Helping Specialty Practices Increase Patient Access to Clinical Research Opportunities
The ION Solutions Precision Medicine Center is your gateway to a single, centralized library of precision medicine testing recommendations and resources. Access all of the testing recommendations created by our physician- and pharmacist-based advisory panel as well as resources curated by ION Solutions and our precision medicine partners to help you make informed decisions for your patients.

View testing recommendations by tumor categories:
- Breast Cancer
- NSCLC
- Colorectal
- Genitourinary
- Lymphoma
- Rare Disease

As precision medicine continues to evolve, ION will continue to provide the tools your practice needs.
Precision Medicine Center

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# Table of Contents

**Winter 2018**

<table>
<thead>
<tr>
<th>Page</th>
<th>Section Title and Descriptive Text</th>
</tr>
</thead>
</table>
| 6    | *Helping Specialty Practices Increase Patient Access to Clinical Research Opportunities*  
By Tricia Musslewhite |
| 14   | **MIPS Tips**  
*It’s Not Too Late to Ask for Help with 2018 MIPS Data Submission* |
| 20   | **What’s News at ION**  
*Michigan Healthcare Professionals Joins ION Solutions GPO Network* |
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To learn what InfoDive can do to improve your operational efficiency, email us at info@intrinsiq.com or contact your Oncology Supply sales representative.
Patient enrollment into clinical trials is a significant challenge as practices lack the specialized staff and dedicated time to support clinical research. To ease this burden, in 2016 IntrinsiQ Specialty Solutions, a part of AmerisourceBergen, launched AdvanceIQ Network to match independent community oncology and urology practices with clinical research opportunities to increase patient access to the most advanced therapies and treatment strategies.

Of course, AdvanceIQ Network helps practices enroll patients in clinical trials, but it is much broader than that. The research network also facilitates investigator research, prospective patient registries, retrospective outcomes research studies and evidence-based studies through a network of life sciences partners. Those partners recognize that one of the networks strengths is its ability to connect with specialty practices and increase patient enrollment into the studies. This is important because “as science propels cancer treatments forward, clinical trials are increasingly designed around very small genetically defined subsets of cancers, making finding eligible patients even more difficult.”

“If a practice has a study in mind or they’re looking for a specific study for a patient they can always contact us,” said Clinical Research Senior Manager Ganiat Mumuney. “We offer studies to practices, but we also want to encourage our practices to reach out to us when they have a patient in need of a new or different therapy option, for which they do not have access.”

Among current activities, the network is working with two pharmaceutical companies on three rare tumor trials. With more than 30 million Americans with rare diseases, safe and effective products are critical to those patients’ quality of life.

“It is hard to find appropriate patients. We are looking for more participation from our practices to better inform available evidence,” said Mumuney.
AdvanceIQ Network also is qualifying practices for a patient registry trial that could begin as early as the end of 2018. This study will compare the different drug delivery options available for an existing marketed drug to see if there is an impact on clinical and economic outcomes.

Specialty practices want to offer patients access to clinical trials and other research, but a lack of resources often creates an administrative burden. And keeping up with the volume of studies that are available can be difficult for research directors and coordinators. AdvanceIQ Network seeks to remove the obstacles practices face by significantly lowering administrative overhead, time commitment and associated costs and streamlining the process of identifying, qualifying for and enrolling in clinical research. As part of the program, participating practices and their physicians will receive support such as contract management resources, ongoing research education and training and grant submission coaching.

“We’ve made so many advancements that enable practices to actively participate on studies more quickly. It used to be it would take nine to 12 months to even get into the study. Today it can be as little as 10 to 14 days. If a practice can’t respond quickly then basically they lose those opportunities. Participating in a research network that is set up to have access to those types of trials significantly changes the game from what it used to be,” said Susan Weidner, Senior Vice President, IntrinsiQ Specialty Solutions.

For more information about clinical research opportunities available through AdvanceIQ Network, send an email to advanceiq@intrinsiq.com.


Tricia Musslewhite is manager, marketing and communications, at AmerisourceBergen.
As true leaders in industry, true innovators in care and true partners in service, ION Solutions has been dedicated to fighting for community oncology for 20 years.

One of the ways we demonstrate our commitment to independent community oncology is through our advocacy efforts on Capitol Hill.

Since 2015, Community Counts has raised awareness on the impact of sequestration, the Part B Demo Project, and other issues paramount to the viability of the community setting. Just last year, more than 500 individuals contacted 280 legislators through this outreach program.

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ION Solutions
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CommunityCountsAdvocacy.org
EXTEND YOUR KNOWLEDGE
ABOUT AN ALL-ORAL TRIPLET REGIMEN

Q&A WITH DR. KEN SHAIN*
Multiple myeloma expert

The multiple myeloma treatment landscape has evolved over the past few years, and more options have emerged. Dr. Shain discusses treatment with a proteasome inhibitor and explains how the NINLARO® (ixazomib) regimen may offer an option for myeloma patients who have received at least 1 prior therapy.

NINLARO is indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy.

Important Safety Information

Warnings and Precautions

- **Thrombocytopenia** has been reported with NINLARO. During treatment, monitor platelet counts at least monthly, and consider more frequent monitoring during the first three cycles. Manage thrombocytopenia with dose modifications and platelet transfusions as per standard medical guidelines. Adjust dosing as needed. Platelet nadirs occurred between Days 14-21 of each 28-day cycle and typically recovered to baseline by the start of the next cycle.

*Dr. Shain is a paid consultant of Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited. This content is intended for informational purposes only and is not a substitute for your clinical knowledge or professional judgment.
LOOKING AT TREATMENT STRATEGIES WITH DR. KEN SHAIN

NINLARO* (ixazomib) is indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy.

Q. How do triplet regimens fit into your approach for long-term* multiple myeloma care?
A. Clinical studies show that triplet therapy improves outcomes vs doublet therapy. Our goal is to gain control of the disease with combination therapy that is specific to the individual needs of our patients. Data have shown that triplet therapy may improve outcomes vs doublet therapy for appropriate patients.1-4

Q. Why is long-term treatment with a proteasome inhibitor (PI) so important in multiple myeloma?
A. Data show that long-term PI-based therapy can improve outcomes.1 While depth of response is important, my ultimate goal is to try to keep my patients’ disease under control for as long as possible, which often means treating with a PI-based regimen until disease progression or unacceptable toxicity.

Q. Is there a benefit of continuing PI-based treatment until disease progression or unacceptable toxicity?
A. This approach is associated with clinical benefits. However, most patients who have had at least 1 prior therapy only receive a PI for 4 to 7 months.5-7 In my experience, common reasons for this are cumulative toxicity and logistical issues. Toxicity becomes a key consideration with triplet regimens, as are the logistical challenges that patients may face with frequent visits to the clinic. For these reasons, many doctors may decide to switch to doublet therapy, often dropping the PI, even if the patient is showing improvement on a triplet regimen.

Q. What do you tell your patients when you place them on a treatment plan with the NINLARO regimen?
A. I explain to my patients that while multiple myeloma is not a disease we can cure currently, we can do our best to control it for as long as possible. I let my patients know that they’re not alone, and we’ll walk alongside them on the path of their treatment journey.

*Defined as treatment to progression or unacceptable toxicity.

Warnings and Precautions (cont’d)

Gastrointestinal Toxicities, including diarrhea, constipation, nausea and vomiting, were reported with NINLARO and may occasionally require the use of antidiarrheal and antiemetic medications, and supportive care. Diarrhea resulted in the discontinuation of one or more of the three drugs in 1% of patients in the NINLARO regimen and < 1% of patients in the placebo regimen. Adjust dosing for severe symptoms.

Peripheral Neuropathy (predominantly sensory) was reported with NINLARO. The most commonly reported reaction was peripheral sensory neuropathy (19% and 14% in the NINLARO and placebo regimens, respectively). Peripheral motor neuropathy was not commonly reported in either regimen (< 1%). Peripheral neuropathy resulted in discontinuation of one or more of the three drugs in 1% of patients in both regimens. Monitor patients for symptoms of peripheral neuropathy and adjust dosing as needed.

Peripheral Edema was reported with NINLARO. Monitor for fluid retention. Investigate for underlying causes when appropriate and provide supportive care as necessary. Adjust dosing of dexamethasone per its prescribing information or NINLARO for Grade 3 or 4 symptoms.

Cutaneous Reactions: Rash, most commonly maculo-papular and macular rash, was reported with NINLARO. Rash resulted in discontinuation of one or more of the three drugs in < 1% of patients in both regimens. Manage rash with supportive care or with dose modification.

Hepatotoxicity has been reported with NINLARO. Drug-induced liver injury, hepatocellular injury, hepatic steatosis, hepatitis cholestatic and hepatotoxicity have each been reported in < 1% of patients treated with NINLARO. Events of liver impairment have been reported (6% in the NINLARO regimen and 5% in the placebo regimen). Monitor hepatic enzymes regularly during treatment and adjust dosing as needed.

Embryo-fetal Toxicity: NINLARO can cause fetal harm. Women should be advised of the potential risk to a fetus, to avoid becoming pregnant, and to use contraception during treatment and for an additional 90 days after the final dose of NINLARO. Women using hormonal contraceptives should also use a barrier method of contraception.
The NINLARO regimen extended median progression-free survival (PFS) by ~6 months vs the placebo regimen.

TOURMALINE-MM1: a global, phase 3, randomized (1:1), double-blind, placebo-controlled study that evaluated the safety and efficacy of NINLARO (ixazomib+lenalidomide+dexamethasone) vs placebo (placebo+lenalidomide+dexamethasone) until disease progression or unacceptable toxicity in 722 patients with relapsed and/or refractory multiple myeloma who received 1-3 prior therapies.¹

Patients who were refractory to lenalidomide or PIs were excluded from the study.

TO LEARN MORE ABOUT NINLARO, VISIT NINLAROHCP.COM

Adverse Reactions
The most common adverse reactions (≥20%) in the NINLARO regimen and greater than the placebo regimen, respectively, were diarrhea (42%, 36%), constipation (34%, 25%), thrombocytopenia (78%, 54%; pooled from adverse events and laboratory data), peripheral neuropathy (28%, 21%), nausea (26%, 21%), peripheral edema (25%, 18%), vomiting (22%, 11%), and back pain (21%, 16%). Serious adverse reactions reported in ≥2% of patients included thrombocytopenia (2%) and diarrhea (2%).

Special Populations
• **Hepatic Impairment:** Reduce the NINLARO starting dose to 3 mg in patients with moderate or severe hepatic impairment.
• **Renal Impairment:** Reduce the NINLARO starting dose to 3 mg in patients with severe renal impairment or end-stage renal disease requiring dialysis. NINLARO is not dialyzable.
• **Lactation:** Advise nursing women not to breastfeed during treatment with NINLARO and for 90 days after the last dose.

Drug Interactions: Avoid concomitant administration of NINLARO with strong CYP3A inducers.


Please see the Brief Summary on the adjacent pages.
BRIEF SUMMARY OF PRESCRIBING INFORMATION

NINLARO (ixazomib) capsules, for oral use

1 INDICATION

NINLARO (ixazomib) is indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy.

5 WARNINGS AND PRECAUTIONS

5.1 Thrombocytopenia: Thrombocytopenia has been reported with NINLARO with platelet nadirs typically occurring between Days 14-21 of each 28-day cycle and recovery to baseline by the start of the next cycle. Three percent of patients in the NINLARO regimen and 1% of patients in the placebo regimen had a platelet count ≤ 10,000/mm3 during treatment. Less than 1% of patients in both regimens had a platelet count ≤ 5000/mm3 during treatment. Discontinuations due to thrombocytopenia were similar in both regimens (< 1% of patients in the NINLARO regimen and 2% of patients in the placebo regimen discontinued one or more of the three drugs). The rate of platelet transfusions was 6% in the NINLARO regimen and 5% in the placebo regimen.

Monitor platelet counts at least monthly during treatment with NINLARO. Consider more frequent monitoring during the first three cycles. Manage thrombocytopenia with dose modifications and platelet transfusions as per standard medical guidelines.

5.2 Gastrointestinal Toxicities: Diarrhea, constipation, nausea, and vomiting, have been reported with NINLARO, occasionally requiring use of antidiarrheal and antiemetic medications, and supportive care. Diarrhea was reported in 42% of patients in the NINLARO regimen and 36% in the placebo regimen, constipation in 34% and 25%, respectively, nausea in 26% and 21%, respectively, and vomiting in 22% and 11%, respectively. Diarrhea resulted in discontinuation of one or more of the three drugs in 1% of patients in the NINLARO regimen and < 1% of patients in the placebo regimen. Adjust dosing for Grade 3 or 4 symptoms.

5.3 Peripheral Neuropathy: The majority of peripheral neuropathy adverse reactions were Grade 1 (18% in the NINLARO regimen and 14% in the placebo regimen) and Grade 2 (8% in the NINLARO regimen and 5% in the placebo regimen). Grade 3 adverse reactions of peripheral neuropathy were reported at 2% in both regimens; there were no Grade 4 or serious adverse reactions. The most commonly reported reaction was peripheral sensory neuropathy (19% and 14% in the NINLARO and placebo regimen, respectively). Peripheral motor neuropathy was not commonly reported in either regimen (< 1%). Peripheral neuropathy resulted in discontinuation of one or more of the three drugs in 1% of patients in both regimens. Patients should be monitored for symptoms of neuropathy. Patients experiencing new or worsening peripheral neuropathy may require dose modification.

5.4 Peripheral Edema: Peripheral edema was reported in 25% and 18% of patients in the NINLARO and placebo regimens, respectively. The majority of peripheral edema adverse reactions were Grade 1 (16% in the NINLARO regimen and 13% in the placebo regimen) and Grade 2 (7% in the NINLARO regimen and 4% in the placebo regimen).

Grade 3 peripheral edema was reported in 2% and 1% of patients in the NINLARO and placebo regimens, respectively. There was no Grade 4 peripheral edema reported. There were no discontinuations reported due to peripheral edema. Evaluate for underlying causes and provide supportive care, as necessary. Adjust dosing of dexamethasone to its prescribing information or NINLARO for Grade 3 or 4 symptoms.

5.5 Cutaneous Reactions: Rash was reported in 19% of patients in the NINLARO regimen and 11% of patients in the placebo regimen. The majority of the rash adverse reactions were Grade 1 (10% in the NINLARO regimen and 7% in the placebo regimen) or Grade 2 (6% in the NINLARO regimen and 3% in the placebo regimen). Grade 3 rash was reported in 3% of patients in the NINLARO regimen and 1% of patients in the placebo regimen. There were no Grade 4 or serious adverse reactions of rash reported. The most common type of rash reported in both regimens included maculo-papular and macular rash. Rash resulted in discontinuation of one or more of the three drugs in < 1% of patients in both regimens. Manage rash with supportive care or with dose modification if Grade 2 or higher.

5.6 Hepatotoxicity: Drug-induced liver injury, hepatocellular injury, hepatic steatosis, hepatic cholesterol and hepatotoxicity have each been reported in < 1% of patients treated with NINLARO. Events of liver impairment have been reported (6% in the NINLARO regimen and 5% in the placebo regimen). Monitor hepatic enzymes regularly and adjust dosing for Grade 3 or 4 symptoms.

5.7 Embryo-Fetal Toxicity: NINLARO can cause fetal harm when administered to a pregnant woman based on the mechanism of action and findings in animals. There are no adequate and well-controlled studies in pregnant women using NINLARO. Ixazomib caused embryo-fetal toxicity in pregnant rats and rabbits at doses resulting in exposures that were slightly higher than those observed in patients receiving the recommended dose.

Females of reproductive potential should be advised to avoid becoming pregnant while being treated with NINLARO. If NINLARO is used during pregnancy or if the patient becomes pregnant while taking NINLARO, the patient should be apprised of the potential hazard to the fetus. Advise females of reproductive potential that they must use effective contraception during treatment with NINLARO and for 90 days following the final dose. Women using hormonal contraceptives should also use a barrier method of contraception.

6 ADVERSE REACTIONS

The following adverse reactions are described in detail in other sections of the prescribing information:

- Thrombocytopenia [see Warnings and Precautions (5.1)]
- Gastrointestinal Toxicities [see Warnings and Precautions (5.2)]
- Peripheral Neuropathy [see Warnings and Precautions (5.3)]
- Peripheral Edema [see Warnings and Precautions (5.4)]
- Cutaneous Reactions [see Warnings and Precautions (5.5)]
- Hepatotoxicity [see Warnings and Precautions (5.6)]

6.1 CLINICAL TRIALS 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 from the randomized, double-blind, placebo-controlled clinical study included 720 patients with relapsed and/or refractory multiple myeloma, who received NINLARO in combination with lenalidomide and dexamethasone (NINLARO regimen; N=360) or placebo in combination with lenalidomide and dexamethasone (placebo regimen; N=360).

The most frequently reported adverse reaction (≥ 20%) in the NINLARO regimen and greater than the placebo regimen were diarrhea, constipation, thrombocytopenia, peripheral neuropathy, nausea, peripheral edema, vomiting, and back pain. Serious adverse reactions reported in ≥ 2% of patients included thrombocytopenia (2%) and diarrhea (2%). For each adverse reaction, one or more of the three drugs was discontinued in ≤ 1% of patients in the NINLARO regimen.

6.2 NON-HEMATOLOGIC ADVERSE REACTIONS OCCURRING IN ≥ 5% OF PATIENTS WITH A ≥ 5% DIFFERENCE BETWEEN THE NINLARO REGIMEN AND THE PLACEBO REGIMEN (ALL GRADES, GRADE 3 AND GRADE 4)

<table>
<thead>
<tr>
<th>System Organ Class / Preferred Term</th>
<th>NINLARO + Lenalidomide and Dexamethasone</th>
<th>Placebo + Lenalidomide and Dexamethasone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=360</td>
<td>N=360</td>
</tr>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>All</td>
<td>N=360</td>
<td>N=360</td>
</tr>
<tr>
<td>All</td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>69 (19)</td>
<td>52 (14)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral neuropathy*</td>
<td>100 (28)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>151 (42)</td>
<td>136 (38)</td>
</tr>
<tr>
<td>Constipation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>92 (26)</td>
<td>74 (21)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>79 (22)</td>
<td>38 (11)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash*</td>
<td>68 (19)</td>
<td>38 (11)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>74 (21)</td>
<td>57 (16)</td>
</tr>
<tr>
<td>Back pain</td>
<td>2 (1)</td>
<td>0</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Edema peripheral</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

Note: Adverse reactions included as preferred terms are based on MedDRA version 16.0.

*Represents a pooling of preferred terms

(Continued on next page)
**Brief Summary (cont’d)**

**Table 5: Thrombocytopenia and Neutropenia (pooled adverse event and laboratory data)**

<table>
<thead>
<tr>
<th></th>
<th>NINLARO + Lenalidomide and Dexamethasone N=360</th>
<th>Placebo + Lenalidomide and Dexamethasone N=360</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade Grade 3-4</td>
<td>Any Grade Grade 3-4</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>281 (78) 93 (26)</td>
<td>196 (54) 39 (11)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>240 (67) 93 (26)</td>
<td>239 (66) 107 (30)</td>
</tr>
</tbody>
</table>

**8 USE IN SPECIFIC POPULATIONS**

**8.1 Pregnancy:**

**Risk Summary:** Based on its mechanism of action and data from animal reproduction studies, NINLARO can cause fetal harm when administered to a pregnant woman. There are no human data available regarding the potential effect of NINLARO on pregnancy or development of the embryo or fetus. Ixazomib caused embryo-fetal toxicity in pregnant rats and rabbits at doses resulting in exposures that were slightly higher then those observed in patients receiving the recommended dose. Advise women of the potential risk to a fetus and to avoid becoming pregnant while being treated with NINLARO. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20% respectively. Animal Data: In an embryo-fetal development study in pregnant rabbits there were increases in fetal skeletal variations/abnormalities (caudal vertebrae, number of lumbar vertebrae, and full supernumerary ribs) at doses that were also maternally toxic (> 0.3 mg/kg). Exposures in the rabbit at 0.3 mg/kg were 1.9 times the clinical time averaged exposures at the recommended dose of 4 mg. In a rat dose range-finding embryo-fetal development study, at doses that were maternally toxic, there were decreases in fetal weights, a trend towards decreased fetal viability, and increased post-implantation losses at 0.6 mg/kg. Exposures in rats at the dose of 0.6 mg/kg was 2.5 times the clinical time averaged exposures at the recommended dose of 4 mg.

**8.2 Lactation:** No data are available regarding the presence of NINLARO or its metabolites in human milk, the effects of the drug on the breast fed infant, or the effects of the drug on milk production. Because the potential for serious adverse reactions from NINLARO in breastfed infants is unknown advise nursing women not to breastfeed during treatment with NINLARO and for 90 days after the last dose.

**8.3 Females and Males of Reproductive Potential:**

**Contraception** - Male and female patients of childbearing potential must use effective contraceptive measures during and for 90 days following treatment. Dexamethasone is known to be a weak to moderate inducer of CYP3A4 as well as other enzymes and transporters. Because NINLARO is administered with dexamethasone, the risk for reduced efficacy of contraceptives needs to be considered. Advise women using hormonal contraceptives to also use a barrier method of contraception.

**8.4 Pediatric Use:** Safety and effectiveness have not been established in pediatric patients.

8.5 Gastrointestinal Use: Of the total number of subjects in clinical studies of NINLARO, 55% were 65 and over, while 17% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

**8.6 Hepatic Impairment:** In patients with moderate or severe hepatic impairment, the mean AUC increased by 20% when compared to patients with normal hepatic function. Reduce the starting dose of NINLARO in patients with moderate or severe hepatic impairment.

**8.7 Renal Impairment:** In patients with severe renal impairment or ESRD requiring dialysis, the mean AUC increased by 39% when compared to patients with normal renal function. Reduce the starting dose of NINLARO in patients with severe renal impairment or ESRD requiring dialysis, NINLARO is not dialyzable and therefore can be administered without regard to the timing of dialysis.

**10 OVERDOSAGE:** There is no known specific antidote for NINLARO overdose. In the event of an overdose, monitor the patient for adverse reactions and provide appropriate supportive care.

**17 PATIENT COUNSELING INFORMATION**

Advising the patient to read the FDA-approved patient labeling (Patient Information).

**Dosing Instructions**

- Instruct patients to take NINLARO exactly as prescribed.
- Advise patients to take NINLARO once a week on the same day and at approximately the same time for the first three weeks of a four week cycle.
- Advise patients to take NINLARO at least one hour before or at least two hours after food.
- Advise patients that NINLARO and dexamethasone should be taken at the same time, because dexamethasone should be taken with food and NINLARO should not be taken with food.
- Advise patients to swallow the capsule whole with water. The capsule should not be crushed, chewed or opened.
- Advise patients that direct contact with the capsule contents should be avoided. In case of capsule breakage, avoid direct contact of capsule contents with the skin or eyes. If contact occurs with the skin, wash thoroughly with soap and water. If contact occurs with the eyes, flush thoroughly with water.
- If a patient misses a dose, advise them to take the missed dose as long as it is within 72 hours after the next scheduled dose.
- If a patient vomits after taking a dose, advise them not to repeat the dose but resume dosing at the time of the next scheduled dose.
- Advise patients to store capsules in original packaging, and not to remove the capsule from the packaging until just prior to taking NINLARO.

**Thrombocytopenia:** Advise patients that they may experience low platelet counts (thrombocytopenia). Signs of thrombocytopenia may include bleeding and easy bruising.

**Gastrointestinal Toxicities:** Advise patients they may experience diarrhea, constipation, nausea and vomiting and to contact their physician if these adverse reactions persist.

**Peripheral Neuropathy:** Advise patients to contact their physicians if they experience new or worsening symptoms of peripheral neuropathy such as numbness, pain, a burning feeling in the feet or hands, or weakness in the arms or legs.

**Peripheral Edema:** Advise patients to contact their physicians if they experience unusual swelling of their extremities or weight gain due to swelling.

**Cutaneous Reactions:** Advise patients to contact their physicians if they experience new or worsening rash.

**Hepatotoxicity:** Advise patients to contact their physicians if they experience signs and symptoms of acute febrile neutrophilic dermatosis (Sweet’s syndrome), Stevens-Johnson syndrome, transverse myelitis, posterior reversible encephalopathy syndrome, tumor lysis syndrome, and thrombotic thrombocytopenic purpura.

**Pregnancy:** Advise women of the potential risk to a fetus and to avoid becoming pregnant while being treated with NINLARO and for 90 days following the final dose. Advise women using hormonal contraceptives to also use a barrier method of contraception. Advise patients to contact their physicians immediately if they or their female partner become pregnant during treatment or within 90 days of the final dose.

**Concomitant Medications:** Advise patients to speak with their physicians about any other medication they are currently taking and before starting any new medications.

Please see full Prescribing Information for NINLARO at NINLARO-hcp.com.

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AUG 2018  MAT-US-KA-18-00350
MIPS Tips

Information to help your practice successfully meet all MIPS measures

It’s Not Too Late to Ask for Help with 2018 MIPS Data Submission

Gathering and submitting data for the Centers for Medicare & Medicaid Services’ Quality Payment Program can be overwhelming – especially to the practice that does not have the luxury of a dedicated resource handling the MIPS (Merit-based Incentive Payment System) performance measures. With the different formats for submission, and differing performance periods (Quality must be submitted for a full year, while Promoting Interoperability must be a minimum of 90 days), the process is complicated.

In addition, the practice must keep a record of all data submitted to ensure it is receiving the accurate number of points and reimbursement adjustment. Also, CMS can audit a practice up to six years after a submission has been completed and recommends maintaining records for up to 10 years.

As the reimbursement adjustment for Medicare Part B payments goes to +/- 9 percent by 2022, the impact to a practice could be significant. Any upward payment adjustment is better than a neutral or downward payment adjustment. Your performance will also be publicly reported on Physician Compare, so your scores may impact your practice reputation.

It is not too late to get help for your 2018 data submission. The Quality Reporting Engagement Group offers a Submission Assistance option to assist your practice in collecting all available data and ensure your clinicians submit the required components to earn you the maximum number of points possible.

If you are interested in speaking to one of the team members about how they can help your practice for 2018, contact sales@intrinsiq.com.
A recent study from the Medical Group Management Association (MGMA) found that physicians are increasingly burdened with both financial pressures on their practices and regulatory issues dealing with reimbursement.

With 426 medical practices responding, the majority (from 68% – 88%) were concerned with regulations around, in order of the top five:

- The Centers for Medicare & Medicaid Services’ (CMS) Quality Payment Program (MIPS/APMS) – as a point of reference, only 9 percent of the respondents in the study were satisfied or very satisfied with the performance feedback in MIPS
- Obtaining Prior Authorizations
- Lack of electronic health record (EHR) interoperability – as different vendors move toward their own version of interoperability, practices feel the software is becoming too costly to implement
- Government EHR requirements
- Audits and appeals processes

With the regulations and the burdens created on practices, physicians believe these are taking away from patient care. Study authors noted, “Empowering a variety of physicians to help shape new programs and initiatives may help to improve physician satisfaction, thereby hastening the move toward value.”

The message and problem were made clear: despite the Administration’s “Patients over Paperwork” plan and other initiatives in the last year, regulatory burden on physician practices continues to increase.

Many smaller practices or solo practitioner practices may be burdened with MIPS reporting, especially without a dedicated resource overseeing MIPS reporting. The Quality Reporting Engagement Group can help identify the most appropriate measures and submission methods and help your practice maximize potential reimbursements under the Quality Payment Program. To speak with one of the experts about how they can help your practice, send an email to sales@intrinsiq.com.
INDICATION
CYRAMZA, in combination with docetaxel, is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with disease progression on or after platinum-based chemotherapy. Patients with epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving CYRAMZA.

WARNING: HEMORRHAGE, GASTROINTESTINAL PERFORATION, AND IMPAIRED WOUND HEALING
Hemorrhage: CYRAMZA increased the risk of hemorrhage and gastrointestinal hemorrhage, including severe and sometimes fatal hemorrhagic events. Permanently discontinue CYRAMZA in patients who experience severe bleeding.

Gastrointestinal Perforation: CYRAMZA can increase the risk of gastrointestinal perforation, a potentially fatal event. Permanently discontinue CYRAMZA in patients who experience a gastrointestinal perforation.

Impaired Wound Healing: Impaired wound healing can occur with antibodies inhibiting the VEGF pathway. Discontinue CYRAMZA therapy in patients with impaired wound healing. Withhold CYRAMZA prior to surgery and discontinue CYRAMZA if a patient develops wound healing complications.

STUDY DESIGN
The phase III REVEL trial evaluated the efficacy and safety of CYRAMZA plus docetaxel vs placebo plus docetaxel in patients with mNSCLC with disease progression on or after platinum-based chemotherapy. Major efficacy outcome measure was OS. Supportive efficacy outcome measures were PFS and ORR. All patients were required to have ECOG PS 0 or 1. Patients were randomized 1:1 to receive either CYRAMZA 10 mg/kg (n=628) or placebo (n=625), in combination with docetaxel at 75 mg/m² every 21 days.

REVEL ITT Population (n=1253)

<table>
<thead>
<tr>
<th>Major Outcome Measure</th>
<th>OS (95% CI)</th>
<th>ORR (%)</th>
<th>PFS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYRAMZA + docetaxel</td>
<td>10.5 months</td>
<td>23%</td>
<td>4.5 months</td>
</tr>
<tr>
<td>Placebo + docetaxel</td>
<td>9.1 months</td>
<td>14%</td>
<td>3.0 months</td>
</tr>
</tbody>
</table>

HR=0.74 (95% CI: 0.68, 0.86) P<0.001

REVEL EXPLORATORY ANALYSIS
The REVEL trial was not adequately powered, nor error-controlled, for subgroup analysis. Treatment differences observed in this subgroup cannot be regarded as statistically significant. The analysis described here was post hoc and exploratory.

<table>
<thead>
<tr>
<th>Major Outcome Measure</th>
<th>OS (95% CI)</th>
<th>Supportive Outcome Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYRAMZA + docetaxel</td>
<td>9.1 months</td>
<td>19% Complete + partial response</td>
</tr>
<tr>
<td>Placebo + docetaxel</td>
<td>5.8 months</td>
<td>9% Complete + partial response</td>
</tr>
</tbody>
</table>

UNSTRATIFIED HR=0.74 (95% CI: 0.54, 1.00) P=0.024

INDICATION
CYRAMZA, in combination with docetaxel, is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with disease progression on or after platinum-based chemotherapy. Patients with epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving CYRAMZA.

IMPORTANT SAFETY INFORMATION FOR CYRAMZA

WARNING: HEMORRHAGE, GASTROINTESTINAL PERFORATION, AND IMPAIRED WOUND HEALING
Hemorrhage: CYRAMZA increased the risk of hemorrhage and gastrointestinal hemorrhage, including severe and sometimes fatal hemorrhagic events. Permanently discontinue CYRAMZA in patients who experience severe bleeding.

Gastrointestinal Perforation: CYRAMZA can increase the risk of gastrointestinal perforation, a potentially fatal event. Permanently discontinue CYRAMZA in patients who experience a gastrointestinal perforation.

Impaired Wound Healing: Impaired wound healing can occur with antibodies inhibiting the VEGF pathway. Discontinue CYRAMZA therapy in patients with impaired wound healing. Withhold CYRAMZA prior to surgery and discontinue CYRAMZA if a patient develops wound healing complications.
IMPORTANT SAFETY INFORMATION FOR CYRAMZA® (CONT’D)

Warnings and Precautions

Hemorrhage

- CYRAMZA increased the risk of hemorrhage and gastrointestinal hemorrhage, including severe and sometimes fatal hemorrhagic events. In study 3, which evaluated CYRAMZA plus docetaxel in metastatic non-small cell lung cancer (NSCLC), the incidence of severe bleeding was 2.4% for CYRAMZA plus docetaxel and 7.3% for placebo plus docetaxel. Patients with NSCLC receiving therapeutic anticancer or chronic therapy with NSAIDs or other antiplatelet therapy other than once-daily aspirin or with radiographic evidence of major airway or blood vessel invasion or intratumor cavitation were excluded from study 3, therefore, the risk of pulmonary hemorrhage in these groups of patients is unknown. Permanently discontinue CYRAMZA in patients who experience severe bleeding.

Arterial Thromboembolic Events (ATEs)

- Serious, sometimes fatal, ATEs including myocardial infarction, cardiac arrest, cerebrovascular accident, and cerebral ischemia occurred in clinical trials. Permanently discontinue CYRAMZA in patients who experience a severe ATE.

Hypertension

- An increased incidence of severe hypertension occurred in patients receiving CYRAMZA plus docetaxel (1.8%) as compared to placebo plus docetaxel (0.2%). Control hypertension prior to initiating treatment with CYRAMZA. Monitor blood pressure every 2 weeks or more frequently as indicated during treatment. Temporarily suspend CYRAMZA for severe hypertension until medically controlled. Permanently discontinue CYRAMZA if medically significant hypertension cannot be controlled with antihypertensive therapy or in patients with hypertensive crisis or hypertensive encephalopathy.

Infusion-Related Reactions (IRR)s

- Prior to the institution of premedication recommendations across clinical trials of CYRAMZA, IRRs occurred in 6 out of 37 patients (16%), including 2 severe events. The majority of IRRs across trials occurred during or following a first or second CYRAMZA infusion. Symptoms of IRRs included rigors/tremors, back pain/ spasms, chest pain and/or tightness, chills, flushing, dyspnea, wheezing, hypoxia, and parenthesis. In severe cases, symptoms included bronchospasm, supraventricular tachycardia, and hypertension. Monitor patients during the infusion for signs and symptoms of IRRs in a setting with available resuscitation equipment. Immediately and permanently discontinue CYRAMZA for grade 3 or 4 IRRs.

Gastrointestinal Perforations

- CYRAMZA is an antiangiogenic therapy that can increase the risk of gastrointestinal perforation, a potentially fatal event. In study 3, the incidence of gastrointestinal perforation was 1% for CYRAMZA plus docetaxel versus 0.3% for placebo plus docetaxel. Permanently discontinue CYRAMZA in patients who experience a gastrointestinal perforation.

Impaired Wound Healing

- Impaired wound healing can occur with antibodies inhibiting the VEGF pathway. CYRAMZA has not been studied in patients with serious or nonhealing wounds. CYRAMZA, as an antiangiogenic therapy, has the potential to adversely affect wound healing. Discontinue CYRAMZA therapy in patients with impaired wound healing. Withhold CYRAMZA prior to surgery. Resume CYRAMZA following the surgical intervention based on clinical judgment of adequate wound healing. If a patient develops wound healing complications during therapy, discontinue CYRAMZA until the wound is fully healed.

Clinical Deterioration in Child-Pugh B or C Cirrhosis

- Clinical deterioration, manifested by new onset or worsening encephalopathy, ascites, or hepatorenal syndrome, was reported in patients with Child-Pugh B or C cirrhosis who received single-agent CYRAMZA. Use CYRAMZA in patients with Child-Pugh B or C cirrhosis only if the potential benefits of treatment are judged to outweigh the risks of clinical deterioration.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

- RPLS has been reported at a rate of <0.1% in clinical studies with CYRAMZA. Confirm the diagnosis of RPLS with MRI and discontinue CYRAMZA in patients who develop RPLS. Symptoms may resolve or improve within days, although some patients with RPLS can experience ongoing neurologic sequelae or death.

Proteinuria Including Nephrotic Syndrome

- Monitor proteinuria by urine dipstick and/or urinary protein creatinine ratio for the development of worsening of proteinuria during CYRAMZA therapy. Withhold CYRAMZA for urine protein levels that are ≥2 g over 24 hours. Reinitiate CYRAMZA at a reduced dose once the urine protein level returns to ≤2 g per 24 hours. Permanently discontinue CYRAMZA for urine protein levels ≥3 g over 24 hours or in the setting of nephrotic syndrome.

Thyroid Dysfunction

- Monitor thyroid function during treatment with CYRAMZA.

Embryofetal Toxicity

- Based on its mechanism of action, CYRAMZA can cause fetal harm when administered to pregnant women. Animal models link angiogenesis, VEGF, and VEGF Receptor 2 (VEGFR2) to critical aspects of female reproduction, embryofetal development, and postnatal development. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with CYRAMZA and for at least 3 months after the last dose of CYRAMZA.

Most Common Adverse Reactions

- The most commonly reported adverse reactions (all grades: grade 3/4) occurring in ≥5% of patients receiving CYRAMZA plus docetaxel and ≥2% higher than placebo plus docetaxel in study 3 were neutropenia (55% vs 46%; 49% vs 40%), fatigue/asthenia (55% vs 50%; 14% vs 11%), stomatitis/mucosal inflammation (37% vs 19%; 7% vs 2%), epistaxis (19% vs 7%; <1% vs <1%), febrile neutropenia (16% vs 10%; 16% vs 10%), peripheral edema (16% vs 9%; 9% vs <1%), thrombocytopenia (13% vs 5%; 3% vs <1%), lactic acidosis increased (13% vs 5%; <1% vs 0%), and hypertension (11% vs 5%; 6% vs 2%).

- The most common serious adverse events with CYRAMZA plus docetaxel in study 3 were febrile neutropenia (14%), pneumonia (6%), and neutropenia (5%). The use of granulocyte colony-stimulating factors was 42% in CYRAMZA plus docetaxel–treated patients versus 37% in patients who received placebo plus docetaxel.

- In patients >65 years of age, there were 18 (8%) deaths on treatment or within 30 days of discontinuation for CYRAMZA plus docetaxel and 9 (4%) deaths for placebo plus docetaxel. The mortality in the placebo plus docetaxel group was 8%. In patients <65 years of age, there were 13 (5%) deaths on treatment or within 30 days of discontinuation for CYRAMZA plus docetaxel and 2 (1%) deaths for placebo plus docetaxel.

- Treatment discontinuation due to adverse reactions occurred more frequently in CYRAMZA plus docetaxel–treated patients (9%) than in placebo plus docetaxel–treated patients (5%). The most common adverse events leading to treatment discontinuation of CYRAMZA were infusion-related reaction (0.5%) and epistaxis (0.3%).

- For patients with nonsquamous histology, the overall incidence of pulmonary hemorrhage was 7% and the incidence of grade ≥3 pulmonary hemorrhage was 1% for CYRAMZA plus docetaxel compared to 6% overall incidence and 1% for grade ≥3 pulmonary hemorrhage for placebo plus docetaxel. For patients with squamous histology, the overall incidence of pulmonary hemorrhage was 10% and the incidence of grade ≥3 pulmonary hemorrhage was 2% for CYRAMZA plus docetaxel compared to 12% overall incidence and 5% for grade ≥3 pulmonary hemorrhage for placebo plus docetaxel.

- Clinically relevant adverse reactions reported in ≥1% and <5% of CYRAMZA plus docetaxel–treated patients in study 3 were hypertension (4.8% CYRAMZA plus docetaxel versus 2.4% for placebo plus docetaxel) and proteinuria (3.3% CYRAMZA plus docetaxel versus 0.8% placebo plus docetaxel).

Drug Interactions

- No pharmacokinetic interactions were observed between ramucirumab and docetaxel.

Use in Specific Populations

- Pregnancy: Based on its mechanism of action, CYRAMZA can cause fetal harm. Animal models link angiogenesis, VEGF, and VEGF Receptor 2 (VEGFR2) to critical aspects of female reproduction, embryofetal development, and postnatal development. There are no available data on CYRAMZA use in pregnant women to inform any drug-associated risks. No animal studies have been conducted to evaluate the effect of ramucirumab on reproduction and fetal development. Advise females of reproductive potential of the potential risk for maintaining pregnancy, risk to the fetus, and risk to newborn and infant development, and to use effective contraception during CYRAMZA therapy and for at least 3 months following the last dose of CYRAMZA.

- Lactation: Because of the potential risk for serious adverse reactions in nursing infants from ramucirumab, advise women that breastfeeding is not recommended during treatment with CYRAMZA.

- Females of Reproductive Potential: Advise females of reproductive potential that based on animal data CYRAMZA may impair fertility.

Please see Brief Summary of Prescribing Information for CYRAMZA, including boxed Warning for hemorrhage, gastrointestinal perforation, and impaired wound healing, on adjacent pages.

RB-4-HCP isi 17SEP2015

Visit CYRAMZAhcp.com to find out more
WARNINGS AND PRECAUTIONS

Hypertension
CYRAMZA increased the risk of hypertension in clinical trials including 1.7% of 236 patients who received CYRAMZA as a single agent for gastric cancer in Study 1. Permanently discontinue CYRAMZA in patients who experience a severe event.

Arterial Thromboembolic Events
Serious, sometimes fatal, arterial thromboembolic events (ATEs) including myocardial infarction, cardiac arrest, cerebrovascular accident, and cerebral ischemia occurred in clinical trials including 1.7% of 236 patients who received CYRAMZA as a single agent for gastric cancer. In Study 1, permanently discontinue CYRAMZA in patients who experience a severe ATE.

Hypertension
An increased incidence of severe hypertension occurred in patients receiving CYRAMZA as a single agent (8%) as compared to placebo (3%) and in patients receiving CYRAMZA plus paclitaxel (15%) as compared to placebo plus paclitaxel (5%), in patients receiving CYRAMZA plus docetaxel (6%) as compared to placebo plus docetaxel (2%), and in patients receiving CYRAMZA plus FOLFIRI (11%) as compared to placebo plus FOLFIRI (3%). Control hypertension prior to initiating treatment with CYRAMZA. Monitor blood pressure every two weeks or more frequently as indicated during treatment.

Infusion-Related Reactions
Prior to the institution of premedication recommendations across clinical trials of CYRAMZA, infusion-related reactions (IRRs) occurred in 6 out of 37 patients (16%), including two severe events. The majority of IRRs across trials occurred during or following a first or second CYRAMZA infusion. Symptoms of IRRs included rigors/tremors, back pain/spasms, chest pain and/or tightness, dyspnea, chills, flushing, dyspepsia, hypotension, and paresthesia. In severe cases, symptoms included cardiac arrest, cerebrovascular accident, and cerebral ischemia occurred in clinical trials including 1.7% of 236 patients who received CYRAMZA as a single agent for gastric cancer in Study 1. Permanently discontinue CYRAMZA in patients who experience a severe ATE.

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The table below provides data on adverse reactions occurring at incidence rate ≥5% and a ≥2% difference between arms in patients receiving CYRAMZA in Study 3.

<table>
<thead>
<tr>
<th>Adverse Reactions (MedDRA) System Organ Class</th>
<th>CYRAMZA plus docetaxel (N=627)</th>
<th>Placebo plus docetaxel (N=618)</th>
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</thead>
<tbody>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stomatitis/Mucosal inflammation</td>
<td>37</td>
<td>7</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>19</td>
<td>2</td>
</tr>
<tr>
<td>Eye Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laccination increased</td>
<td>13</td>
<td>&lt;1</td>
</tr>
<tr>
<td>General Disorders and Administration Site Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue/Athens</td>
<td>55</td>
<td>14</td>
</tr>
<tr>
<td>Periperal edema</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory, Thoracic, and Mediastinal Disorders</td>
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<td></td>
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<tr>
<td>Epistaxis</td>
<td>19</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>11</td>
<td>6</td>
</tr>
</tbody>
</table>

Clinically relevant adverse drug reactions reported in ≥1% and <5% of the CYRAMZA plus docetaxel-treated patients in Study 3 were hypotension (4.8% CYRAMZA plus docetaxel versus 2.4% for placebo plus docetaxel) and proteinuria (5.3% CYRAMZA plus docetaxel versus 0.8% placebo plus docetaxel).

Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity. In 23 clinical trials, 36% (95% CI: 34, 38) of CYRAMZA-treated patients tested positive for treatment-emergent anti-ramucirumab antibodies by an enzyme-linked immunosorbent assay (ELISA). Neutralizing antibodies were detected in 14 of the 86 patients who tested positive for treatment-emergent anti-ramucirumab antibodies.

Hypertension

Advise patients of the potential risk for serious adverse reactions in infants from ramucirumab, advise women that breastfeeding is not recommended during treatment from CYRAMZA.

Hypertension

Advise patients to contact their health care provider for bleeding or symptoms of bleeding including lightheadedness.

Arterial thromboembolic events

Advise patients of the potential risk for arterial thromboembolic events.

Gastrointestinal perforation

Advise patients of the potential risk for gastrointestinal perforation.

Hemorrhage

Advise patients of the potential risk for hematochezia.

Wound Healing Complications

Advise patients to notify their health care provider for bleeding or symptoms of bleeding including lightheadedness.

Arterial thromboembolic events

Advise patients of the potential risk for arterial thromboembolic events.

Hypertension

Advise patients to undergo routine blood pressure monitoring and to contact their health care provider if blood pressure is elevated or if symptoms from hypertension occur including severe headache, lightheadedness, or neurologic symptoms.

Gastrointestinal perforations

Advise patients not to breastfeed during CYRAMZA treatment.

Infertility

Advise patients of the potential risk for infertility.

Additional information can be found at www.CYRAMZAhcp.com.

Eli Lilly and Company, Indianapolis, IN 46285, USA

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RB-L HCP BS 27MAR2017
Making the Case for Medically Integrated Dispensing

An article written by Barry Fortner, Ph.D., Senior Vice President and President of Specialty Physician Services at AmerisourceBergen, was published in November 2018 to Oncology Live’s website.

“Making the Case for Medically Integrated Dispensing” showcases the potential of medically integrated dispensing within practices and the challenges physicians currently face with implementation. Barry walks readers through best practices and recommendations for implementing an in-office dispensing program – from leveraging data and hiring a technician to getting involved in advocacy efforts on Capitol Hill.

Practices interested in learning more about how in-office dispensing can maximize your practice’s revenue and enhance patient care should contact SON@iononline.com.

AmerisourceBergen, ION Solutions Join Groups Opposing New Part B Demo

In December 2018, AmerisourceBergen and ION Solutions joined 337 other patient, provider and caregiver organizations in a letter to congressional leadership asking them to help stop the U.S. Department of Health and Human Services’ (HHS) recently announced advance notice of the International Pricing Index Model for Medicare Part B Drugs (IPI).

As proposed, the IPI model could be implemented in 2020 and would institute a mandatory demonstration project for 50 percent of the U.S. that would replace Medicare’s existing Part B drug reimbursement mechanism with a new benchmark based on foreign drug prices. It would change provider reimbursement to a flat add-on fee and restructure the current buy and bill model so that a new vendor system would be implemented whereby the medicines would be purchased and delivered to the physician by a vendor that would then be reimbursed by Medicare, a revised version of the failed 2006 Competitive Acquisition Program (CAP). The letter articulates myriad concerns with the proposal, including potential disruptions to beneficiary access to needed medications, provider reimbursement cuts and dampening medical innovation.

AmerisourceBergen will continue to collaborate with aligned stakeholders to ensure these concerns are heard by congressional and administration policymakers heading into 2019.

APP Programs are Essential to Ensure Access to Quality Cancer Care

Successfully managing clinical workloads and maximizing both the quality of care delivered and staff productivity are synonymous with your practice’s operational health. As the demand for oncology services increases, practices need to find a way to improve access to care, engage patients and offer services such as patient education and advance care planning. One of the most successful strategies is the addition of an Advanced Practice Provider (APP) program.

Integrating an APP program can have complexities that benefit from an outside view. ION Solutions’ Clinical Quality Consultants can help navigate those issues after a 360° practice assessment. The consultant provides an on-site assessment to either start or strengthen a current APP program and reviews the current roles within the practice to provide guidance on potentially implementing the program or finding other opportunities for improvement.

The consultant will use an ROI tool to guide decision making for implementing a program, as well as identifying those services that would best help the practice. Evaluating the need for additional provider-based services in the clinical workflow will also be discussed.
Following an APP 360° practice assessment, the practice can engage the consultant for implementation services that will provide support, resources and tools to aid in the onboarding and orientation of an APP, as well as develop, implement and/or optimize a standardized APP practice model. The focus will also be on revenue enhancing services such as patient education, same day visit schedules and survivorship.

“Given the increasing number of patients with and survivors of cancer, APPs are important to ensure access to quality cancer care now and in the future.”

If you are interested in learning more about how an APP program can help balance the demands for your physicians’ time while providing patient-centered care, contact clinicalqualityconsulting@iononline.com


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**MHP Joins ION Solutions GPO Network and Selects Oncology Supply as Exclusive Specialty Distributor**

Michigan Healthcare Professionals (MHP) has selected ION Solutions for GPO contracting and Oncology Supply for exclusive specialty distribution. This marks a six-year strategic relationship focused on supporting patient outcomes and driving economic competitiveness.

With more than 400 physicians, MHP is a large-specialty group spanning numerous specialties. MHP’s community oncology practice consists of 24 physicians, including radiation oncologists and surgeons, staffing 11 different sites of care that span the entire metro-Detroit area. As an Oncology Care Model practice, MHP provides high-quality, efficient, coordinated, appropriate and cost-effective healthcare. MHP has two retail pharmacies and offers, fast, safe and free delivery anywhere in Michigan within 24 hours. MHP participates in TACO, the Medicare Shared Savings Program Accountable Care Organization.

“As the largest physician service organization and GPO specializing in the support of independent oncology practices, we pride ourselves in the strength and caliber of our membership, and MHP certainly adds to both,” said Barry Fortner, Ph.D., Senior Vice President & President of Specialty Physician Services at AmerisourceBergen. “We look forward to leveraging the full power of our ION GPO and AmerisourceBergen’s integrated service and technology offerings to support MHP as the practice builds on the exceptional work they’re already doing to create efficiencies, deliver positive clinical outcomes and enhance the patient experience.”

Through this new agreement, MHP will have a dedicated account team that acts as an extension of the practice and actively consults on contract performance, purchasing activities and creating operational efficiencies. MHP will have access to Oncology Supply’s robust inventory of specialty and full-line oral, infusible and injectable products.

“The strongest differentiator for ION Solutions and Oncology Supply is the VIP level of service that we receive.”

- Dr. Jeffrey Margolis, President of Michigan Healthcare Professionals
## 2019 Meeting Schedule

<table>
<thead>
<tr>
<th>Meeting Date</th>
<th>Meeting Name</th>
<th>Location</th>
<th>Venue</th>
</tr>
</thead>
<tbody>
<tr>
<td>January 25</td>
<td>Multiple Myeloma</td>
<td>Orlando, FL</td>
<td>Renaissance Sea World</td>
</tr>
<tr>
<td>January 25-26</td>
<td>ASH Review</td>
<td>Orlando, FL</td>
<td>Renaissance Sea World</td>
</tr>
<tr>
<td>March 8-9</td>
<td>Oral Therapies</td>
<td>Plano, TX</td>
<td>Renaissance Plano</td>
</tr>
<tr>
<td>May 16-17</td>
<td>Smart ID</td>
<td>Charlotte, NC</td>
<td>Westin Charlotte</td>
</tr>
<tr>
<td>May 17-18</td>
<td>National Healthcare Practitioners</td>
<td>Charlotte, NC</td>
<td>Westin Charlotte</td>
</tr>
</tbody>
</table>

*Meeting Dates Subject to Change*

Registration will be available approximately 60 days prior to each event. To register, visit www.iononline.com.
Along the MBC journey* – explore Verzenio1

Verzenio is indicated for the treatment of hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2−) advanced or metastatic breast cancer (MBC):

- In combination with fulvestrant for women with disease progression following endocrine therapy
- In combination with an aromatase inhibitor (AI) for postmenopausal women as initial endocrine-based therapy
- As a single agent for adult patients with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting

*Patients who received prior therapy with a CDK4 & 6 inhibitor were excluded from the MONARCH trials.2-4 There are currently no data regarding the use of Verzenio following use of another CDK4 & 6 inhibitor.

For patients with HR+, HER2− MBC, including those with concerning clinical characteristics1-14†

†Disease characteristics that typically confer a less favorable prognosis. Visceral disease and progression on ET and prior chemotherapy in the metastatic setting were concerning clinical characteristics in MONARCH 1. Primary resistance and visceral disease were concerning clinical characteristics in MONARCH 2. Liver metastases and treatment-free interval <36 months were concerning clinical characteristics in MONARCH 3. Exploratory subgroup analyses of PFS were performed for patients with liver metastases and for patients with a treatment-free interval <36 months.2-14

CDK4 & 6 = cyclin-dependent kinases 4 and 6; ET = endocrine therapy; PFS = progression-free survival.

Select Important Safety Information

Diarrhea occurred in 81% of patients receiving Verzenio plus an aromatase inhibitor in MONARCH 3, 86% of patients receiving Verzenio plus fulvestrant in MONARCH 2 and 89% of patients receiving Verzenio alone in MONARCH 1. Grade 3 diarrhea occurred in 9% of patients receiving Verzenio plus an aromatase inhibitor in MONARCH 3, 13% of patients receiving Verzenio plus fulvestrant in MONARCH 2 and in 20% of patients receiving Verzenio alone in MONARCH 1. Episodes of diarrhea have been associated with dehydration and infection.

Diarrhea incidence was greatest during the first month of Verzenio dosing. In MONARCH 3, the median time to onset of the first diarrhea event was 8 days, and the median duration of diarrhea for Grades 2 and 3 were 9 days and 6 days, respectively. In MONARCH 2, the median time to onset of the first diarrhea event was 6 days, and the median duration of diarrhea for Grades 2 and 3 were 7 days and 6 days, respectively. In MONARCH 3, 19% of patients with diarrhea required a dose omission and 15% required a dose reduction. In MONARCH 2, 22% of patients with diarrhea required a dose omission and 22% required a dose reduction. The time to onset and resolution for diarrhea were similar across MONARCH 3, MONARCH 2, and MONARCH 1.

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

Please see additional Important Safety Information and Brief Summary of full Prescribing Information for Verzenio on the following pages.
Verzenio + AI

For women with HR+, HER2− MBC

Verzenio + AI as first-line endocrine-based therapy\(^1,3\)

>-28-month median PFS as initial endocrine-based therapy\(^1\)

<table>
<thead>
<tr>
<th>ITT(^1)</th>
<th>28.2 months mPFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>(95% CI: 23.5-NR) vs 14.8 months with AI alone (95% CI: 11.2-19.2)</td>
<td>HR=0.540 (95% CI: 0.418-0.698) (P&lt;0.001)</td>
</tr>
</tbody>
</table>

- The percentage of events at the time of analysis was 42.1% (n=138) and 65.5% (n=108) in the Verzenio + AI and AI alone arms, respectively\(^1\)
- At the time of the PFS analysis, 19% of patients had died, and overall survival data were immature\(^1\)

Exploratory subgroup analyses

PFS results in women with concerning clinical characteristics were consistent with the ITT population\(^1,3,9-14\)§

<table>
<thead>
<tr>
<th>Liver metastases(^13)</th>
<th>Treatment-free interval &lt;36 months(^14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15.0 months (95% CI: 7.4-23.7) (n=47) vs 7.2 months median PFS with AI alone (95% CI: 2.1-14.0) (n=31) HR=0.477 (95% CI: 0.272-0.837)</td>
<td>29.5 months (95% CI: 11.6-NR) (n=44) vs 9.0 months median PFS with AI alone (95% CI: 3.7-14.2) (n=32) HR=0.441 (95% CI: 0.241-0.805)</td>
</tr>
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</table>

- Exploratory subgroup analyses of PFS were performed for the subgroups of patients with liver metastases or with treatment-free interval <36 months after completion of adjuvant ET. Estimated HRs and CIs for the within group analyses that were adjusted for treatment interaction are shown. The analyses were not adjusted for multiplicity and the study was not powered to test the effect of Verzenio + AI among subgroups.\(^1,3,4\)

MONARCH 3 was a multicenter trial that enrolled 493 patients with HR+, HER2− locoregionally recurrent or MBC in combination with a nonsteroidal AI as initial endocrine-based therapy. The median patient age was 63 years (range, 32 to 88 years). Forty-seven percent of patients had received prior ET and 39% of patients had received chemotherapy in the adjuvant setting. Patients were randomized 2:1 to Verzenio + AI or placebo + AI. Patients received either letrozole (80%) or anastrozole (20%). Verzenio was dosed continuously until disease progression or unacceptable toxicity. The primary endpoint was PFS. Key secondary endpoints were ORR and DoR.\(^1,3\)

Select Important Safety Information (cont’d)

Neutropenia occurred in 41% of patients receiving Verzenio plus an aromatase inhibitor in MONARCH 3. 46% of patients receiving Verzenio plus fulvestrant in MONARCH 2 and 37% of patients receiving Verzenio alone in MONARCH 1. A Grade ≥3 decrease in neutrophil count (based on laboratory findings) occurred in 22% of patients receiving Verzenio plus an aromatase inhibitor in MONARCH 3, 32% of patients receiving Verzenio plus fulvestrant in MONARCH 2 and in 27% of patients receiving Verzenio alone in MONARCH 1. In MONARCH 3, the median time to first episode of Grade ≥3 neutropenia was 33 days, and in MONARCH 2 and MONARCH 1, was 29 days. In MONARCH 3, median duration of Grade ≥3 neutropenia was 11 days, and for MONARCH 2 and MONARCH 1 was 15 days. 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.

Febrile neutropenia has been 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 provider.

Grade ≥3 increases in alanine aminotransferase (ALT) (6% versus 2%) and aspartate aminotransferase (AST) (3% versus 1%) were reported in the Verzenio and placebo arms, respectively, in MONARCH 3. Grade ≥3 increases in ALT (4% versus 2%) and AST (2% versus 3%) were reported in the Verzenio and placebo arms respectively, in MONARCH 2.
For women with HR+, HER2− MBC

Verzenio + fulvestrant in patients who recurred or progressed on or after ET

>16-month median PFS in women who recurred or progressed on or after ET

16.4 months

\(95\%\text{ CI: }14.4-19.3\) vs \(9.3\) months

\(\text{mPFS}\)

\(\text{HR}=0.553\) (95% CI: 0.449-0.681)

\(P<.0001^\dagger\)

- The percentage of events at the time of analysis was 49.8% (n=222) and 70.4% (n=157) in the Verzenio + fulvestrant and fulvestrant alone arms, respectively.
- At the time of the primary analysis of PFS, overall survival data were not mature (20% of patients had died)\(\dagger\)

PFS results in women with concerning clinical characteristics were consistent with the ITT population\(1,2,5-8\dagger\)

\dagger\text{Disease characteristics that typically confer a less favorable prognosis. Primary resistance and visceral disease were concerning clinical characteristics in MONARCH 2.}

Primary resistance\(5\)

15.3 months

\(95\%\text{ CI: }12.4-24.1\) (n=111) vs \(7.9\) months

\(\text{mPFS}\)

\(\text{HR}=0.454\) (95% CI: 0.306-0.674)

- Primary resistance is 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\(1\)
- Preplanned subgroup analyses of PFS were performed for stratification factors of disease site, including visceral disease, and endocrine resistance, including primary resistance. The analyses were not adjusted for multiplicity and the study was not powered to test the effect of Verzenio + fulvestrant among subgroups\(8\)

Visceral disease\(5\)

14.7 months

\(95\%\text{ CI: }13.0-17.4\) (n=245) vs \(6.5\) months

\(\text{mPFS}\)

\(\text{HR}=0.481\) (95% CI: 0.369-0.627)

- Visceral disease was defined as at least 1 lesion on an internal organ or in the third space and could have included lung, liver, pleural, or peritoneal metastatic involvement\(1\)

MONARCH 2 was a phase III, randomized, double-blind, placebo-controlled trial that enrolled 669 patients with HR+, HER2− MBC who progressed on ET. Patients were randomized 2:1 to Verzenio + fulvestrant or placebo + fulvestrant. Verzenio was dosed on a continuous dosing schedule until disease progression or unacceptable toxicity. The primary endpoint was PFS. Key secondary endpoints were ORR, overall survival, and DoR.\(1,2\)

Select Important Safety Information (cont’d)

In MONARCH 3, for patients receiving Verzenio plus an aromatase inhibitor with Grade ≥3 increases in ALT or AST, median time to onset was 61 and 71 days, respectively, and median time to resolution to Grade <3 was 14 and 15 days, respectively. In MONARCH 2, for patients receiving Verzenio plus fulvestrant with Grade ≥3 increases in ALT or AST, median time to onset was 57 and 185 days, respectively, and median time to resolution to Grade <3 was 14 and 13 days, respectively.

For assessment of potential hepatotoxicity, 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.

Please see additional Important Safety Information and Brief Summary of full Prescribing Information for Verzenio on the following pages.

Venous thromboembolic events were reported in 5% of patients treated with Verzenio plus an aromatase inhibitor as compared to 0.6% of patients treated with an aromatase inhibitor plus placebo in MONARCH 3. Venous thromboembolic events were reported in 5% of patients treated with Verzenio plus fulvestrant in MONARCH 2 as compared to 0.9% of patients treated with fulvestrant plus placebo. Venous thromboembolic events included deep vein thrombosis, pulmonary embolism, pelvic venous thrombosis, cerebral venous sinus thrombosis, subclavian and axillary vein thrombosis, and inferior vena cava thrombosis. Across the clinical development program, deaths due to venous thromboembolism have been reported.
Single agent

For heavily pretreated women with HR+, HER2− MBC

The only CDK4 & 6 inhibitor approved as a single agent

ORR1

19.7% ORR

(95% CI: 13.3-27.5)

per investigator assessment1

ORR was defined as the proportion of patients with CR + PR, and does not include stable disease154

• 17.4% ORR (95% CI: 11.4-25.0), per independent review2

MONARCH 1 was a single-arm, open-label, multicenter study in 132 women with measurable HR+, HER2− MBC whose disease progressed during or after ET, had received a taxane in any setting, and who received 1 or 2 prior chemotherapy regimens in the metastatic setting. Patients had an Eastern Cooperative Oncology Group Performance Status of 0 (55% of patients) or 1 (45% of patients). Patients took 200 mg of Verzenio orally twice daily on a continuous schedule unless disease progression or unacceptable toxicity occurred. The primary endpoint was ORR. A key secondary endpoint was DoR.1,8

Select Important Safety Information (cont’d)

Monitor patients for signs and symptoms of venous thrombosis and pulmonary embolism and treat as medically appropriate. Verzenio can cause fetal harm when administered to a pregnant woman based on findings from animal studies and the mechanism of action. In animal reproduction studies, administration of abemaciclib to pregnant rats during the period of organogenesis caused teratogenesis 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 at least 3 weeks after the last dose. There are no data on the presence of Verzenio in human milk or its effects on the breastfed child or on milk production. Advise lactating women not to breastfeed during Verzenio treatment and for at least 3 weeks after the last dose because of the potential for serious adverse reactions in breastfed infants. Based on findings in animals, Verzenio may impair fertility in males of reproductive potential.

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

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

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

The most frequently reported ≥5% Grade 3 or 4 adverse reactions that occurred in the Verzenio arm vs the placebo arm of MONARCH 3 were neutropenia (22% vs 2%), diarrhea (9% vs 1%), leukopenia (8% vs 1%), ALT increased (7% vs 2%), and anemia (6% vs 1%).

The most frequently reported ≥5% Grade 3 or 4 adverse reactions that occurred in the Verzenio arm vs the placebo arm of MONARCH 2 were neutropenia (27% vs 2%), diarrhea (13% vs <1%), leukopenia (9% vs 0%), anemia (7% vs 1%), and infections (6% vs 3%)

The most frequently reported ≥5% Grade 3 or 4 adverse reactions from MONARCH 1 with Verzenio were neutropenia (24%), diarrhea (20%), fatigue (13%), infections (7%), leukopenia (6%), anemia (5%), and nausea (5%)

Median duration of response (mDoR)38

• 3.7-month median time to response (range: 11-14.2 months)38

• 7.2-month mDoR (95% CI: 5.6-NR), per independent review1

*PR defined as ≥30% reduction in target lesion size per RECIST 1.1

†Among 26 patients (investigator assessed) and 23 patients (independent review) who had a PR.
Abemaciclib (Verzenio®): recommended by the National Comprehensive Cancer Network® (NCCN®) 19

Abemaciclib (Verzenio®) + fulvestrant 19

Recommended option for the treatment of postmenopausal women with HR+, HER2– MBC after disease progression on prior ET

Abemaciclib (Verzenio®) + an AI 19

Recommended option for the treatment of postmenopausal women with HR+, HER2– MBC as initial endocrine-based therapy

Select Important Safety Information (cont’d)

Lab abnormalities (all grades; Grade 3 or 4) for MONARCH 3 in ≥10%

- For Verzenio plus anastrozole or letrozole, and ≥2% higher than placebo plus anastrozole or letrozole were increased serum creatinine (98% vs 84%; 2% vs 0%), decreased white blood cells (82% vs 27%; 13% vs <1%), anemia (82% vs 28%; 2% vs 0%), decreased neutrophil count (80% vs 21%; 22% vs 3%), decreased lymphocyte count (53% vs 26%; 8% vs 2%), decreased platelet count (36% vs 12%; 2% vs <1%), increased ALT (48% vs 25%; 7% vs 2%), and increased AST (37% vs 23%; 4% vs <1%).

Lab abnormalities (all grades; Grade 3 or 4) for MONARCH 2 in ≥10% for Verzenio plus fulvestrant and ≥2% higher than placebo plus fulvestrant versus placebo plus fulvestrant were increased serum creatinine (98% vs 74%; 1% vs 0%), decreased white blood cells (90% vs 33%; 23% vs 1%), decreased neutrophil count (87% vs 30%; 33% vs 4%), anemia (84% vs 33%; 3% vs <1%), decreased lymphocyte count (63% vs 32%; 12% vs 2%), decreased platelet count (53% vs 15%; 2% vs 0%), increased ALT (41% vs 32%; 5% vs 1%), and increased AST (37% vs 25%; 4% vs 4%).

Lab abnormalities (all grades; Grade 3 or 4) for MONARCH 1 with Verzenio were increased serum creatinine (98%; <1%), decreased white blood cells (91%; 28%), decreased neutrophil count (88%; 27%), anemia (68%; 0%), decreased lymphocyte count (42%; 14%), decreased platelet count (41%; 2%), increased ALT (31%; 3%), and increased AST (30%; 4%).

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

Avoid concomitant use of strong CYP3A inducers and consider alternative agents. Coadministration of Verzenio with rifampin, a strong CYP3A inducer, decreased the plasma concentrations of abemaciclib and its active metabolites to a clinically meaningful extent and may lead to reduced activity.

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

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Please see Brief Summary of full Prescribing Information for Verzenio on the following pages.
Please see Brief Summary of full Prescribing Information for Verzenio on the following pages.

VERZENIO™ (abemaciclib) tablets, for oral use
Initial U.S. Approval: 2017

BRIEF SUMMARY: Consult the package insert for complete prescribing information.

INDICATIONS AND USAGE
VERZENIO™ (abemaciclib) is indicated:
- in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women 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 women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer with disease progression following endocrine therapy.
- as monotherapy for the treatment of adult patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting.

CONTRAINDICATIONS: None

WARNINGS AND PRECAUTIONS
Diarrhea
Diarrhea occurred in 81% of patients receiving VERZENIO plus an aromatase inhibitor in MONARCH 3, 86% of patients receiving VERZENIO plus fulvestrant in MONARCH 2, and 90% of patients receiving VERZENIO alone in MONARCH 1. Grade 3 diarrhea occurred in 9% of patients receiving VERZENIO plus an aromatase inhibitor in MONARCH 3, 13% of patients receiving VERZENIO plus fulvestrant in MONARCH 2, and in 20% of patients receiving VERZENIO alone in MONARCH 1. Episodes of diarrhea have been associated with dehydration and infection.

Diarrhea incidence was greatest during the first month of VERZENIO dosing. In MONARCH 3, the median time to onset of the first diarrhea event was 8 days, and the median duration of diarrhea for Grades 2 and 3 were 11 and 8 days, respectively. In MONARCH 2, the median time to onset of the first diarrhea event was 6 days, and the median duration of diarrhea for Grades 2 and 3 were 9 days and 6 days, respectively. In MONARCH 3, 19% of patients with diarrhea required a dose omission and 13% required a dose reduction. In MONARCH 2, 22% of patients with diarrhea required a dose omission and 22% required a dose reduction. The time to onset and resolution for diarrhea were similar across MONARCH 3, MONARCH 2, and MONARCH 1.

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

Neutropenia
Neutropenia occurred in 41% of patients receiving VERZENIO plus an aromatase inhibitor in MONARCH 3, 46% of patients receiving VERZENIO plus fulvestrant in MONARCH 2, and 37% of patients receiving VERZENIO alone in MONARCH 1. A Grade 3 or 4 decrease in neutrophil count (based on laboratory findings) occurred in 22% of patients receiving VERZENIO plus an aromatase inhibitor in MONARCH 3, 32% of patients receiving VERZENIO plus fulvestrant in MONARCH 2, and in 27% of patients receiving VERZENIO in MONARCH 1. In MONARCH 3, the median time to first episode of Grade 3 or 4 neutropenia was 33 days, and in MONARCH 2 and MONARCH 1 was 29 days. In MONARCH 3, median duration of Grade 3 or 4 neutropenia was 11 days, and for MONARCH 2 and MONARCH 1 was 15 days.

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.

Fever and neutropenia has been 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 provider.

Hepatotoxicity
In MONARCH 3, Grade 3 increases in ALT (6% versus 2%) and AST (3% versus 1%) were reported in the VERZENIO and placebo arms, respectively. In MONARCH 2, Grade 3 increases in ALT (4% versus 2%) and AST (2% versus 3%) were reported in the VERZENIO and placebo arms, respectively.

In MONARCH 3, for patients receiving VERZENIO plus an aromatase inhibitor with Grade ≥3 ALT increased, median time to onset was 61 days, and median time to resolution to Grade <3 was 14 days. In MONARCH 2, for patients receiving VERZENIO plus fulvestrant with Grade ≥3 ALT increased, median time to onset was 57 days, and median time to resolution to Grade <3 was 14 days. In MONARCH 3, for patients receiving VERZENIO plus an aromatase inhibitor with Grade ≥3 AST increased, median time to onset was 71 days, and median time to resolution was 15 days. In MONARCH 2, for patients receiving VERZENIO plus fulvestrant with Grade ≥3 AST increased, median time to onset was 185 days, and median time to resolution was 13 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.

Venous Thromboembolism
In MONARCH 3, venous thromboembolic events were reported in 5% of patients treated with VERZENIO plus an aromatase inhibitor as compared to 0.6% of patients treated with an aromatase inhibitor plus placebo. In MONARCH 2, venous thromboembolic events were reported in 5% of patients treated with VERZENIO plus fulvestrant as compared to 0.9% of patients treated with fulvestrant plus placebo. Venous thromboembolic events included deep vein thrombosis, pulmonary embolism, pelvic venous thrombosis, cerebral venous sinus 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 patients for signs and symptoms of venous thrombosis and pulmonary embolism and treat as medically appropriate.

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 at least 3 weeks after the last dose.

ADVERSE REACTIONS
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.

MONARCH 3: VERZENIO in Combination with an 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
MONARCH 3 was a study of 488 women receiving VERZENIO plus an aromatase inhibitor or placebo plus an aromatase inhibitor. Patients were randomly assigned to receive 150 mg of VERZENIO or placebo orally twice daily, plus physician’s choice of anastrozole or letrozole once daily. Median duration of treatment was 15.1 months for the VERZENIO arm and 13.9 months for the placebo arm. Median dose compliance was 96% for the VERZENIO arm and 99% for the placebo arm.

Dose reductions due to an adverse reaction occurred in 43% of patients receiving VERZENIO plus anastrozole or letrozole. Adverse reactions leading to dose reductions in ≥5% of patients were diarrhea and neutropenia. VERZENIO dose reductions due to diarrhea of any grade occurred in 13% of patients receiving VERZENIO plus an aromatase inhibitor compared to 2% of patients receiving placebo plus an aromatase inhibitor. VERZENIO dose reductions due to neutropenia of any grade occurred in 11% of patients receiving VERZENIO plus an aromatase inhibitor compared to 0.6% of patients receiving placebo plus an aromatase inhibitor.

Permanent treatment discontinuation due to an adverse event was reported in 13% of patients receiving VERZENIO plus an aromatase inhibitor and in 3% placebo plus an aromatase inhibitor. Adverse reactions leading to permanent discontinuation for patients receiving VERZENIO plus an aromatase inhibitor were diarrhea (2%), ALT increased (2%), infection (1%), venous thromboembolic events (VTE) (1%), neutropenia (0.9%), renal impairment (0.9%), AST increased (0.6%), dyspnea (0.6%), pulmonary fibrosis (0.6%) and anemia, rash, weight decreased and thrombocytopenia (each 0.3%).
Deaths during treatment or during the 30-day follow up, regardless of causality, were reported in 11 cases (3%) of VERZENIO plus an aromatase inhibitor treated patients versus 3 cases (2%) of placebo plus an aromatase inhibitor treated patients. Causes of death for patients receiving VERZENIO plus an aromatase inhibitor included: 3 (1%) patient deaths due to underlying disease, 3 (0.9%) due to lung infection, 3 (0.9%) due to VTE event, 1 (0.3%) due to pneumonitis, and 1 (0.3%) due to cerebral infarction.

The most common adverse reactions reported (>20%) in the VERZENIO arm and ≥2% than the placebo arm were diarrhea, neutropenia, fatigue, infections, nausea, abdominal pain, anemia, vomiting, alopecia, decreased appetite, and leukopenia (Table 6). 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. The median time to onset of the first diarrhea event was 8 days, and the median durations of diarrhea for Grades 2 and for Grade 3 were 11 days and 8 days, respectively. Most diarrhea events recovered or resolved (88%) with supportive treatment and/or dose reductions. Nineteen percent of patients with diarrhea required a dose omission and 13% required a dose reduction. The median time to the first dose reduction due to diarrhea was 38 days.

Table 6: Adverse Reactions ≥10% of Patients Receiving VERZENIO Plus Anastrozole or Letrozole in MONARCH 3

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>VERZENIO plus Anastrozole or Letrozole N=327</th>
<th>Placebo plus Anastrozole or Letrozole N=161</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades %</td>
<td>Grade 3 %</td>
<td>Grade 4 %</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>81 9 0</td>
<td>30 1 0</td>
</tr>
<tr>
<td>Nausea</td>
<td>39 &lt;1 0</td>
<td>20 1 0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>29 1 0</td>
<td>12 1 0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>28 1 0</td>
<td>12 2 0</td>
</tr>
<tr>
<td>Constipation</td>
<td>16 &lt;1 0</td>
<td>12 0 0</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection&lt;sup&gt;a&lt;/sup&gt;</td>
<td>39 4 &lt;1</td>
<td>29 2 &lt;1</td>
</tr>
<tr>
<td>Blood and Lymphatic System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>41 20 2</td>
<td>2 &lt;1 &lt;1</td>
</tr>
<tr>
<td>Anemia</td>
<td>28 6 0</td>
<td>5 1 0</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>21 7 &lt;1</td>
<td>2 0 &lt;1</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>10 2 &lt;1</td>
<td>2 &lt;1 &lt;1</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>40 2 0</td>
<td>32 0 0</td>
</tr>
<tr>
<td>Influenza like illness</td>
<td>10 0 0</td>
<td>8 0 0</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>27 0 0</td>
<td>11 0 0</td>
</tr>
<tr>
<td>Rash</td>
<td>14 &lt;1 0</td>
<td>5 0 0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>13 0 0</td>
<td>9 0 0</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>24 1 0</td>
<td>9 &lt;1 &lt;1</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood creatinine increased</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alamine aminotransferase increased</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight decreased</td>
<td>10 &lt;1 0</td>
<td>3 &lt;1 &lt;1</td>
</tr>
<tr>
<td>Respiratory, Thoracic, and Mediastinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>11 &lt;1 0</td>
<td>9 0 0</td>
</tr>
</tbody>
</table>

<sup>a</sup> Includes all reported preferred terms that are part of the Infections and Infestations system organ class. Most common infections (>1%) include upper respiratory tract infection, lung infection, and pharyngitis.

Table 7: Laboratory Abnormalities ≥10% in Patients Receiving VERZENIO Plus Anastrozole or Letrozole and ≥2% Higher Than Placebo in MONARCH 3

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>VERZENIO plus Anastrozole or Letrozole N=327</th>
<th>Placebo plus Anastrozole or Letrozole N=161</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades %</td>
<td>Grade 3 %</td>
<td>Grade 4 %</td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>98 2 0</td>
<td>84 0 0</td>
</tr>
<tr>
<td>White blood cell decreased</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphocyte count decreased</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Creatinine Increased

Abemaciclib has been shown to increase serum creatinine due to inhibition of renal tubular secretion transporters, without affecting glomerular function. Across the 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 BUN, cystatin C, or calculated GFR, which are not based on creatinine, may be considered to determine whether renal function is impaired.

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 (150 mg twice daily) plus fulvestrant (500 mg) versus placebo plus fulvestrant was evaluated in MONARCH 2. The data described below reflect exposure to VERZENIO in 441 patients with HR-positive, HER2-negative advanced breast cancer who received at least one dose of VERZENIO plus fulvestrant in MONARCH 2.

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. Adverse reactions leading to dose reductions in ≥5% of patients were diarrhea and neutropenia. VERZENIO dose reductions due to diarrhea of any grade occurred in 19% of patients receiving VERZENIO plus fulvestrant compared to 0.4% of patients receiving placebo and fulvestrant. VERZENIO dose reductions due to neutropenia of any grade occurred in 10% of patients receiving VERZENIO plus fulvestrant compared to no patients receiving placebo plus fulvestrant.

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 were infection (2%), diarrhea (1%), hepatotoxicity (1%), fatigue (0.7%), nausea (0.2%), abdominal pain (0.2%), acute kidney injury (0.2%), and cerebral infarction (0.2%).

Deaths during treatment or during the 30-day follow up, regardless of causality, were reported in 18 cases (4%) of VERZENIO plus fulvestrant treated patients versus 10 cases (5%) of placebo plus fulvestrant treated patients. Causes of death for patients receiving VERZENIO plus fulvestrant included: 7 (2%) patient deaths due to underlying disease, 4 (0.9%) due to sepsis, 2 (0.5%) due to pneumonitis, 2 (0.5%) due to hepatotoxicity, and one (0.2%) due to cerebral infarction.
The most common adverse reactions reported (≥20%) in the VERZENIO arm were diarrhea, fatigue, neutropenia, nausea, infections, abdominal pain, anemia, leukopenia, decreased appetite, vomiting, and headache (Table 8). The most frequently reported (≥5%) Grade 3 or 4 adverse reactions were neutropenia, diarrhea, leukopenia, anemia, and infections.

### Table 8: Adverse Reactions ≥10% in Patients Receiving VERZENIO Plus Fulvestrant and ≥2% Higher Than Placebo Plus Fulvestrant in MONARCH 2

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>VERZENIO plus Fulvestrant N=441</th>
<th>Placebo plus Fulvestrant N=223</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>86</td>
<td>13</td>
</tr>
<tr>
<td>Nausea</td>
<td>45</td>
<td>3</td>
</tr>
<tr>
<td>Abdominal Paina</td>
<td>35</td>
<td>2</td>
</tr>
<tr>
<td>Vomiting</td>
<td>26</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>15</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infectionsb</td>
<td>43</td>
<td>5</td>
</tr>
<tr>
<td>Blood and Lymphatic System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropeniaa</td>
<td>46</td>
<td>24</td>
</tr>
<tr>
<td>Anemia</td>
<td>29</td>
<td>7</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>28</td>
<td>9</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>16</td>
<td>2</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>46</td>
<td>3</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>11</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>27</td>
<td>1</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>Dysesthesia</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>12</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>10</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

a Includes abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, abdominal tenderness.

b Includes upper respiratory tract infection, urinary tract infection, lung infection, pharyngitis, conjunctivitis, sinusitis, vaginal infection, sepsis.

c Includes neutropenia, neutrophil count decreased.

d Includes anemia, hematocrit decreased, hemoglobin decreased, red blood cell count decreased.

e Includes leukopenia, white blood cell count decreased.

f Includes platelet count decreased, thrombocytopenia.

g Includes asthenia, fatigue.

Additional adverse reactions in MONARCH 2 include venous thromboembolic events (deep vein thrombosis, pulmonary embolism, cerebral venous sinus thrombosis, subclavian vein thrombosis, axillary vein thrombosis, and DVT inferior vena cava), which were reported in 5% of patients treated with VERZENIO plus fulvestrant as compared to 0.9% of patients treated with fulvestrant plus placebo.

### Table 9: Laboratory Abnormalities ≥10% in Patients Receiving VERZENIO Plus Fulvestrant and ≥2% Higher Than Placebo Plus Fulvestrant in MONARCH 2

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>VERZENIO plus Fulvestrant N=441</th>
<th>Placebo plus Fulvestrant N=223</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>98</td>
<td>1</td>
</tr>
<tr>
<td>White blood cell decreased</td>
<td>90</td>
<td>23</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>87</td>
<td>29</td>
</tr>
<tr>
<td>Anemia</td>
<td>84</td>
<td>3</td>
</tr>
<tr>
<td>Lymphocyte count decreased</td>
<td>63</td>
<td>12</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>53</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>41</td>
<td>4</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>37</td>
<td>4</td>
</tr>
</tbody>
</table>

Creatinine Increased

Abemaciclib has been shown to increase serum creatinine due to inhibition of renal tubular secretion transporters, without affecting glomerular function. In clinical studies, increases in serum creatinine (mean increase, 0.2 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 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.

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

Patients with HR-positive, HER2-negative breast cancer who received prior endocrine therapy and 1-2 chemotherapy regimens in the metastatic setting

Safety data below are based on MONARCH 1, a single-arm, open-label, multicenter study in 132 women with measurable HR+, HER2- metastatic breast cancer. Patients received 200 mg VERZENIO orally twice daily until development of progressive disease or unacceptable toxicity. Median duration of treatment was 4.5 months.

Ten patients (8%) discontinued study treatment from adverse reactions due to (1 patient each) abdominal pain, arterial thrombosis, aspartate aminotransferase (AST) increased, blood creatinine increased, chronic kidney disease, diarrhea, ECG QT prolonged, fatigue, hip fracture, and lymphopenia. Forty-nine percent of patients had dose reductions due to an adverse reaction. The most frequent adverse reactions that led to dose reductions were diarrhea (20%), neutropenia (11%), and fatigue (9%).

Deaths during treatment or during the 30-day follow up were reported in 2% of patients. Cause of death in these patients was due to infection.

The most common reported adverse reactions (≥20%) were diarrhea, fatigue, nausea, decreased appetite, abdominal pain, neutropenia, vomiting, infections, anemia, headache, and thrombocytopenia (Table 10). Severe (Grade 3 and 4) neutropenia was observed in patients receiving abemaciclib.

### Table 10: Adverse Reactions ≥10% of Patients in MONARCH 1

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>VERZENIO N=132</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>90</td>
</tr>
<tr>
<td>Nausea</td>
<td>64</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>39</td>
</tr>
<tr>
<td>Constipation</td>
<td>17</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>14</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>14</td>
</tr>
</tbody>
</table>
Table 10: Adverse Reactions (≥10% of Patients) in MONARCH 1 (Cont.)

<table>
<thead>
<tr>
<th>Infections and Infestations</th>
<th>31</th>
<th>5</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td>Fatigue^</td>
<td>65</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Pyrexia</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Blood and Lymphatic System Disorders</td>
<td>Neutropenia^</td>
<td>37</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Anemia^</td>
<td>25</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia^</td>
<td>20</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Leukopenia^</td>
<td>17</td>
<td>5</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td>Decreased appetite</td>
<td>45</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Dehydration</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td>Cough</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td>Arthralgia</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>Headache</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Dysequisia</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td>Alopecia</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Investigations</td>
<td>Creatinine increased</td>
<td>13</td>
<td>&lt;1</td>
</tr>
<tr>
<td></td>
<td>Weight decreased</td>
<td>14</td>
<td>0</td>
</tr>
</tbody>
</table>

^ Includes asthenia, fatigue.

^ Includes neutropenia, neutrophil count decreased.

^ Includes anemia, hematocrit decreased, hemoglobin decreased, red blood cell count decreased.

^ Includes platelet count decreased, thrombocytopenia.

^ Includes leukopenia, white blood cell count decreased.

Table 11: Laboratory Abnormalities for Patients Receiving VERZENIO in MONARCH 1

<table>
<thead>
<tr>
<th>VERZENIO N=132</th>
<th>All Grades %</th>
<th>Grade 3 %</th>
<th>Grade 4 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine increased</td>
<td>98</td>
<td>&lt;1</td>
<td>0</td>
</tr>
<tr>
<td>White blood cell decreased</td>
<td>91</td>
<td>28</td>
<td>0</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>88</td>
<td>22</td>
<td>5</td>
</tr>
<tr>
<td>Anemia</td>
<td>68</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lymphocyte count decreased</td>
<td>42</td>
<td>13</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>41</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>ALT increased</td>
<td>31</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>AST increased</td>
<td>30</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>

Creatinine Increased

Abemaciclib has been shown to increase serum creatinine due to inhibition of renal tubular secretion transporters, without affecting glomerular function. In clinical studies, increases in serum creatinine (mean increase, 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 BUN, cystatin C, or calculated GFR, which are not based on creatinine, may be considered to determine whether renal function is impaired.

Table 12: Laboratory Abnormalities for Patients Receiving VERZENIO in MONARCH 1

<table>
<thead>
<tr>
<th>VERZENIO N=132</th>
<th>All Grades %</th>
<th>Grade 3 %</th>
<th>Grade 4 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT increased</td>
<td>31</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>AST increased</td>
<td>30</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>

Drug Interactions

Effect of Other Drugs on VERZENIO

Strong CYP3A Inhibitors

Strong CYP3A 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.

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 other strong CYP3A inhibitors. 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 other 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 strong inhibitor. Patients should avoid grapefruit products.

Strong CYP3A Inducers

Concomitant administration of VERZENIO with rifampin, a strong CYP3A inducer, decreased the plasma concentrations of abemaciclib plus its active metabolites and may lead to reduced activity. Avoid concomitant use of strong CYP3A inducers and consider alternative agents.

Use in Specific Populations

Pregnancy

Risk Summary

Based on findings in animals and its mechanism of action, VERZENIO can cause fetal harm when administered to a pregnant woman. 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 sternum, biparietal effacement of thoracic centroid, 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.

Lactation

Risk Summary

There are no data on the presence of abemaciclib in human milk, or its effects on the breastsed 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 at least 3 weeks after the last dose.

Females and Males of Reproductive Potential

Pregnancy Testing

Based on animal studies, VERZENIO can cause fetal harm when administered to a pregnant woman. Pregnancy testing is recommended for females of reproductive potential prior to initiating treatment with VERZENIO.

Contraception

Females

VERZENIO can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during VERZENIO treatment and for at least 3 weeks after the last dose.

Infertility

Males

Based on findings in animals, VERZENIO may impair fertility in males of reproductive potential.
Pediatric Use

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

Geriatric Use

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. The most common adverse reactions (≥5%) Grade 3 or 4 in patients ≥65 years of age across MONARCH 1, 2, and 3 were neutropenia, diarrhea, fatigue, nausea, dehydration, leukopenia, anemia, infections, and ALT increased. No overall differences in safety or effectiveness of VERZENIO were observed between these patients and younger patients.

Renal Impairment

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

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).

OVERDOSAGE

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

Rx only.

Additional information can be found at www.verzenio.com.
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