Pfizer Logo

Pfizer Brings Three New Biosimilars to U.S. Patients at Substantial Discounts

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Pfizer will become the first company to bring three oncology monoclonal antibody (mAb) biosimilar treatments to the U.S. market

Pfizer announced that it is introducing three new biosimilars, ZIRABEV™ (bevacizumab-bvzr), RUXIENCE™ (rituximab-pvvr) and TRAZIMERA™ (trastuzumab-qyyp) in the United States (U.S.). The medicines are expected to launch at the lowest Wholesale Acquisition Cost (WAC) among bevacizumab, rituximab or trastuzumab products currently on the market, becoming available at a substantially discounted price to the originator product.

“We’re proud to expand our leading biosimilars portfolio by launching these three treatments, which can potentially create significant savings for the U.S. healthcare system while increasing access to critical therapies,” said Angela Lukin, Regional President, North America Oncology at Pfizer. “We look forward to working with payers and providers to deliver these important medicines to patients that are living with certain cancers and autoimmune conditions.”

Pfizer’s oncology mAb biosimilars which have and/or will soon launch include:

- ZIRABEV, which was introduced to the U.S. market on December 31, 2019 at a WAC of $61.34 per 10 mg. This represents a 23% discount to the WAC of Avastin® (bevacizumab).[1]
    - ZIRABEV is available for the treatment of five types of cancer: metastatic colorectal cancer; unresectable, locally advanced, recurrent or metastatic non-squamous non-small cell lung cancer; recurrent glioblastoma; metastatic renal cell carcinoma; and persistent, recurrent or metastatic cervical cancer. Pfizer intends to seek expansion of the ZIRABEV label to include the treatment of epithelial ovarian, fallopian tube and primary peritoneal cancer as early as January 2021, pending regulatory approval.
- RUXIENCE, which was introduced to the U.S. market today at a WAC of $71.68 per 10 mg. This represents a 24% discount to the WAC of Rituxan® (rituximab).[2]
    - RUXIENCE is available for the treatment of adult patients with non-Hodgkin’s lymphoma, chronic lymphocytic leukemia, and granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA). It is the first licensed biosimilar for the treatment of GPA and MPA.
- TRAZIMERA, which will be made available on February 15, 2020 at a WAC of $80.74 per 10 mg. This represents a 22% discount to the WAC of Herceptin® (trastuzumab).[3]
    - TRAZIMERA will become available for the treatment of human epidermal growth factor receptor 2 (HER2) overexpressing breast cancer and HER2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma.

The WAC of each treatment applies to all approved uses. WAC is not inclusive of discounts to payers, providers, distributors and other purchasing organizations.

Pass-through status is being pursued for each of the three biosimilars. Pass-through payment is a program which supports reimbursement and incentivizes access for Medicare patients for certain treatments.

“The introduction of three new biosimilars is significant, delivering additional treatment options for patients across nine cancer types,” said Dr. Mark Pegram, associate director for clinical research at the Stanford Comprehensive Cancer Institute, and director of the Breast Oncology Program at the Stanford Women’s Cancer Center. “Biosimilars can play an important role in the care of people living with cancer, and I am encouraged by the possibility for improved access for providers to these medicines which are highly similar to their reference product.”

Biosimilars have been a significant catalyst for change for the global healthcare industry over the last decade, with the potential to create a more sustainable healthcare system. Pfizer is proud to be at the forefront of this vital healthcare segment, bringing over 30 years of experience in manufacturing biologics paired with more than 10 years of global in-market experience in biosimilars and an industry-leading eight approved biosimilar products in the U.S.

About ZIRABEV (bevacizumab-bvzr)

ZIRABEV is a mAb biosimilar of the reference product, Avastin, which is believed to work by inhibiting the formation of new blood vessels (angiogenesis) by specifically recognizing and binding to vascular endothelial growth factor (VEGF) protein. As part of the REFLECTIONS clinical trial program, ZIRABEV has been studied in more than 350 patients to date.[4,5,6,7]

ZIRABEV INDICATIONS AND IMPORTANT SAFETY INFORMATION

INDICATIONS

Metastatic colorectal cancer

ZIRABEV, in combination with intravenous fluorouracil-based chemotherapy, is indicated for the first- or second-line treatment of patients with metastatic colorectal cancer (mCRC).

ZIRABEV, in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy, is indicated for the second-line treatment of patients with mCRC who have progressed on a first-line bevacizumab product-containing regimen.

Limitation of Use: ZIRABEV is not indicated for adjuvant treatment of colon cancer.

First-line non-squamous non-small cell lung cancer

ZIRABEV, in combination with carboplatin and paclitaxel, is indicated for the first-line treatment of patients with unresectable, locally advanced, recurrent or metastatic non–squamous non–small cell lung cancer (NSCLC).

Recurrent glioblastoma

ZIRABEV is indicated for the treatment of recurrent glioblastoma (GBM) in adults.

Metastatic renal cell carcinoma

ZIRABEV, in combination with interferon alfa, is indicated for the treatment of metastatic renal cell carcinoma (mRCC).

Persistent, recurrent, or metastatic cervical cancer

ZIRABEV, in combination with paclitaxel and cisplatin or paclitaxel and topotecan, is indicated for the treatment of patients with persistent, recurrent, or metastatic cervical cancer.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

- Gastrointestinal (GI) perforation ranged from 0.3% to 3% across clinical studies. Discontinue ZIRABEV in patients with GI perforation
- Surgery and wound healing complications. Discontinue in patients with wound healing complications requiring medical intervention
- Severe or fatal hemorrhage, including hemoptysis, GI bleeding, hematemesis, central nervous system hemorrhage, epistaxis, and vaginal bleeding occurred up to 5-fold more frequently in patients receiving bevacizumab. In clinical studies, the incidence of grade ?3 hemorrhagic events among patients receiving bevacizumab ranged from 0.4% to 7%. Do not administer ZIRABEV to patients with serious hemorrhage or a recent history of hemoptysis (?1/2 tsp of red blood). Discontinue ZIRABEV in patients who develop grade 3-4 hemorrhage
- Non-GI fistulae (10% were: o Epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration, dry skin, rectal hemorrhage, lacrimation disorder, back pain, exfoliative dermatitis
- Renal injury and proteinuria
    - Grade 3–4 proteinuria ranged from 0.7% to 7% in clinical studies
    - Nephrotic syndrome (<1%)
- Additional serious adverse events with increased incidence in the bevacizumab-treated arm vs chemotherapy arm included:
    - Venous thromboembolism (grade ?3, 11% seen in GOG-0240)
    - Hypertension (grade 3–4, 5%–18%)
    - Posterior reversible encephalopathy syndrome (PRES) (<0.5%)
    - Congestive heart failure (CHF) (1%)
- Infusion-related reactions with the first dose of bevacizumab occurred in <3% of patients, and severe reactions occurred in 0.2% of patients
- Inform females of reproductive potential of the risk of ovarian failure prior to initiating treatment with ZIRABEV

Pregnancy warning

- Based on the mechanism of action and animal studies, bevacizumab products may cause fetal harm
- Advise female patients that bevacizumab products may cause fetal harm and to inform their healthcare provider of a known or suspected pregnancy

- Advise females of reproductive potential to use effective contraception during treatment with ZIRABEV and for 6 months after the last dose of ZIRABEV
- Advise nursing women that breastfeeding is not recommended during treatment with ZIRABEV and for 6 months following their last dose of treatment
- Bevacizumab products may impair fertility

Most common adverse events

- Across studies, the most common adverse reactions observed in bevacizumab patients at a rate >10% were:
    - Epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration, dry skin, rectal hemorrhage, lacrimation disorder, back pain, exfoliative dermatitis
- Across all studies, bevacizumab was discontinued in 8% to 22% of patients because of adverse reactions

Injection: 100 mg/4 mL (25 mg/mL) or 400 mg/16 mL (25 mg/mL) in single-dose vials

Indication-specific adverse events

- In CC, grade 3 or 4 adverse reactions in Study GOG-0240, occurring at a higher incidence (?2%) in 218 patients receiving Avastin plus chemotherapy compared to 222 patients receiving chemotherapy alone, were abdominal pain (12% vs 10%), diarrhea (6% vs 3%), anal fistula (4% vs 0%), proctalgia (3% vs 0%), urinary tract infection (8% vs 6%), cellulitis (3% vs 0.5%), fatigue (14% vs 10%), hypertension (11% vs 0.5%), thrombosis (8% vs 3%), hypokalemia (7% vs 4%), hyponatremia (4% vs 1%), dehydration (4% vs 0.5%), neutropenia (8% vs 4%), lymphopenia (6% vs 3%), back pain (6% vs 3%), and pelvic pain (6% vs 1%)
- In mRCC, the most common grade 3–5 adverse events in AVOREN, occurring at a ?2% higher incidence in Avastin-treated patients vs controls, were fatigue (13% vs 8%), asthenia (10% vs 7%), proteinuria (7% vs 0%), hypertension (6% vs 1%, including hypertension and hypertensive crisis), and hemorrhage (3% vs 0.3%, including epistaxis, small intestinal hemorrhage, aneurysm ruptured, gastric ulcer hemorrhage, gingival bleeding, hemoptysis, hemorrhage intracranial, large intestinal hemorrhage, respiratory tract hemorrhage, and traumatic hematoma)
- In rGBM Study EORTC 26101, 22% of patients discontinued treatment in the Avastin with lomustine arm due to adverse reactions compared with 10% of patients in the lomustine arm. In patients receiving Avastin with lomustine, the adverse reaction profile was similar to that observed in other approved indications
- In first-line MCRC, the most common grade 3–4 events in Study 2107, which occurred at a ?2% higher incidence in the Avastin plus IFL vs IFL groups, were asthenia (10% vs 7%), abdominal pain (8% vs 5%), pain (8% vs 5%), hypertension (12% vs 2%), deep vein thrombosis (9% vs 5%), intra-abdominal thrombosis (3% vs 1%), syncope (3% vs 1%), diarrhea (34% vs 25%), constipation (4% vs 2%), leukopenia (37% vs 31%), and neutropenia (21% vs 14%)
- In second-line MCRC, the most common grade 3–5 (nonhematologic) and 4–5 (hematologic) events in Study E3200, which occurred at a higher incidence (?2%) in the Avastin plus FOLFOX4 vs FOLFOX4 groups, were fatigue (19% vs 13%), diarrhea (18% vs 13%), sensory neuropathy (17% vs 9%), nausea (12% vs 5%), vomiting (11% vs 4%), dehydration (10% vs 5%), hypertension (9% vs 2%), abdominal pain (8% vs 5%), hemorrhage (5% vs 1%), other neurological (5% vs 3%), ileus (4% vs 1%), and headache (3% vs 0%). These data are likely to underestimate the true adverse event rates due to the reporting mechanisms used in this study

- When continued beyond first progression in MCRC, no new safety signals were observed in the TML study (ML18147) when Avastin was administered in second-line MCRC patients who progressed on an Avastin containing regimen in first-line MCRC. The safety data was consistent with the known safety profile established in first- and second-line MCRC5
- In NSCLC, grade 3–5 (nonhematologic) and grade 4–5 (hematologic) adverse events in Study E4599 occurring at a ?2% higher incidence in Avastin-treated patients vs controls were neutropenia (27% vs 17%), fatigue (16% vs 13%), hypertension (8% vs 0.7%), infection without neutropenia (7% vs 3%), venous thromboembolism (5% vs 3%), febrile neutropenia (5% vs 2%), pneumonitis/pulmonary infiltrates (5% vs 3%), infection with grade 3 or 4 neutropenia (4% vs 2%), hyponatremia (4% vs 1%), headache (3% vs 1%), and proteinuria (3% vs 0%)
- In mRCC, the most common grade 3–5 adverse events in AVOREN, occurring at a ?2% higher incidence in Avastin-treated patients vs controls, were fatigue (13% vs 8%), asthenia (10% vs 7%), proteinuria (7% vs 0%), hypertension (6% vs 1%, including hypertension and hypertensive crisis), and hemorrhage (3% vs 0.3%, including epistaxis, small intestinal hemorrhage, aneurysm ruptured, gastric ulcer hemorrhage, gingival bleeding, hemoptysis, hemorrhage intracranial, large intestinal hemorrhage, respiratory tract hemorrhage, and traumatic hematoma)
- In CC, grade 3 or 4 adverse reactions in Study GOG-0240, occurring at a higher incidence (?2%) in 218 patients receiving Avastin plus chemotherapy compared to 222 patients receiving chemotherapy alone, were abdominal pain (12% vs 10%), diarrhea (6% vs 3%), anal fistula (4% vs 0%), proctalgia (3% vs 0%), urinary tract infection (8% vs 6%), cellulitis (3% vs 0.5%), fatigue (14% vs 10%), hypertension (11% vs 0.5%), thrombosis (8% vs 3%), hypokalemia (7% vs 4%), hyponatremia (4% vs 1%), dehydration (4% vs 0.5%), neutropenia (8% vs 4%), lymphopenia (6% vs 3%), back pain (6% vs 3%), and pelvic pain (6% vs 1%)

Please see full Prescribing Information here for ZIRABEV (bevacizumab-bvzr) .

About RUXIENCE (rituximab-pvvr)

RUXIENCE is a mAb biosimilar to Rituxan which works by targeting a protein called CD20, which is present on the surface of B lymphocytes, also known as B cells. When it attaches to CD20, rituximab helps destroy these B cells.[8]

RUXIENCE INDICATIONS AND IMPORTANT SAFETY INFORMATION

RUXIENCE™ (rituximab-pvvr) is indicated for the treatment of adult patients with:

- Non-Hodgkin’s Lymphoma (NHL)
  - Relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL as a single agent
  - Previously untreated follicular, CD20-positive, B-cell NHL in combination with first-line chemotherapy, and in patients achieving a complete or partial response to a rituximab product in combination with chemotherapy, as single-agent maintenance therapy
  - Non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL, as a single agent, after first-line CVP chemotherapy
  - Previously untreated diffuse large B-cell, CD20- positive NHL in combination with CHOP or other anthracycline-based chemotherapy regimens
- Chronic Lymphocytic Leukemia (CLL)
  - Previously untreated and previously treated CD20- positive CLL in combination with fludarabine and cyclophosphamide

- Granulomatosis with Polyangiitis (GPA) (Wegener’s Granulomatosis) and Microscopic Polyangiitis (MPA) in adult patients in combination with glucocorticoids

BOXED WARNINGS AND ADDITIONAL IMPORTANT SAFETY INFORMATION

(A) FATAL INFUSION-RELATED REACTIONS, (B) SEVERE MUCOCUTANEOUS REACTIONS, (C) HEPATITIS B VIRUS REACTIVATION, (D) PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

(A) Infusion-Related Reactions: Rituximab product administration can result in serious, including fatal, infusion-related reactions. Deaths within 24 hours of rituximab infusion have occurred. Approximately 80% of fatal infusion-related reactions occurred in association with the first infusion. Monitor patients closely. Discontinue RUXIENCE infusion for severe reactions and provide medical treatment for Grade 3 or 4 infusion-related reactions

(B) Severe Mucocutaneous Reactions: Severe, including fatal, mucocutaneous reactions can occur in patients receiving rituximab products. Discontinue RUXIENCE in patients who experience a severe mucocutaneous reaction. The safety of readministration of RUXIENCE to patients with severe mucocutaneous reactions has not been determined

(C) Hepatitis B Virus (HBV) Reactivation: HBV reactivation can occur in patients treated with rituximab products, in some cases resulting in fulminant hepatitis, hepatic failure, and death. Screen all patients for HBV infection before treatment initiation, and monitor patients during and after treatment with RUXIENCE. Discontinue RUXIENCE and concomitant medications in the event of HBV reactivation

(D) Progressive Multifocal Leukoencephalopathy (PML), including fatal PML, can occur in patients receiving rituximab products. Discontinue RUXIENCE and consider discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy in patients who develop PML

Infusion-Related Reactions (IRR)

- Rituximab products can cause severe, including fatal, infusion-related reactions. Severe reactions typically occurred during the first infusion with time to onset of 30– 120 minutes
- Rituximab product?induced infusion-related reactions and sequelae include urticaria, hypotension, angioedema, hypoxia, bronchospasm, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, anaphylactoid events, or death
- Premedicate patients with an antihistamine and acetaminophen prior to dosing. Institute medical management (e.g., glucocorticoids, epinephrine, bronchodilators, or oxygen) for infusion-related reactions as needed. Depending on the severity of the infusion-related reaction and the required interventions, temporarily or permanently discontinue RUXIENCE. Resume infusion at a minimum 50% reduction in rate after symptoms have resolved
- Closely monitor the following patients: those with preexisting cardiac or pulmonary conditions, those who experienced prior cardiopulmonary adverse reactions, and those with high numbers of circulating malignant cells (?25,000/mm^3)

Severe Mucocutaneous Reactions

- Mucocutaneous reactions, some with fatal outcome, can occur in patients treated with rituximab products. These reactions include paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis
- The onset of these reactions has been variable and includes reports with onset on the first day of rituximab exposure. Discontinue RUXIENCE in patients who experience a severe mucocutaneous reaction. The safety of readministration of rituximab products to patients with severe mucocutaneous reactions has not been determined

Hepatitis B Virus Reactivation (HBV)

- HBV reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, can occur in patients treated with drugs classified as CD20-directed cytolytic antibodies, including rituximab products. Cases have been reported in patients who are hepatitis B surface antigen (HBsAg) positive and also in patients who are HBsAg negative but are hepatitis B core antibody (anti-HBc) positive. Reactivation has also occurred in patients who appear to have resolved hepatitis B infection (i.e., HBsAg negative, anti-HBc positive, and hepatitis B surface antibody [anti-HBs] positive)

- HBV reactivation is defined as an abrupt increase in HBV replication manifesting as a rapid increase in serum HBV DNA level or detection of HBsAg in a person who was previously HBsAg negative and anti-HBc positive. Reactivation of HBV replication is often followed by hepatitis, i.e., increase in transaminase levels. In severe cases, increase in bilirubin levels, liver failure, and death can occur
- Screen all patients for HBV infection by measuring HBsAg and anti-HBc before initiating treatment with RUXIENCE. For patients who show evidence of prior hepatitis B infection (HBsAg positive [regardless of antibody status] or HBsAg negative but anti-HBc positive), consult with physicians with expertise in managing hepatitis B regarding monitoring and consideration for HBV antiviral therapy before and/or during RUXIENCE treatment
- Monitor patients with evidence of current or prior HBV infection for clinical and laboratory signs of hepatitis or HBV reactivation during and for several months following RUXIENCE therapy. HBV reactivation has been reported up to 24 months following completion of rituximab therapy
- In patients who develop reactivation of HBV while on RUXIENCE, immediately discontinue RUXIENCE and any concomitant chemotherapy, and institute appropriate treatment. Insufficient data exist regarding the safety of resuming rituximab product treatment in patients who develop HBV reactivation. Resumption of RUXIENCE treatment in patients whose HBV reactivation resolves should be discussed with physicians with expertise in managing HPV.

Progressive Multifocal Leukoencephalopathy (PML)

- John Cunningham (JC) virus infection resulting in progressive multifocal leukoencephalopathy (PML) and death can occur in rituximab product?treated patients with hematologic malignancies or with autoimmune diseases. The majority of patients with hematologic malignancies diagnosed with PML received rituximab in combination with chemotherapy or as part of a hematopoietic stem cell transplant. Most cases of PML were diagnosed within 12 months of their last infusion of rituximab
- Consider the diagnosis of PML in any patient presenting with new-onset neurologic manifestations. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain MRI, and lumbar puncture. Discontinue RUXIENCE and consider discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy in patients who develop PML

Tumor Lysis Syndrome (TLS)

- Acute renal failure, hyperkalemia, hypocalcemia, hyperuricemia, or hyperphosphatemia from tumor lysis, some fatal, can occur within 12–24 hours after the first infusion of RUXIENCE in patients with non-Hodgkin's lymphoma (NHL). A high number of circulating malignant cells (?25,000/mm3), or high tumor burden, confers a greater risk of TLS
- Administer aggressive intravenous hydration and antihyperuricemic therapy in patients at high risk for TLS. Correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis as indicated

Infections

- Serious, including fatal, bacterial, fungal, and new or reactivated viral infections can occur during and following the completion of rituximab product?based therapy. Infections have been reported in some patients with prolonged hypogammaglobulinemia (defined as hypogammaglobulinemia >11 months after rituximab exposure)
- New or reactivated viral infections included cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis B and C. Discontinue RUXIENCE for serious infections and institute appropriate anti-infective therapy
- RUXIENCE is not recommended for use in patients with severe, active infections

Cardiovascular Adverse Reactions

- Cardiac adverse reactions, including ventricular fibrillation, myocardial infarction, and cardiogenic shock, may occur in patients receiving rituximab products. Discontinue infusions for serious or life-threatening cardiac arrhythmias. Perform cardiac monitoring during and after all infusions of RUXIENCE for patients who develop clinically significant arrhythmias, or who have a history of arrhythmia or angina

Renal Toxicity

- Severe, including fatal, renal toxicity can occur after rituximab product administration in patients with NHL. Renal toxicity has occurred in patients who experience TLS and in patients with NHL administered concomitant cisplatin therapy during clinical trials. The combination of cisplatin and RUXIENCE is not an approved treatment regimen. Monitor closely for signs of renal failure and discontinue RUXIENCE in patients with a rising serum creatinine or oliguria

Bowel Obstruction and Perforation

- Abdominal pain, bowel obstruction, and perforation, in some cases leading to death, can occur in patients receiving rituximab products in combination with chemotherapy. In postmarketing reports, the mean time to documented gastrointestinal perforation was 6 (range 1–77) days in patients with NHL. Evaluate if symptoms of obstruction such as abdominal pain or repeated vomiting occur

Immunization

- The safety of immunization with live viral vaccines following rituximab product therapy has not been studied, and vaccination with live virus vaccines is not recommended before or during treatment

Embryo-Fetal Toxicity

- Based on human data, rituximab products can cause fetal harm due to B-cell lymphocytopenia in infants exposed to rituximab in utero. Advise pregnant women of the risk to a fetus. Females of childbearing potential should use effective contraception while receiving RUXIENCE and for 12 months following the last dose of RUXIENCE

Concomitant Use With Biologic Agents and DMARDs Other Than Methotrexate

- Observe patients closely for signs of infection if biologic agents and/or DMARDs are used concomitantly. Use of concomitant immunosuppressants other than corticosteroids has not been studied in granulomatosis with polyangiitis (GPA) (wegener's granulomatosis) or microscopic polyangiitis (MPA) patients exhibiting peripheral B-cell depletion following treatment with RUXIENCE

Adverse Reactions

- The most common Grade 3 or 4 adverse reactions in clinical trials of NHL and chronic lymphocytic leukemia (CLL) were infusion-related reactions, neutropenia, leukopenia, anemia, thrombocytopenia, and infections. Additionally, lymphopenia and lung disorder were seen in NHL trials; and febrile neutropenia, pancytopenia, hypotension, and hepatitis B were seen in CLL trials
- The most common adverse reactions (incidence ?25%) in clinical trials of NHL and CLL were infusion-related reactions. Additionally, fever, lymphopenia, chills, infection, and asthenia were seen in NHL trials; and neutropenia was seen in CLL trials

Nursing Mothers

- There are no data on the presence of rituximab products in human milk, the effect on the breastfed child, or the effect on milk production. Since many drugs, including antibodies, are present in human milk, advise a lactating woman not to breastfeed during treatment and for at least 6 months after the last dose of RUXIENCE, due to the potential for serious adverse reactions in breastfed infants

Clinical Trials Experience in GPA and MPA

- Adverse reactions reported in ?15% of rituximab-treated patients were infections, nausea, diarrhea, headache, muscle spasms, anemia, and peripheral edema (other important adverse reactions include infusion-related reactions)

Induction Treatment of Patients With Active GPA/MPA (GPA/MPA Study 1)

Infusion-Related Reactions

- In GPA/MPA Study 1, 12% vs 11% (rituximab-treated vs cyclophosphamide-treated, respectively) of patients experienced at least one infusion-related reaction. Infusion-related reactions included cytokine release syndrome, flushing, throat irritation, and tremor. In the rituximab group, the proportion of patients experiencing an infusion reaction was 12%, 5%, 4%, and 1% following the first, second, third, and fourth infusions, respectively. Patients were premedicated with antihistamine and acetaminophen before each rituximab infusion and were on background oral corticosteroids, which may have mitigated or masked an infusion-related reaction; however, there is insufficient evidence to determine whether premedication diminishes the frequency or severity of infusion-related reactions

Infections

- In GPA/MPA Study 1, 62% vs 47% (rituximab-treated vs cyclophosphamide-treated, respectively) of patients experienced an infection by Month 6. The most common infections in the rituximab group were upper respiratory tract infections, urinary tract infections, and herpes zoster. The incidence of serious infections was 11% vs 10% (rituximab-treated vs cyclophosphamide-treated, respectively), with rates of approximately 25 and 28 per 100 patient-years, respectively. The most common serious infection was pneumonia

Hypogammaglobulinemia

- Hypogammaglobulinemia (IgA, IgG, or IgM below the lower limit of normal) has been observed in patients with GPA and MPA treated with rituximab in GPA/MPA Study 1. At 6 months, in the rituximab group, 27%, 58%, and 51% of patients with normal immunoglobulin levels at baseline had low IgA, IgG, and IgM levels, respectively, compared to 25%, 50%, and 46% in the cyclophosphamide group

Immunogenicity

- A total of 23/99 (23%) rituximab-treated patients with GPA or MPA tested positive for anti-rituximab antibodies by 18 months in GPA/MPA Study 1. The clinical relevance of anti-rituximab antibody formation in RUXIENCE-treated patients is unclear

Treatment of Patients With GPA/MPA Who Have Achieved Disease Control With Induction Treatment (GPA/MPA Study 2)

- In GPA/MPA Study 2, the safety profile was consistent with the known safety profile of rituximab in immunologic indications

Infusion-Related Reactions

- In GPA/MPA Study 2, 7/57 (12%) patients in the non-US-licensed approved rituximab arm reported infusion-related reactions. The incidence of IRR symptoms was highest during or after the first infusion (9%) and decreased with subsequent infusions (<4%). One patient had two serious IRRs; two IRRs led to a dose modification; and no IRRs were severe, fatal, or led to withdrawal from the study

Infections

- In GPA/MPA Study 2, 30/57 (53%) patients in the non-US-licensed approved rituximab arm and 33/58 (57%) in the he incidence of all-grade infections was similar between the arms. The incidence of serious infections was similar in both arms (12%). The most commonly reported serious infection in the group was mild or moderate bronchitis

Please see full Prescribing Information here for RUXIENCE (rituximab-pvvr), including BOXED WARNING.

About TRAZIMERA (trastuzumab-qyyp)

TRAZIMERA is a mAb biosimilar of the originator biologic medicine, Herceptin, which targets HER2, a protein found on the surface of some cancer cells which can stimulate the cells to divide and grow.[9] TRAZIMERA locks on to the HER2 protein and blocks the receptors, stopping cell division and growth.[10]

As part of the REFLECTIONS clinical trial program, TRAZIMERA has been studied in nearly 500 patients and across more than 20 countries to date.[11,12,13,14,15]

TRAZIMERA INDICATIONS AND IMPORTANT SAFETY INFORMATION

INDICATIONS

Adjuvant Breast Cancer

TRAZIMERA is indicated for adjuvant treatment of HER2-overexpressing node positive or node negative (ER/PR negative or with one high risk feature*) breast cancer

- As part of a treatment regimen containing doxorubicin, cyclophosphamide and either paclitaxel or docetaxel
- As part of a treatment regimen with docetaxel and carboplatin
- As a single agent following multi-modality anthracycline based therapy

Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product.

*High risk is defined as ER/PR positive with one of the following features: tumor size (2 cm, age <35 years, or tumor grade 2 or 3.

Metastatic Breast Cancer

TRAZIMERA is indicated:

- In combination with paclitaxel for the first-line treatment of HER2- overexpressing metastatic breast cancer
- As a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease

Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product.

Metastatic Gastric Cancer

TRAZIMERA is indicated, in combination with cisplatin and capecitabine or 5-fluorouracil, for the treatment of patients with HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma, who have not received prior treatment for metastatic disease.

Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product.

BOXED WARNINGS AND ADDITIONAL IMPORTANT SAFETY INFORMATION

Cardiomyopathy

- **Administration of trastuzumab products can result in sub-clinical and clinical cardiac failure. The incidence and severity was highest in patients receiving trastuzumab with anthracycline-containing chemotherapy regimens**
- **Evaluate left ventricular function in all patients prior to and during treatment with TRAZIMERA. Discontinue TRAZIMERA treatment in patients receiving adjuvant therapy and withhold TRAZIMERA in patients with metastatic disease for clinically significant decrease in left ventricular function**

Infusion Reactions; Pulmonary Toxicity

- **Administration of trastuzumab products can result in serious and fatal infusion reactions and pulmonary toxicity. Symptoms usually occur during or within 24 hours of administration. Interrupt TRAZIMERA infusion for dyspnea or clinically significant hypotension. Monitor patients until symptoms completely resolve. Discontinue TRAZIMERA for anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome**

Embryo-Fetal Toxicity

- **Exposure to trastuzumab products during pregnancy can result in oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Advise patients of these risks and the need for effective contraception**

Cardiomyopathy

- **Administration of trastuzumab products can result in sub-clinical and clinical cardiac failure. The incidence and severity was highest in patients receiving trastuzumab with anthracycline-containing chemotherapy regimens. In a pivotal adjuvant breast cancer trial, one patient who developed CHF died of cardiomyopathy**
- Trastuzumab products can cause left ventricular cardiac dysfunction, arrhythmias, hypertension, disabling cardiac failure, cardiomyopathy, and cardiac death
- Trastuzumab products can also cause asymptomatic decline in LVEF
- **Discontinue TRAZIMERA treatment in patients receiving adjuvant breast cancer therapy and withhold TRAZIMERA in patients with metastatic disease for clinically significant decrease in left ventricular function**

Cardiac Monitoring

- **Evaluate cardiac function prior to and during treatment. For adjuvant breast cancer therapy, also evaluate cardiac function after completion of TRAZIMERA**
- Conduct thorough cardiac assessment, including history, physical examination, and determination of LVEF by echocardiogram or MUGA scan
- Monitor frequently for decreased left ventricular function during and after TRAZIMERA treatment

- Monitor more frequently if TRAZIMERA is withheld for significant left ventricular cardiac dysfunction

Infusion Reactions

- **Administration of trastuzumab products can result in serious and fatal infusion reactions**
- **Symptoms usually occur during or within 24 hours of administration of trastuzumab products**
- **Interrupt TRAZIMERA infusion for dyspnea or clinically significant hypotension**
- **Monitor patients until symptoms completely resolve**
- **Discontinue TRAZIMERA for infusion reactions manifesting as anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome. Strongly consider permanent discontinuation in all patients with severe infusion reactions**
- Infusion reactions consist of a symptom complex characterized by fever and chills, and on occasion include nausea, vomiting, pain (in some cases at tumor sites), headache, dizziness, dyspnea, hypotension, rash, and asthenia

Embryo-Fetal Toxicity

- **Exposure to trastuzumab products during pregnancy can result in oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Advise patients of these risks and the need for effective contraception**
- Verify the pregnancy status of females of reproductive potential prior to the initiation of TRAZIMERA
- Advise pregnant women and females of reproductive potential that exposure to TRAZIMERA during pregnancy or within 7 months prior to conception can result in fetal harm
- Advise females of reproductive potential to use effective contraception during treatment and for at least 7 months following the last dose of TRAZIMERA
- Consider the developmental and health benefits of breastfeeding along with the mother’s clinical need for TRAZIMERA treatment and any potential adverse effects on the breastfed child from TRAZIMERA or from the underlying maternal condition

Pulmonary Toxicity

- **Administration of trastuzumab products can result in serious and fatal pulmonary toxicity,** which includes dyspnea, interstitial pneumonitis, pulmonary infiltrates, pleural effusions, noncardiogenic pulmonary edema, pulmonary insufficiency and hypoxia, acute respiratory distress syndrome, and pulmonary fibrosis. Such events can occur as sequelae of infusion reactions
- Patients with symptomatic intrinsic lung disease or with extensive tumor involvement of the lungs, resulting in dyspnea at rest, appear to have more severe toxicity
- Discontinue TRAZIMERA in patients experiencing pulmonary toxicity

Exacerbation of Chemotherapy-Induced Neutropenia

- In randomized, controlled clinical trials, the numbers of per-patient incidences of NCI-CTC Grade 3-4 neutropenia and of febrile neutropenia were higher in patients receiving trastuzumab in combination with myelosuppressive chemotherapy as compared to those who received chemotherapy alone. The incidence of septic death was similar among patients who received trastuzumab and those who did not

Most Common Adverse Reactions

- The most common adverse reactions associated with trastuzumab products in breast cancer were fever, nausea, vomiting, infusion reactions, diarrhea, infections, increased cough, headache, fatigue, dyspnea, rash, neutropenia, anemia, and myalgia
- The most common adverse reactions associated with trastuzumab products in metastatic gastric cancer were neutropenia, diarrhea, fatigue, anemia, stomatitis, weight loss, upper respiratory tract infections, fever, thrombocytopenia, mucosal inflammation, nasopharyngitis, and dysgeusia

Please see full Prescribing Information here for TRAZIMERA (trastuzumab-qyyp), including BOXED WARNING.

About Pfizer Oncology

At Pfizer Oncology, we are committed to advancing medicines wherever we believe we can make a meaningful difference in the lives of patients. Today, Pfizer Oncology has an industry-leading portfolio of 22 approved innovative cancer medicines and biosimilars across more than 30 indications, including breast, prostate, kidney and lung cancers, as well as leukemia and melanoma. Pfizer Oncology is striving to change the trajectory of cancer.

Pfizer Inc.: Breakthroughs that change patients' lives

At Pfizer, we apply science and our global resources to bring therapies to people that extend and significantly improve their lives. We strive to set the standard for quality, safety and value in the discovery, development and manufacture of health care products, including innovative medicines and vaccines. Every day, Pfizer colleagues work across developed and emerging markets to advance wellness, prevention, treatments and cures that challenge the most feared diseases of our time. Consistent with our responsibility as one of the world's premier innovative biopharmaceutical companies, we collaborate with health care providers, governments and local communities to support and expand access to reliable, affordable health care around the world. For more than 150 years, we have worked to make a difference for all who rely on us. We routinely post information that may be important to investors on our website at www.pfizer.com. In addition, to learn more, please visit us on www.pfizer.com and follow us on Twitter at @Pfizer and @Pfizer_News, LinkedIn, YouTube and like us on Facebook at Facebook.com/Pfizer.

DISCLOSURE NOTICE: The information contained in this statement is as of January 23, 2020. Pfizer assumes no obligation to update forward-looking statements contained in this statement as the result of new information or future events or developments. This statement contains forward-looking information about ZIRABEV (bevacizumab-bvzr), TRAZIMERA (trastuzumab-gyyp) and RUXIENCE (rituximab-pvvr), including their potential benefits, that involves substantial risks and uncertainties that could cause actual results to differ materially from those expressed or implied by such statements. Risks and uncertainties include, among other

things, uncertainties regarding the commercial success of ZIRABEV, TRAZIMERA or RUXIENCE in the United States; the uncertainties inherent in research and development, including the ability to meet anticipated clinical endpoints, commencement and/or completion dates for our clinical trials, regulatory submission dates, regulatory approval dates and/or launch dates, as well as the possibility of unfavorable new clinical data and further analyses of existing clinical data; the risk that clinical trial data are subject to differing interpretations and assessments by regulatory authorities; whether regulatory authorities will be satisfied with the design of and results from our clinical studies; whether and when applications for ZIRABEV, TRAZIMERA or RUXIENCE may be filed in any other jurisdictions; whether and when the European Medicines Agency will approve the pending application for RUXIENCE and whether and when regulatory authorities in any other jurisdictions may approve any other applications for ZIRABEV, TRAZIMERA or RUXIENCE that may be pending or filed, which will depend on myriad factors, including making a determination as to whether such product's benefits outweigh its known risks and determination of the product's efficacy and, if approved, whether ZIRABEV, TRAZIMERA or RUXIENCE will be commercially successful; intellectual property and/or litigation implications; decisions by regulatory authorities impacting labeling, manufacturing processes, safety and/or other matters that could affect the availability or commercial potential of ZIRABEV, TRAZIMERA or RUXIENCE; uncertainties regarding access challenges for our biosimilar products where our product may not receive appropriate formulary access or remains in a disadvantaged position relative to the innovator product; and competitive developments. A further description of risks and uncertainties can be found in Pfizer's Annual Report on Form 10-K for the fiscal year ended December 31, 2018 and in its subsequent reports on Form 10-Q, including in the sections thereof captioned "Risk Factors" and "Forward-Looking Information and Factors That May Affect Future Results", as well as in its subsequent reports on Form 8-K, all of which are filed with the U.S. Securities and Exchange Commission and available at www.sec.gov and www.pfizer.com. # # # # # 1 Avastin® is a registered trademark of Genentech, Inc. 2 Rituxan® is a registered trademark of Genentech, Inc. and Biogen, Inc. 3 Herceptin® is a registered trademark of Genentech, Inc. 4 Socinski MA, Von Pawel J, Kasahara K, et al. A comparative clinical study of PF-06439535, a candidate bevacizumab biosimilar, and reference bevacizumab, in patients with advanced nonsquamous non-small cell lung cancer. Abstract 109. Presented at ASCO 2018. 5 Knight B, Rassam D, Liao S, et al. A phase I pharmacokinetics study comparing PF-06439535 (a potential biosimilar) with bevacizumab in healthy male volunteers. Cancer Chemother Pharmacol. 2016. 77:839-846. 6 Clinicaltrials.gov. NCT02031991. A pharmacokinetic study comparing PF-06439535 and bevacizumab in healthy male volunteers (REFLECTIONS B739-01). Available at https://clinicaltrials.gov/ct2/show/NCT02031991?term=reflections+bevacizuma b&rank=1. Accessed January 2020. 7 Pfizer. Pfizer announces positive top-line results from the comparative REFLECTIONS B7391003 study for PF-06439535, a potential biosimilar to Avastin® (bevacizumab). Available at https://www.pfizer.com/news/press-release/press-release-detail/pfizer_announces_positive_top_line_results_from_the_comparative_refl ections_b7391003_study_for_pf_06439535_a_potential_biosimilar_to_avastin_1_ bevacizumab. Accessed January 2020. 8 RUXIENCE™ (rituximab-pvvr) Prescribing Information. New York. NY: Pfizer Inc: 2019. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761103s000lbl.pdf . Accessed January 2020. 9 Macmillan Cancer Support. Trastuzumab. Available at https://www.macmillan.org.uk/cancerinformation/cancertreatment/treatmenttyp es/biologicaltherapies/monoclonalantibodies/trastuzumab.aspx. Accessed January 2020. 10 European Medicines Agency. Herceptin Summary of Product Characteristics. Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000278/WC500074922.pdf. Accessed January 2020. 11 Pegram M, Tan-Chiu E, Freyman A, et al. Abstract 238PD. A randomized, double-blind study of PF-05280014 (a potential trastuzumab biosimilar) vs trastuzumab, both in combination with paclitaxel, as first-line treatment for HER2-positive metastatic breast cancer. Presented at ESMO 2017. 12 Lammers PE, Dank M, Masetti R, et al. A randomized, double-blind study of PF-05280014 (a potential biosimilar) vs trastuzumab, both given with docetaxel (D) and carboplatin (C), as neoadjuvant treatment for operable human epidermal growth factor receptor 2-positive (HER2+) breast cancer. Abstract 154PD. Presented at ESMO 2017. 13 Yin D, Barker K B, Li R, et al. A

randomized phase 1 pharmacokinetic trial comparing the potential biosimilar PF-05280014 with trastuzumab in healthy volunteers (REFLECTIONS B327-01). BR J Clin Pharmacol. 2014. 78(6): 1281-90. 14 Clinicaltrials.gov. NCT01989676. A study of PF-05280014 [trastuzumab-Pfizer] or Herceptin (trastuzumab) plus paclitaxel in HER2 positive first line metastatic breast cancer treatment (REFLECTIONS B327-02). Available at https://clinicaltrials.gov/ct2/show/NCT01989676?term=NCT01989676&rank=1. Accessed January 2020. 15 Clinicaltrials.gov. NCT02187744. A study of PF-05280014 or trastuzumab plus taxotere and carboplatin in HER2 positive breast cancer in the neoadjuvant setting (REFLECTIONS B327-04). Available at https://clinicaltrials.gov/ct2/show/NCT02187744?term=NCT02187744&rank=1. Accessed January 2020. Media Contact: Amy Rose M: +1 646-592-3157 E: Amy.Rose@pfizer.com Investor Contact: Ryan Crowe O: +1 212-733-8160 E:Amy.Rose@pfizer.com