plus NSAI versus Placebo plus NSAI – MONARCH 3

A series of prespecified subgroup PFS analyses were performed based on prognostic factors and baseline characteristics. Consistent benefit was observed across predefined patient subgroups (Figure 2).

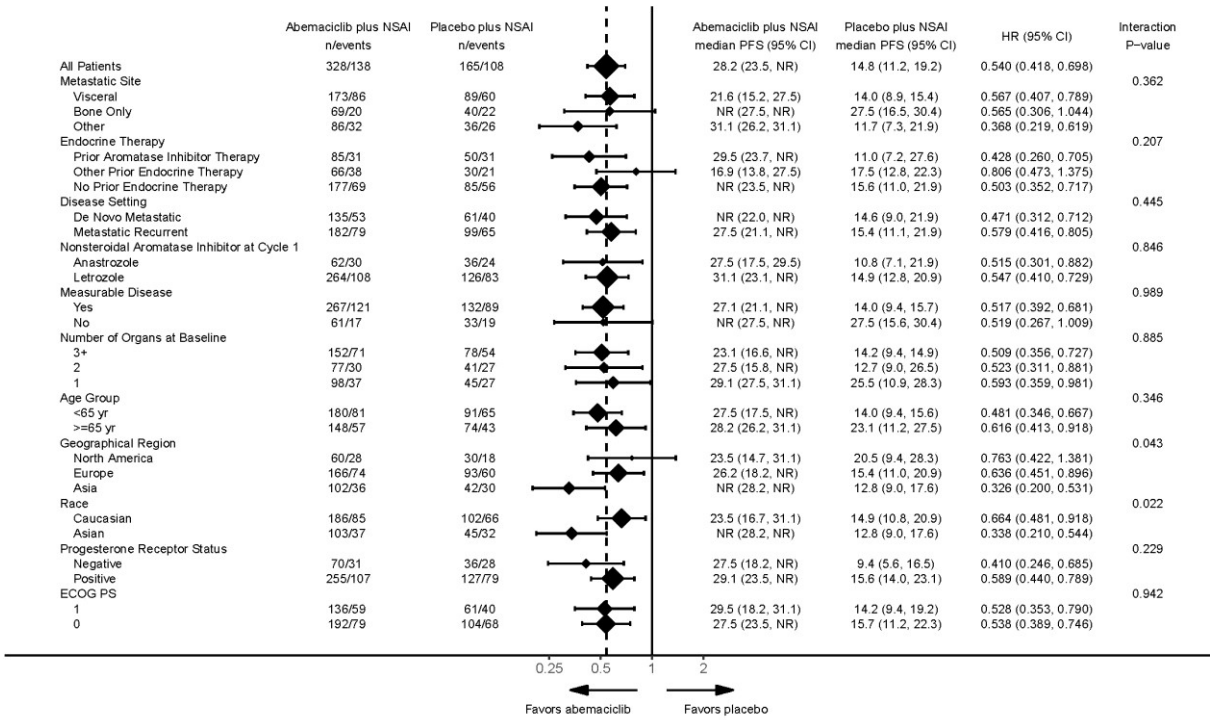


Figure 2. Forest Plot of Subgroup Analyses of Progression-Free Survival by Investigator Assessment, Intent-to-Treat Population – MONARCH 3

Overall survival data were not mature at the time of the final PFS analysis. With a total of 93 events observed (63 events in the VERZENIO plus NSAI arm and 30 events in the placebo plus NSAI arm), the hazard ratio (HR) was 1.057.

14.3 MONARCH 2 – Trial Design and Study Demographics

MONARCH 2 – VERZENIO in combination with fulvestrant in women with HR-positive, HER2-negative advanced breast cancer with disease progression on or after prior (neo)adjuvant or metastatic endocrine therapy

Table 21: Summary of Trial Design and Patient Demographics in MONARCH 2

Trial design	Dosage, route of administration and duration	Study subjects (n)	Median age (Range)
Randomized (2:1), Phase III, placebo-controlled, multicenter study	Patients received VERZENIO (150mg orally twice daily on a continuous schedule), or placebo, plus intramuscular injection of 500 mg fulvestrant on day 1 and 15 of cycle 1 and day 1 of cycle 2 and beyond.	VERZENIO + fulvestrant (N=446) Placebo + Fulvestrant (N=223) (669 total)	VERZENIO + Fulvestrant = 59 (32-91) Placebo + Fulvestrant = 62 (32-87)

The efficacy of VERZENIO in combination with fulvestrant was evaluated in MONARCH 2, a randomized, placebo-controlled, multicenter study in women with HR-positive, HER2-negative advanced or metastatic breast cancer who had disease progression following endocrine therapy and who had not received chemotherapy in the metastatic setting. Randomization was stratified by metastatic disease site (visceral, bone only, or other) and by sensitivity to prior endocrine therapy (primary or secondary resistance).

VERZENIO or placebo was given orally, without regard to food, every 12 (±2) hours on Days 1 through 28 of a 28-day cycle. Patients received study treatment until disease progression or unacceptable toxicity. Pre-/perimenopausal women enrolled in the study received a gonadotropin-releasing hormone agonist (e.g. goserelin) for at least 4 weeks prior to and for the duration of treatment. Crossover between treatment arms was not allowed.

Demographics and baseline characteristics are outlined in Table 22.

Table 22: Baseline Demographic and Disease Characteristics for the Intent to Treat (ITT) Population – MONARCH 2

	Demographic Parameter	VERZENIO + Fulvestrant (N=446)	Placebo + Fulvestrant (N=223)	Total (N=669)
Age (years)	Median age (range)	59.0 (32.0-91.0)	62.0 (32.0-87.0)	60.0 (32.0-91.0)
Age group n (%)	Age <65 years Age ≥65 years	291 (65.3) 155 (34.8)	133 (59.6) 90 (40.4)	424 (63.4) 245 (36.6)
Menopausal status, n (%)	Pre-/perimenopausal Postmenopausal	72 (16.1) 371 (83.2)	42 (18.8) 180 (80.7)	114 (17.0) 551 (82.4)
Race, n (%)[a]	White Asian Black Other	237 (53.1) 149 (33.4) 9 (2.0) 18 (4.0)	136 (61.0) 65 (29.1) 5 (2.2) 8 (3.6)	373 (55.8) 214 (32.0) 14 (2.1) 26 (3.9)
ECOG performance status (PS), n (%)	0 1	264 (59.2) 176 (39.5)	136 (61.0) 87 (39.0)	400 (59.8) 263 (39.3)
Stage of disease at initial diagnosis, n (%)	Stage III Stage IV	113 (25.4) 86 (19.3)	51 (22.9) 45 (20.2)	164 (24.5) 131 (19.6)
Progesterone receptor (PgR) status, n (%)	Positive Negative	339 (76.0) 96 (21.5)	171 (76.7) 44 (19.7)	510 (76.2) 140 (20.9)
Endocrine therapy resistance, n (%)	Primary resistance Secondary resistance	111 (24.9) 326 (73.1)	58 (26.0) 163 (73.1)	169 (25.3) 489 (73.1)
Metastatic disease site, n (%)	Visceral Non-visceral Bone only Other	245 (54.9) 123 (27.6) 75 (16.8)	128 (57.4) 57 (25.6) 38 (17.0)	373 (55.8) 180 (26.9) 113 (16.9)
Treatment in locally advanced/ metastatic setting, n (%)	Endocrine Letrozole Anastrozole Exemestane Tamoxifen	173 (38.8) 95 (21.3) 28 (6.3) 14 (3.1) 48 (10.8)	86 (38.6) 41 (18.4) 15 (6.7) 9 (4.0) 24 (10.8)	259 (38.7) 136 (20.3) 43 (6.4) 23 (3.4) 72 (10.8)

Abbreviation: ECOG = Eastern Cooperative Oncology Group.

[a] Race not reported for 4.2%.

14.4 MONARCH 2 – Study Results

The primary efficacy outcome measure was investigator-assessed progression-free survival (PFS) evaluated according to RECIST v1.1. Secondary efficacy endpoints included OS and ORR.

The efficacy analyses, performed at a median follow-up time of 20 months for both treatment arms, indicated that patients who received VERZENIO with fulvestrant had a statistically significant 44.7% reduction in the risk of disease progression or death compared to those treated with placebo plus fulvestrant. Data from an independent radiographic review was supportive of this treatment effect. Efficacy results from the MONARCH 2 study are summarized in Table 23 and the Kaplan-Meier curve for PFS is shown in Figure 3.

Table 23: Efficacy Results of MONARCH 2 (Investigator Assessment) – Intent-to-Treat (ITT) Population

	VERZENIO + Fulvestrant	**Placebo + Fulvestrant**
Progression-Free Survival[a]	**N=446**	**N=223**
Median, months (95% CI)	16.4 (14.4, 19.3)	9.3 (7.4, 11.4)
Hazard ratio (95% CI)	0.553 (0.449, 0.681)	
p-value (2-sided) log-rank stratified	p<.0001	
Objective Response Rate for Patients with Measurable Disease	**N=318**	**N=164**
Objective response rate[a,b], n (%)	153 (48.1)	35 (21.3)
95% CI	42.6, 53.6	15.1, 27.6
Complete response, n (%)	11 (3.5)	0 (0.0)
Partial response, n (%)	142 (44.7)	35 (21.3)

Abbreviation: CI = confidence interval, RECIST = Response Evaluation Criteria in Solid Tumors.

[a] Evaluated according to RECIST version 1.1.

[b] Complete response + partial response.

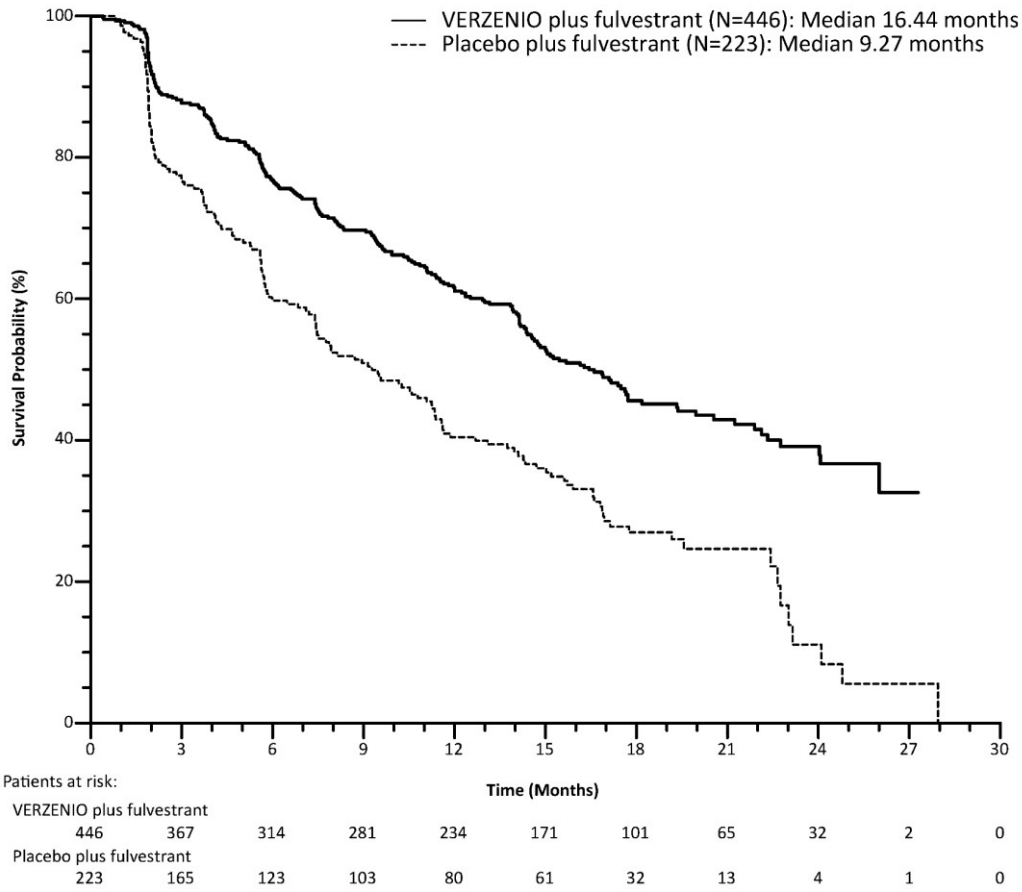


Figure 3. Kaplan-Meier Curves of Progression-Free Survival: VERZENIO plus Fulvestrant versus Placebo plus Fulvestrant – MONARCH 2

Consistent benefit was observed across predefined patient subgroups and menopausal status (Figure 4). At the time of the final PFS analysis, overall survival data were immature.

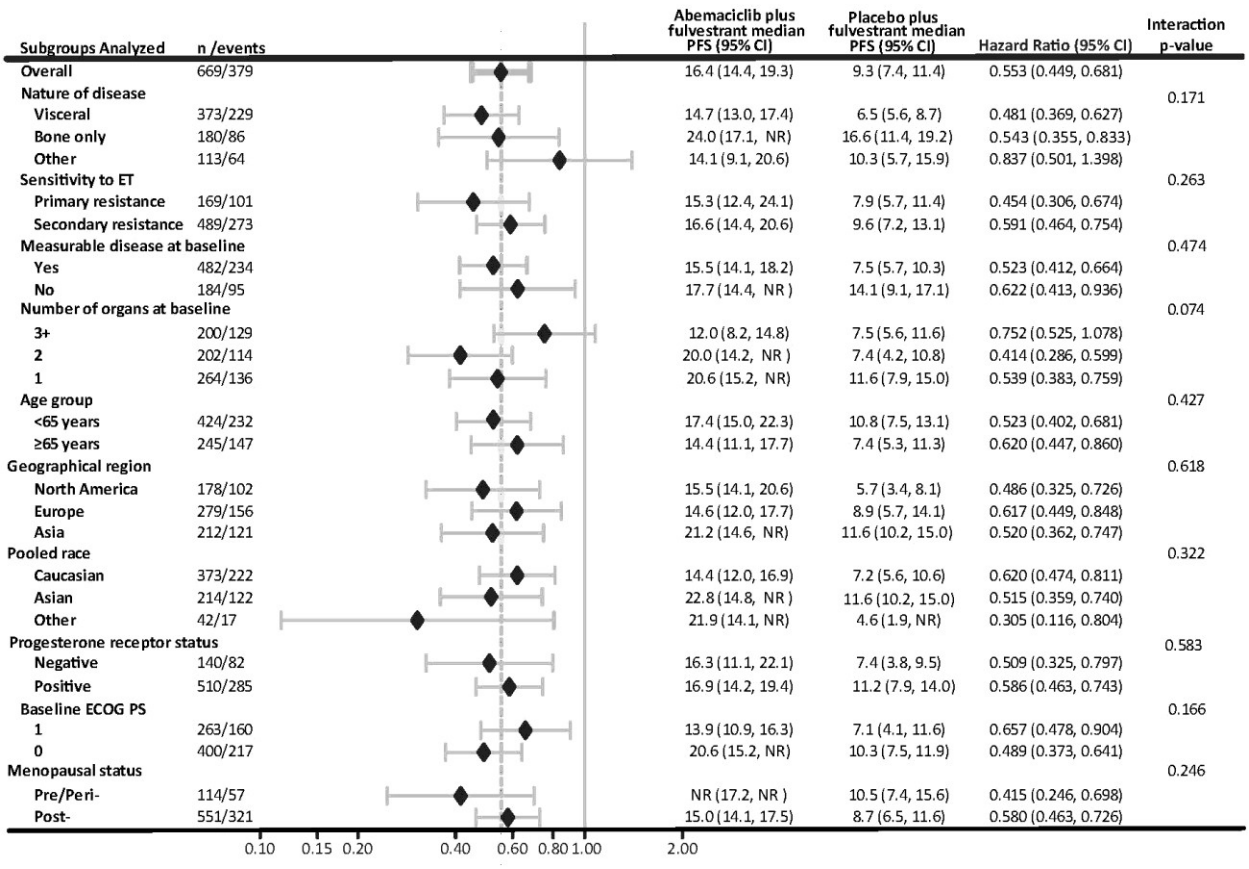


Figure 4. Forrest Plot of Summary of Progression-Free Survival by Select Subgroups, Intent-to-Treat Population – MONARCH 2

14.5 MONARCH 1 – Trial Design and Study Demographics

MONARCH 1– VERZENIO administered as a single agent in patients with refractory HR-positive, HER2-negative metastatic breast cancer, whose disease progressed after endocrine therapy and who received 1 or 2 prior chemotherapy regimens in the metastatic setting

Table 24: Summary of Trial Design and Patient Demographics in MONARCH 1

Trial design	Dosage, route of administration and duration	Study subjects (n)	Median age (Range)
Single arm, Phase II, open-label, multicenter study	Patients received VERZENIO 200 mg orally twice daily on a continuous schedule.	Single-agent VERZENIO (N=132)	Single-agent VERZENIO = 58 (36-89) years

The efficacy of single agent VERZENIO was evaluated in MONARCH 1, a single-arm, open-label, multicenter study in women with previously treated HR-positive, HER2-negative

metastatic breast cancer with disease progression on or following prior endocrine therapy and at least 2 chemotherapy regimens (including a taxane in any setting and no more than 2 regimens in the metastatic setting). All patients had measurable disease at study entry. VERZENIO was given orally (with no food 1 hour before or 1 hour after drug administration) every 12 (±2) hours on Days 1 through 28 of a 28-day cycle. Study treatment continued until disease progression or unacceptable toxicity. The median number of cycles received per patient was 5, with a median duration of therapy of 138.5 days.

In the metastatic setting, patients had received a median of 3 (range, 1-8) prior lines of systemic therapy and 2 (range, 1-6) lines of endocrine therapy. In the metastatic setting, chemotherapy regimens (no more than 2) included taxane-based (68.9%) capecitabine (55.3%), gemcitabine (7.6%), vinorelbine (6.8%), and eribulin (4.5%), and targeted therapies (everolimus, 28.0%).

The duration of metastatic disease (date of Stage IV disease diagnosis to date of first dose of study drug) was 27.6 months (range 0.1 to 228.9).

Demographics and baseline characteristics are outlined in Table 25.

Table 25: Baseline Demographic and Pre-Treatment Disease Characteristics for the Intent to Treat (ITT) Population – MONARCH 1

	Demographic Parameter	Single Agent VERZENIO (N=132)
Age (years)	Median age (range)	58.0 (36.0-89.0)
Age group n (%)	Age <65 years Age ≥65 years	90 (68.2) 42 (31.8)
Race, n (%)[a]	White Black Asian	112 (84.8) 6 (4.5) 2 (1.5)
ECOG performance status (PS), n (%)	0 1	73 (55.3) 59 (44.7)

Disease site, n (%)	Visceral
	  Liver
	  Lung
	Bone
	  Bone Only
		119 (90.2)
		93 (70.5)
		31 (23.5)
		82 (62.1)
		3 (2.3)

Number of Metastatic Sites, n (%)	1 2 ≥3	19 (14.4) 46 (34.8) 67 (50.8)

Prior Therapy Regimens in Metastatic Setting, n (%)	Prior Endocrine Therapy
	  1 regimen
	  2 regimens
	  3 regimens
	  ≥4 regimes
	Prior Chemotherapy
	  1 regimen
	  2 regimens
	  3 regimens
		
		48 (36.4)
		25 (18.9)
		24 (18.2)
		18 (13.6)
		
		67 (50.8)
		64 (48.5)
		1 (0.8)

Abbreviation: ECOG = Eastern Cooperative Oncology Group.

[a] Race not reported for 9.1%.

14.6 MONARCH 1 – Study Results

The primary efficacy outcome measure was confirmed objective response rate (ORR) by investigator assessment as defined by RECIST V1.1. Secondary efficacy endpoints included Duration of Response (DoR). An independent radiographic review of scans was also performed for efficacy assessment.

Efficacy results from the MONARCH 1 study are summarized in Table 26.

Table 26: Efficacy Results of MONARCH 1– Intent-to-Treat (ITT) Population

	Single Agent VERZENION=132	
	Investigator Assessed	**Independent Review**
Objective Response Rate[a], n (%)	26 (19.7)	23 (17.4)
95% CI (%)	13.3, 27.5	(11.4, 25.0)
Best Overall Response[a]		
Partial response, n (%)	26 (19.7)	23 (17.4)
Complete response, n (%)	0	0
Duration of Response[a]		
Duration of response, median, months	8.6	7.2
95% CI (%)	5.8, 10.2	5.6, NR

Abbreviations: CI = confidence interval, NR = not reached, RECIST = Response Evaluation Criteria in Solid Tumors.

[a] Evaluated according to RECIST version 1.1.

15 NON-CLINICAL TOXICOLOGY

General Toxicity

Repeat-dose oral toxicity studies were conducted in rats and dogs for up to 3 months. The primary target organs associated with daily dosing of abemaciclib in rats and dogs were the bone marrow, gastrointestinal tract, lymphoid tissues, and male reproductive tract. Morphologic changes in these organs were consistent with antiproliferative effects in rapidly dividing cells, including peripheral blood cytopenias and bone marrow hypocellularity; crypt necrosis/hyperplasia and villous atrophy in the intestines; lymphoid depletion; and hypospermatogenesis and atrophy in the testis. Effects in lung (alveolar macrophage accumulation and bronchoalveolar inflammation) were observed in rats and dogs at exposure levels approximately 2 times and 0.1 times the exposure (AUC) in humans at the recommended dose, respectively. Effects in kidney (tubular degeneration/regeneration, vacuolation, dilatation) and skeletal muscles (myofiber degeneration) only occurred in rats at exposure levels approximately 6 times higher than the human exposure levels. Complete or partial recovery was observed for all target organs at the end of the 28-day recovery period, with the exception of the effects on the male reproductive tract.

Carcinogenicity

Long-term studies to assess carcinogenic potential of abemaciclib have not been performed.

Genotoxicity

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 was not clastogenic in an in vivo rat bone marrow micronucleus assay.

Reproductive and Developmental Toxicity

Fertility Studies

Studies to assess the effects of abemaciclib on fertility have not been performed. 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. No effects on female reproductive organs were observed in repeat-dose toxicity studies.

Embryo-Fetal Development Studies

In an embryo-fetal development study, pregnant rats received oral doses of abemaciclib up to 15 mg/kg/day during the period of organogenesis; abemaciclib was teratogenic. 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.

Special Toxicity Studies

Abemaciclib was not phototoxic in a rat phototoxicity study at oral dose levels up to 40 mg/kg. Abemaciclib did not cause dermal toxicity in a rat study in which abemaciclib was applied to the skin at dose levels up to 2000 mg/kg. Abemaciclib was not an irritant in a bovine corneal opacity and permeability test.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

PrVERZENIO™
Abemaciclib Tablets

Read this carefully before you start taking **VERZENIO™** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **VERZENIO**.

Your breast cancer may be treated with VERZENIO in combination with another drug. Read the patient leaflet for the other drug as well as this one.

Serious Warnings and Precautions

Only a doctor who has experience treating cancer should treat you with this drug.
Venous Thromboembolism
Venous thromboembolism refers to a blood clot. Blood clots can happen in any vein. Together they are called **Venous Thromboembolism**. In some patients it can lead to death.
It includes:

- deep vein thrombosis (DVT): blood clot in a large vein
- pulmonary embolism: blood clot in the lung
- pelvic venous thrombosis: blood clot in the pelvis
- cerebral venous thrombosis: blood clot in the brain
- blood clots in other veins such as in the abdomen, armpit, or on the way to the heart

The symptoms are listed in the serious side effects and what to do about them table. It is found later in this leaflet.

What is VERZENIO used for?
VERZENIO is used to treat breast cancer in adult women, only when it has spread to other parts of the body. The breast cancer must be hormone receptor positive. It is taken:

- **with another drug for breast cancer** called an aromatase inhibitor. You must have already gone through menopause to take VERZENIO this way. This is an initial therapy.

Or

- **with another drug for breast cancer** called fulvestrant. This is used when the cancer gets worse after initial therapy. If you have not yet gone through menopause, you must take a medicine that will stop your ovaries from making estrogen.

Or

- **by itself**. You must have breast cancer that came back after having had hormone therapy and at least two kinds of prior chemotherapy treatment.

How does VERZENIO work?
Abemaciclib is a type of drug called a kinase inhibitor. It works by stopping cancer cells from dividing and growing. This may slow the growth and spread of breast cancer cells. It is given by itself, or together with other drugs (aromatase inhibitor or fulvestrant).

What are the ingredients in VERZENIO?
Medicinal ingredients: abemaciclib
Non-medicinal ingredients**:** croscarmellose sodium, lactose monohydrate, microcrystalline cellulose 101, microcrystalline cellulose 102, polyethylene glycol, polyvinyl alcohol, silicon dioxide, sodium stearyl fumarate, talc, titanium dioxide

Also contains:
50 mg and 200 mg tablets: iron oxide red, iron oxide yellow
150 mg tablet: iron oxide yellow

VERZENIO comes in the following dosage forms:
Tablets: 50 mg, 100 mg, 150 mg, and 200 mg

Do not use VERZENIO if:
- You are allergic to abemaciclib or any of the other ingredients of VERZENIO.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take VERZENIO. Talk about any health conditions or problems you may have, including if you:
- Have fever, chills, or any other signs of an infection
- Have liver or kidney problems
- Are pregnant or plan to become pregnant
- Are breast-feeding
- Are over 65 years old.

Other warnings you should know about:

Pregnancy, breast-feeding and fertility
Avoid getting pregnant while receiving this medicine and for at least 3 weeks after the last dose of VERZENIO. If you have not gone through menopause, you should have a pregnancy test done before you start treatment with VERZENIO. Talk to your healthcare professional about the best birth control for you. VERZENIO may cause harm to your unborn child. If you become pregnant, inform your doctor right away. Do not breast-feed your baby during treatment with VERZENIO and for at least 3 weeks after the last dose.

Sexual Health Male Patients
Before starting on VERZENIO you should know that it may affect your fertility. This may affect your ability to father a child. Talk to your healthcare professional if this is a concern for you.

Low white blood cell counts (neutropenia)
Low white blood cell counts are common while taking VERZENIO. They may cause serious infections that can cause death.

Infections
Serious infections can occur while taking VERZENIO. They may cause death.

Liver problems
VERZENIO can cause serious liver problems.

Diarrhea
VERZENIO can cause diarrhea. It may be severe at times. The most common time to start having diarrhea is during the first month of treatment. If you start having diarrhea, your healthcare professional may tell you to stop taking VERZENIO for a short time, decrease your dose, or stop your treatment. Cases of diarrhea have occurred with dehydration or an infection.

- **If you have any loose or liquid stools,** tell your healthcare professional right away. Start taking an antidiarrheal medicine (such as loperamide), and drink more fluids.

Children and adolescents
VERZENIO should not be given to patients under the age of 18 years.

Driving and Using Machines: Fatigue and dizziness can occur with VERZENIO. Before you do this wait until you know how you respond.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Keep a list of the medicines you are taking. Show your healthcare professional or pharmacist when you get a new medicine.

The following may interact with VERZENIO:

- Some medicines for fungal infections, such as ketoconazole, itraconazole, posaconazole and voriconazole
- Some medicines for infections (antibiotics), such as clarithromycin, ciprofloxacin, and rifampin
- Some medicines for high blood pressure, such as verapamil, and diltiazem
- HIV medicines, such as saquinavir, ritonavir, and nelfinavir
- Medicines to treat epilepsy, such as carbamazepine and phenytoin
- The diabetes medicine metformin
- Some medicines for acid reflux such as ranitidine
- Medicines used to treat congestive heart failure and abnormal heart rhythms, such as digoxin
- St. John's wort, a herbal product used to treat depression and other conditions (also known as *hypericum perforatum*)
- Do not eat grapefruit or drink grapefruit juice while on VERZENIO. This includes any products with grapefruit. Grapefruit may increase the amount of VERZENIO in your blood.

Other drugs not listed here may also interact.

How to take VERZENIO:

- Take exactly as your healthcare provider tells you.
- Take with or without food.
- Swallow tablets whole.
  - Do NOT chew, crush, or split the tablets.
  - Do NOT take damaged tablets.
- Take doses at approximately the same time every day.
- If you vomit after taking a dose, take your next dose at your regular time.
- Your healthcare professional may decide to delay, stop, interrupt, decrease, or reduce your dose. This may occur if you get side effects.

- Take VERZENIO for as long as your healthcare professional recommends.

Usual adult dose: 1 tablet two times a day.

When VERZENIO **is taken with another drug for breast cancer:** 150 mg two times a day (total of 300 mg a day).

When VERZENIO **is taken by itself**: 200 mg two times a day (total of 400 mg a day).

The smallest dose is: 50 mg two times a day.

If you have severe liver problems your dose will be 1 tablet once a day.

If you start having side effects including diarrhea, you may be told to delay or stop taking VERZENIO for a short time. Or, you may need to decrease your dose, or stop your treatment.

Overdose:

If you think you have taken too much VERZENIO, contact your healthcare professional, hospital emergency department or regional poison control center immediately, even if there are no symptoms.

Missed dose:
If you miss a dose of VERZENIO, take your next dose at your regular time. Do not take 2 doses of VERZENIO at the same time.

What are possible side effects from using VERZENIO?

These are not all the possible side effects you may feel when taking VERZENIO. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:
- Nausea, vomiting, decreased appetite, abdominal pain
- Headache, dizziness
- Hair loss or thinning
- Feel faint or light-headed
- Tiredness, fatigue, muscle weakness
- Fracture or break a bone
- Rash, dry, itchy, infected or darkenedor painful skin
- Ongoing itchy inflammation of the skin, inflamed fat layer below the skin
- Palmar-plantar erythrodysesthesia syndrome: pain, swelling, numbness, tingling, redness, and sometimes flaking or blistering of the palms or soles
- Increased tears
- Eye pain and blurred vision
- Changes to your sense of taste, dry mouth, sores in mouth, difficulty swallowing

If you have not gone through menopause, you should have a pregnancy test before you start VERZENIO.

VERZENIO can cause abnormal blood test results. This includes increased creatinine and liver enzymes. Your healthcare professional will test your blood before you start on VERZENIO. They will then test it every 2 weeks for the first two months. Then once a month for two months and whenever they think it is needed. Your healthcare professional will tell you if your test results are abnormal and if you need treatment to correct these side effects.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON			
Leukopenia, neutropenia, lymphopenia (Low white blood cells): Chills, fever, infection. Fatigue, aches and pains, and flulike symptoms.		√	
Anemia (Low red blood cells): Being short of breath, feeling very tired, loss of energy, weakness.		√	
Thrombocytopenia (Low blood platelets): Bruising or bleeding for longer than usual if you hurt yourself. Fatigue, weakness.		√	
Liver Problems: Feeling very tired with loss of appetite, pain on the upper right side of your stomach area (abdomen).		√	
Diarrhea: At the first sign of loose or liquid stools.		√	
COMMON			
Venous Thromboembolism (Blood clots in veins): Swelling, redness and pain in one part of the body, arms or legs. This can be warm to touch. Sudden chest pain, rapid breathing and heart rate, shortness of breath. If it is in your brain: severe headache. Feel numb, weak or cannot move arms, legs or face. Difficulty talking or seeing, fainting or passing out. Confusion. Dizziness, blurred vision, seizure (fit).		√	

Infections: Chills, cough, fever, runny nose, shortness of breath, or sore throat.		√	
Hypokalemia (Decreased potassium in the blood): Irregular heartbeats, muscle weakness and generally feeling unwell.		√	
Hypocalcemia (Low Level of Calcium in the Blood): Muscle cramps in the back and legs. Dry skin. Confusion and memory loss.		√	
Pneumonia (Infection in the lungs), Pneumonitis (Lung inflammation), or Pulmonary Fibrosis: New or worsening shortness of breath, cough, wheezing or fever. Difficult and painful breathing. Feel tired.		√	
Heart Problems (Tachycardia, atrial fibrillation, palpitations, heart failure): Fast or irregular heartbeat. Heart racing or skips a beat. Short of breath, fatigue and inability to exercise. Fluid in the legs.		√	
Kidney Problems (Inability of the kidneys to properly clean the blood): A change in the amount of urine you pass. Water retention with weight gain swelling of legs and ankles, puffy face or hands. Lack of appetite, nausea, vomiting, weakness. Itchy skin. Decreased concentration. Flank or lower back pain.		√	
Sepsis (Blood infection that is body wide): High fever, fast heart rate, and breathing.		√	
UNKNOWN FREQUENCY			
Allergic Reactions: Itch, rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing.			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Store at room temperature between 15°C to 30°C.

Keep VERZENIO and all medicines out of the reach and sight of children.

If you want more information about VERZENIO:
- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (http://hc-sc.gc.ca/index-eng.php); the manufacturer's website www.lilly.ca, or by calling 1-888-545-5972.

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