HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use RYZNEUTA ®safely and effectively. See full prescribing information for RYZNEUTA.

RYZNEUTA ®(efbemalenograstim alfa-vuxw) injection, for subcutaneous use
Initial U.S. Approval: 2023

INDICATIONS AND USAGE

RYZNEUTA is a leukocyte growth factor indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in adult patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia. (1)

Limitations of Use

RYZNEUTA is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation. (1)

DOSAGE AND ADMINISTRATION

- Recommended Dose: 20 mg administered subcutaneously once per chemotherapy cycle. (2.1)
- Administer approximately 24 hours after cytotoxic chemotherapy. Do not administer between 14 days before and 24 hours after administration of cytotoxic chemotherapy. (2.1)

DOSAGE FORMS AND STRENGTHS

- Injection: 20 mg/mL solution in a single-dose prefilled syringe. (3)

CONTRAINDICATIONS

Patients with a history of serious allergic reactions to granulocyte stimulating factors such as efbemalenograstim alfa-vuxw, pegfilgrastim, or filgrastim products. (4)

WARNINGS AND PRECAUTIONS

- Fatal splenic rupture: Evaluate patients who report left upper abdominal or shoulder pain for an enlarged spleen or splenic rupture. (5.1)
- Acute respiratory distress syndrome (ARDS): Evaluate patients who develop fever, lung infiltrates, or respiratory distress. Discontinue RYZNEUTA in patients with ARDS. (5.2)
- Serious allergic reactions, including anaphylaxis: Permanently discontinue RYZNEUTA in patients with serious allergic reactions. (5.3)
- Sickle cell crises in Patients with Sickle Cell Disorders: Discontinue RYZNEUTA if sickle cell crisis occurs. (5.4)
- Glomerulonephritis: Evaluate and consider dose-reduction or interruption of RYZNEUTA if causality is likely. (5.5)
- Thrombocytopenia: Monitor platelet counts. (5.7)
- Capillary Leak Syndrome: Monitor patients with symptoms; consider intensive care. (5.8)
- Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML) in Patients with Breast and Lung Cancer: Monitor patients with breast and lung cancer using RYZNEUTA in conjunction with chemotherapy and/or radiotherapy for signs and symptoms of MDS/AML. (5.10)

ADVERSE REACTIONS

Most common adverse reactions (≥10%) were nausea, anemia, and thrombocytopenia. (6.1)
To report SUSPECTED ADVERSE REACTIONS, contact Acrotech Biopharma Inc at 1-888-292-9617 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.
See 17 for FDA-approved patient labeling.

Revised: 12/2024

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FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

RYZNEUTA is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in adult patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

Limitations of Use

RYZNEUTA is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.

2. DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage of RYZNEUTA is a single subcutaneous injection of 20 mg administered once per chemotherapy cycle at least 24 hours after cytotoxic chemotherapy. Do not administer RYZNEUTA within 14 days before and <24 hours after administration of cytotoxic chemotherapy.

2.2 Administration

RYZNEUTA is administered subcutaneously via a single-dose prefilled syringe by a healthcare professional.

Prior to use, remove the carton from the refrigerator (keeping the prefilled syringe inside the carton) for a minimum of 30 minutes to allow the product to reach room temperature. Discard any product left at room temperature for greater than 48 hours.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not administer RYZNEUTA if discoloration or particulates are observed.

Caution: This product contains natural rubber latex which may cause allergic reactions. The needle cap on the prefilled syringe contains natural rubber; people with latex allergies should not administer this product.

The RYZNEUTA prefilled syringe does not bear graduation marks and is intended only to deliver the entire contents of the syringe (20 mg/mL) for direct administration to adult patients.

Administer injection by pinching the skin and holding. Inject into the abdomen, the back or side of the upper arms, or the thighs. Rotate injection sites. Do not inject into scar tissue or areas that are reddened, inflamed, or swollen. If injecting into the abdomen, avoid a 2-inch diameter circle around the navel. Once the entire dose has been injected, the needle safety device will be triggered, pulling the needle automatically from the skin, and into the barrel; the entire needle will be covered by the needle guard.

3. DOSAGE FORMS AND STRENGTHS

Injection: 20 mg/mL clear, colorless, preservative-free solution in a single-dose prefilled syringe.

4. CONTRAINDICATIONS

RYZNEUTA is contraindicated in patients with a history of serious allergic reactions to granulocyte stimulating factors such as efbemalenograstim alfa-vuxw, pegfilgrastim, or filgrastim products *[see Warnings and Precautions (5.3)]* .

5. WARNINGS AND PRECAUTIONS

5.1 Splenic Rupture

Splenic rupture, including fatal cases, can occur following the administration of recombinant human granulocyte colony-stimulating factor (rhG-CSF) products, such as RYZNEUTA. Evaluate for an enlarged spleen or splenic rupture in patients who report left upper abdominal or shoulder pain after receiving RYZNEUTA.

5.2 Acute Respiratory Distress Syndrome

Acute respiratory distress syndrome (ARDS) can occur in patients receiving rhG-CSF products, such as RYZNEUTA. Evaluate patients who develop fever and lung infiltrates or respiratory distress after receiving RYZNEUTA for ARDS. Discontinue RYZNEUTA in patients with ARDS.

5.3 Serious Allergic Reactions

Serious allergic reactions, including anaphylaxis, can occur in patients receiving rhG-CSF products, such as RYZNEUTA. Permanently discontinue RYZNEUTA in patients with serious allergic reactions. RYZNEUTA is contraindicated in patients with a history of serious allergic reactions to RYZNEUTA or other rhG-CSF products such as pegfilgrastim, eflapegrastim or filgrastim products.

5.4 Sickle Cell Crisis in Patients with Sickle Cell Disorders

Severe and sometimes fatal sickle cell crises can occur in patients with sickle cell disorders receiving rhG-CSF products, such as RYZNEUTA. Discontinue RYZNEUTA if sickle cell crisis occurs.

5.5 Glomerulonephritis

Glomerulonephritis has occurred in patients receiving rhG-CSF products. The diagnoses were based upon azotemia, hematuria (microscopic and macroscopic), proteinuria, and renal biopsy. Generally, events of glomerulonephritis resolved after dose-reduction or discontinuation of rhG-CSF. If glomerulonephritis is suspected, evaluate for cause. If causality is likely, consider dose-reduction or interruption of RYZNEUTA.

5.6 Leukocytosis

White blood cell (WBC) counts of 100×10^9/L or greater have been observed in patients receiving rhG-CSF products. Monitor complete blood count (CBC) during RYZNEUTA therapy. Discontinue RYZNEUTA treatment if WBC count of 100×10^9/L or greater occurs.

5.7 Thrombocytopenia

Thrombocytopenia has been reported in patients receiving rhG-CSF products. Thrombocytopenia occurred in 11% of RYZNEUTA-treated patients. One patient (0.4%) experienced severe thrombocytopenia. Monitor platelet counts.

5.8 Capillary Leak Syndrome

Capillary leak syndrome has been reported after administration of rhG-CSF products and is characterized by hypotension, hypoalbuminemia, edema and hemoconcentration. Episodes vary in frequency and severity, and may be life-threatening if treatment is delayed. Patients who develop symptoms of capillary leak syndrome should be closely monitored and receive standard symptomatic treatment, which may include a need for intensive care.

5.9 Potential for Tumor Growth Stimulatory Effects on Malignant Cells

The granulocyte colony-stimulating factor (G-CSF) receptor through which RYZNEUTA acts has been found on tumor cell lines. The possibility that RYZNEUTA acts as a growth factor for any tumor type, including myeloid malignancies and myelodysplasia, diseases for which RYZNEUTA is not approved, cannot be excluded.

5.10 Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML) in Patients with Breast and Lung Cancer

MDS and AML have been associated with the use of rhG-CSF products in conjunction with chemotherapy and/or radiotherapy in patients with breast and lung cancer. Monitor patients for signs and symptoms of MDS/AML in these settings.

5.11 Aortitis

Aortitis has been reported in patients receiving rhG-CSF products. It may occur as early as the first week after start of therapy. Manifestations may include generalized signs and symptoms such as fever, abdominal pain, malaise, back pain, and increased inflammatory markers (e.g., c-reactive protein and white blood cell count). Consider aortitis in patients who develop these signs and symptoms without known etiology. Discontinue RYZNEUTA if aortitis is suspected.

5.12 Nuclear Imaging

Increased hematopoietic activity of the bone marrow in response to growth factor therapy has been associated with transient positive bone imaging changes. This should be considered when interpreting bone imaging results.

6. ADVERSE REACTIONS

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

- Splenic Rupture *[see Warnings and Precautions (5.1)]*
- Acute Respiratory Distress Syndrome *[see Warnings and Precautions (5.2)]*
- Serious Allergic Reactions *[see Warnings and Precautions (5.3)]*
- Sickle Cell Crisis in Patients with Sickle Cell Disorders *[see Warnings and Precautions (5.4)]*
- Glomerulonephritis *[see Warnings and Precautions (5.5)]*
- Leukocytosis *[see Warnings and Precautions (5.6)]*
- Thrombocytopenia *[see Warnings and Precautions (5.7)]*
- Capillary Leak Syndrome *[see Warnings and Precautions (5.8)]*
- Potential for Tumor Growth Stimulatory Effects on Malignant Cells *[see Warnings and Precautions (5.9)]*
- Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML) in Patients with Breast and Lung Cancer *[see Warnings and Precautions (5.10)]*
- Aortitis *[see Warnings and Precautions (5.11)]*

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 with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The following adverse reaction data are based on two studies [see Clinical Studies (14)]. The first was a randomized, double-blind, placebo-controlled study in patients with metastatic or non-metastatic breast cancer receiving doxorubicin 60 mg/m ^{2} and docetaxel 75 mg/m ^{2} every 21 days (Study GC-627-04). A total of 122 female patients were randomized to receive either 20 mg RYZNEUTA (n=83) or placebo (n=39) in chemotherapy cycle 1; all patients received RYZNEUTA in cycles 2-4. The second was a randomized, open-label, active-controlled study in patients with stage I to III invasive breast cancer receiving docetaxel 75 mg/m ^{2} and cyclophosphamide 600 mg/m ^{2} (Study GC-627-05). A total of 393 patients were randomized to receive either 20 mg RYZNEUTA (n=197) or pegfilgrastim (n=196) in chemotherapy cycles 1 through 4.

In Study GC-627-04, the most common adverse reactions (≥10%) in the RYZNEUTA arm through cycle 1 were nausea, anemia, and thrombocytopenia (see Table 1). Other adverse reactions reported by ≥ 20% of RYZNEUTA-treated Patients with Breast Cancer Receiving Myelosuppressive Chemotherapy in Study GC-627-05 were fatigue and bone pain.

Table 1. Adverse Reactions * in Study GC-627-04 in RYZNEUTA-treated Patients with Breast Cancer Receiving Myelosuppressive Chemotherapy Through Cycle 1

Adverse Reactions	Ryzneuta (n=83)	Placebo (n=39)
Nausea	42 (51)	15 (39)
Anemia	12 (15)	4 (10)
Thrombocytopenia	10 (12)	1 (3)

* Adverse reactions that occurred in ≥10% of Ryzneuta-treated patients and ≥5% more than placebo-treated patients.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Although available data with RYZNEUTA use in pregnant women are insufficient to establish whether there is a drug associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes, there are available data from published studies in pregnant women exposed to other human G-CSF products. These studies have not established an association of G-CSF product use during pregnancy with major birth defects, miscarriage, or adverse maternal or fetal outcomes.

In animal studies, no evidence of reproductive/developmental toxicity occurred in the offspring of pregnant rats and rabbits that received cumulative doses of efbemalenograstim alfa-vuxw approximately 2.6 and 0.7 times, respectively, the recommended human dose (based on body surface area).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Three studies were conducted in pregnant rats dosed with efbemalenograstim alfa-vuxw at cumulative doses up to approximately 2.6 times the recommended human dose at the following stages of gestation: during the period of organogenesis, from mating through the first half of pregnancy, and from the first trimester through delivery and lactation. No evidence of fetal loss or structural malformations was observed in any study. Growth and learning were also unaffected.

Pregnant rabbits were dosed with efbemalenograstim alfa-vuxw every other day during organogenesis at cumulative doses up to 0.7 times the recommended human dose showed no signs of fetal loss or structural malformations.

Maternal toxicity (decreased weight gain or weight loss and/or death) was observed when higher cumulative doses of efbemalenograstim alfa-vuxw were used in an early dose-ranging study in rabbits.

8.2 Lactation

Risk Summary

There are no data on the presence of efbemalenograstim alfa-vuxw or its metabolite in either human or animal milk, the effects on the breastfed child, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for efbemalenograstim alfa-vuxw and any potential adverse effects on the breastfed child from efbemalenograstim alfa-vuxw or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of RYZNEUTA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience with RYZNEUTA has not identified differences in responses between the elderly and younger patients.

10. OVERDOSAGE

Overdosage of RYZNEUTA may result in leukocytosis and bone pain. In the event of overdose, general supportive measures should be instituted, as necessary. Monitor the patient for adverse reactions *[see Adverse Reactions (6)]* .

11. DESCRIPTION

Efbemalenograstim alfa-vuxw, a leukocyte growth factor, is a 413 amino acid recombinant fusion protein consisting of human G-CSF, a 16 amino-acid linker, and the Fc portion of human IgG2. In solution, efbemalenograstim alfa-vuxw forms covalently-linked dimers (disulfide bonds between Fc moieties), resulting in an immunoglobulin-like structure. The dimer is a water-soluble, glycosylated protein with a molecular weight of approximately 93.4 kilodaltons (kDa), of which 89.5 kDa is attributed to amino acids (protein sequence) and the remainder is from glycosylation. Efbemalenograstim alfa-vuxw is obtained from genetically-engineered strain of Chinese hamster ovary (CHO) cells grown in a serum-free medium.

RYZNEUTA (efbemalenograstim alfa-vuxw) injection is supplied in 1 mL prefilled single-dose syringes for manual subcutaneous injection. The prefilled syringe does not bear graduation marks and is designed to deliver the entire contents of the syringe (20 mg/mL). Each syringe contains 20 mg efbemalenograstim alfa-vuxw in a sterile, clear, colorless, preservative-free solution (pH 5.2) containing acetate (0.6 mg), EDTA (0.29 mg), polysorbate 20 (0.1 mg), sodium (0.23 mg), and sorbitol (50 mg) in Water for Injection, USP.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Efbemalenograstim alfa-vuxw is a colony-stimulating factor that acts on hematopoietic cells by binding to specific cell surface receptors, thereby stimulating proliferation, differentiation, commitment, and end cell functional activation.

12.2 Pharmacodynamics

Over the tested dose range of 30 to 360 µg/kg in healthy adult males, neutrophils generally increased in a dose-dependent manner; however, the effect on neutrophils plateaued at the top two doses of 240 and 360 µg/kg.

In patients with breast cancer given EC chemotherapy, in cycle 1, median ANC peaked on Day 4 (about 24 hours after efbemalenograstim alfa-vuxw administration) for the 240 and 320 µg/kg doses, declined to nadir on Days 8–9, and then recovered to a count of 2.0×10^{9}/L and higher by Day 11. The ANC levels in cycles 2, 3, and 4 tended to be higher than those observed in cycle 1.

In patients with breast cancer given TAC chemotherapy, in cycle 1, median ANC peaked on Day 3 (about 24 hours after efbemalenograstim alfa-vuxw administration) in cycle 1 and 3, reached nadir on Day 8, and recovered to 2.0 x 10^{9}/L on Days 9 and 10 for the 320 µg/kg and 240 µg/kg doses, respectively. Mean ANC nadir was higher with 320 µg/kg compared to 240 µg/kg in both cycle 1 (0.75 x 10^{9}/L and 0.29 x 10^{9}/L, respectively), and cycle 3 (1.19 x 10^{9}/L and 0.57 x 10^{9}/L, respectively).

12.3 Pharmacokinetics

The pharmacokinetics of efbemalenograstim alfa-vuxw was studied in female patients with breast cancer and healthy male subjects. Efbemalenograstim alfa-vuxw exhibited nonlinear and time-dependent pharmacokinetics over the dose range of 30 to 360 µg/kg. At the approved recommended dose in healthy subjects, the mean (%CV) $C_{max}$was 1202 ng/mL (56%), and the $AUC_{0\text{-}inf}$was 76357 h*ng/mL (65%). At the approved recommended dose in patients with breast cancer, the geometric mean (CV%) Cmax was 1085 ng/mL (92%) in Cycle 1 and 525 ng/mL (163%) in Cycle 3; the geometric mean (CV%) $AUC_{0\text{-}inf}$was 54858 h*ng/mL (110%) in Cycle 1 and 26217 h*ng/mL (167%) in Cycle 3.

Absorption

The median t_{max} of efbemalenograstim alfa-vuxw administered as 80 to 320 µg/kg in female patients with breast cancer receiving EC chemotherapy ranged from 24 hours to 48 hours in Cycle 1 and 9 to 30 hours in Cycle 3. The median t_{max} of efbemalenograstim alfa-vuxw administered as 240 to 320 µg/kg in female participants with breast cancer receiving TAC chemotherapy was 36 hours in Cycle 1 and ranged from 24 to 30 hours in Cycle 3.

Distribution

The geometric mean (CV%) apparent volume of distribution of efbemalenograstim alfa-vuxw was 18.8 L (257%) in Cycle 1 and 40.7 L (387%) in Cycle 3 in female patients with breast cancer.

Elimination

The geometric mean (CV%) apparent clearance of efbemalenograstim alfa-vuxw was 0.36 L/h (110%) in Cycle 1 and 0.76 L/h (167%) in Cycle 3. The geometric mean (CV%) elimination half-life of efbemalenograstim alfa-vuxw was 35.6 h (108%) in Cycle 1 and 36.9 h (120%) in Cycle 3. Neutrophil receptor binding is an important component of the clearance of efbemalenograstim alfa-vuxw, and serum clearance is directly related to the number of neutrophils.

Metabolism

Efbemalenograstim alfa-vuxw is expected to be metabolized into small peptides by catabolic pathways.

Specific Populations

No clinically significant differences were observed based on age (20 to 83 years) or body weight (40 to 137 kg) *[see Use in Specific Populations (8.5)]*. The impact of sex, race/ethnicity, renal impairment, hepatic impairment, and pregnancy on the pharmacokinetics of efbemalenograstim alfa-vuxw are unknown.

12.6 Immunogenicity

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies, including those of efbemalenograstim alfa-vuxw or of other efbemalenograstim alfa products.

During the 3-month treatment period and 6-month follow-up in studies GC-627-04, GC-627-05 and SP11631, 20/438 (4.6%) RYZNEUTA-treated subjects developed treatment-emergent anti-drug antibodies to efbemalenograstim alfa-vuxw (3/121, 17/197 and 0/120, respectively). Additionally, 16/438 (3.7%) of RYZNUETA-treated subjects developed treatment-emergent antibodies to G-CSF (1/121, 15/197 and 0/120, respectively). None of these patients who were positive for antibodies to efbemalenograstim alfa-vuxw or G-CSF had evidence of neutralizing antibodies using a cell-based bioassay, and there was no evidence of altered pharmacokinetics or allergic-type reactions. In Study GC-627-05, the incidence of antibodies to G-CSF was similar in patients treated with RYZNEUTA (15/197, 7.6%) and pegfilgrastim

(13/195, 6.7%). None of these patients had evidence of neutralizing antibodies to G-CSF based on a cell-based bioassay and clinical observations, including absolute neutrophil counts.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity or mutagenesis studies have been conducted with efbemalenograstim alfa-vuxw.

Efbemalenograstim alfa did not affect reproductive performance or fertility in male or female rats at cumulative weekly doses approximately 2.2 times higher than the recommended human dose (based on body surface area).

14. CLINICAL STUDIES

The efficacy of RYZNEUTA to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs was evaluated in two randomized, controlled studies.

Study GC-627-04 [NCT02872103] was a randomized, double-blind, placebo-controlled study that employed doxorubicin 60 mg/m ^{2} and docetaxel 75 mg/m ^{2} administered every 21 days for up to 4 cycles for the treatment of metastatic or non-metastatic breast cancer. In this study, 122 patients were randomized to receive a single subcutaneous injection of RYZNEUTA (20 mg) or placebo on day 2 of chemotherapy cycle 1. All patients received RYZNEUTA (20 mg) on day 2 of chemotherapy cycles 2 – 4. The patients were 30 to 69 years of age and all female. The race was 99% Caucasian, and 1% Black. The ethnicity was 2% Hispanic or Latino.

Efficacy was based upon the mean duration of severe (Grade 4) neutropenia in cycle 1 which was lower for RYZNEUTA-treated patients as compared to placebo-treated patients (LS mean: 1.4 days versus 4.3 days, respectively, p<0.001 [95% CI: 2.4, 3.5]). The incidence of febrile neutropenia (defined as temperature ≥38.3°C, or >38.0°C sustained for at least 1 hour, and ANC < 0.5 × 10 ^{9}/L) was also lower for RYZNEUTA-treated patients compared to placebo-treated patients in cycle 1 (4.8% versus 25.6%, respectively, p=0.0016; 20.8% difference [95% CI: 1.8%, 38.8%].

Study GC-627-05 [NCT03252431] was a randomized, active-controlled study that compared RYZNEUTA to pegfilgrastim. Study GC-627-05 employed docetaxel 75 mg/m ^{2}and cyclophosphamide 600 mg/m ^{2}administered every 21 days for up to 4 cycles for the treatment of non-metastatic breast cancer. In this study, 393 patients were randomized to receive a single subcutaneous injection of RYZNEUTA (20 mg) or pegfilgrastim (6 mg) on day 2 of each chemotherapy cycle. The patients were 26 to 83 years of age and all female and Caucasian. The ethnicity was 0.3% Hispanic or Latino.

The study demonstrated that the mean days of severe (Grade 4) neutropenia of RYZNEUTA-treated patients did not exceed that of pegfilgrastim-treated patients by more than 0.6 days in cycle 1 of chemotherapy. The mean days of severe neutropenia in cycle 1 were 0.2 days in both the RYZNEUTA and pegfilgrastim arms (difference in means 0.0 days [95% CI -0.1, 0.1]).

Subgroup analyses of treatment effect were not useful due to small subgroup sizes.

16. HOW SUPPLIED/STORAGE AND HANDLING

RYZNEUTA (efbemalenograstim alfa-vuxw) injection is a clear, colorless, preservative-free solution supplied in a prefilled single-dose syringe with a 27-gauge, 1/2-inch needle and an UltraSafe Passive™ Needle Guard, containing 20 mg of efbemalenograstim alfa-vuxw.

Caution: This product contains natural rubber latex which may cause allergic reactions. The needle cap of the prefilled syringe contains natural rubber; persons with latex allergies should not administer this product.

RYZNEUTA is provided in a dispensing pack containing one 20 mg/mL prefilled syringe (NDC 72893-016-02).

RYZNEUTA prefilled syringe does not bear graduation marks and is intended only to deliver the entire contents of the syringe (20 mg/mL) for direct administration to adult patients.

Store refrigerated at 2°C to 8°C (36°F to 46°F) in the carton to protect from light. Do not shake. Discard syringes stored at room temperature for more than 48 hours. Do not freeze. Discard syringe if frozen.

17. PATIENT COUNSELING INFORMATION

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

Advise patients of the following risks and potential risks with RYZNEUTA:

- Rupture or enlargement of the spleen may occur. Symptoms include left upper quadrant abdominal pain or left shoulder pain. Advise patients to report pain in these areas to their healthcare provider immediately *[see Warnings and Precautions (5.1)]* .
- Dyspnea, with or without fever, progressing to acute respiratory distress syndrome, may occur. Advise patients to report dyspnea to their healthcare provider immediately *[see Warnings and Precautions (5.2)]* .
- Serious allergic reactions may occur, which may be signaled by rash, facial edema, wheezing, dyspnea, hypotension, or tachycardia. Advise patients to seek immediate medical attention if signs or symptoms of hypersensitivity reaction occur *[see Warnings and Precautions (5.3)]* .
- In patients with sickle cell disease, sickle cell crisis and death have occurred with use of human granulocyte colony-stimulating factors. Discuss potential risks and benefits for patients with sickle cell disease prior to the administration of RYZNEUTA *[see Warnings and Precautions (5.4)]* .
- Glomerulonephritis may occur. Symptoms include swelling of the face or ankles, dark colored urine or blood in the urine, or a decrease in urine production. Advise patients to report signs or symptoms of glomerulonephritis to their healthcare provider immediately *[see Warnings and Precautions (5.5)]* .
- Capillary leak syndrome may occur. Symptoms include hypotension and edema. Advise patients to report signs and symptoms of capillary leak syndrome to their healthcare provider immediately *[see Warnings and Precautions (5.9)]* .
- There may be an increased risk of Myelodysplastic Syndrome and/or Acute Myeloid Leukemia in patients with breast and lung cancer who receive RYZNEUTA in conjunction with chemotherapy and/or radiation therapy. Symptoms of MDS and AML may include tiredness, fever, and easy bruising or bleeding. Advise patients to report to their physician signs and symptoms of MDS/AML *[see Warnings and Precautions (5.9)]* .
- Aortitis may occur. Symptoms may include fever, abdominal pain, malaise, back pain, and increased inflammatory markers. Advise patients to report signs and symptoms of aortitis to their physician immediately *[see Warnings and Precautions (5.11)]* .

RYZNEUTA ®(efbemalenograstim alfa-vuxw)

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Singapore, 189720

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For more information, go to **www.ryzneuta.com or call 1-888-292-9617**

Patient Information
RYZNEUTA® (rīz-new-ta)
(efbemalenograstim alfa-vuxw)
injection
Single-Dose Prefilled Syringe

What is RYZNEUTA?
RYZNEUTA is a is a man-made form of granulocyte colony-stimulating factor (G-CSF). G-CSF is a substance produced by the body. It stimulates the growth of neutrophils, a type of white blood cell important in the body's fight against infection.

- RYZNEUTA is used in adults.
- It is not known if RYZNEUTA is safe and effective in children.

Do not take RYZNEUTAif you have had a serious allergic reaction to granulocyte stimulating factors such as efbemalenograstim alfa-vuxw, pegfilgrastim products or filgrastim products.

Before you receive RYZNEUTA, tell your healthcare provider about all of your medical conditions, including if you:

- have a sickle cell disorder.
- have kidney problems.
- are allergic to latex. The needle cap on the prefilled syringe contains dry natural rubber (derived from latex).
- are pregnant or plan to become pregnant. It is not known if RYZNEUTA will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if RYZNEUTA passes into your breast milk.

Tell your healthcare provider about all of the medicines you take,including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive RYZNEUTA?

- RYZNEUTA is given as an injection under your skin (subcutaneous injection) by a healthcare provider.
- RYZNEUTA should be injected at least 24 hours after your dose of chemotherapy and at least 14 days before your next dose of chemotherapy.
- If you miss a dose of RYZNEUTA, talk to your healthcare provider about when you should receive your next dose.

What are possible side effects of RYZNEUTA?
RYZNEUTA may cause serious side effects, including:

- **Spleen rupture.**Your spleen may become enlarged and can rupture. A ruptured spleen can cause death. Call your healthcare provider right away if you have pain in the left upper stomach area or your left shoulder.
- **A serious lung problem called Acute Respiratory Distress Syndrome (ARDS).**Call your healthcare provider or get emergency care right away if you have shortness of breath with or without a fever, trouble breathing, or a fast rate of breathing.
- **Serious allergic reactions.RYZNEUTA can cause serious allergic reactions.** These reactions can cause a rash over your whole body, swelling around your mouth or eyes, wheezing, shortness of breath, dizziness, and fast heart rate. If you have any of these symptoms, stop using RYZNEUTA and call your healthcare provider or get emergency medical help right away.
- **Risk of Sickle cell crises.**You may have a serious sickle cell crisis, which could lead to death, if you have a sickle cell disorder and receive RYZNEUTA. Call your healthcare provider right away if you have symptoms of sickle cell crisis such as pain or difficulty breathing.
- **Kidney injury (glomerulonephritis).**Products like RYZNEUTA can cause kidney injury. Call your healthcare provider right away if you develop any of the following symptoms:
  - swelling of your face or ankles
  - dark colored urine or blood in your urine
  - you urinate less than usual
- **Increased white blood cell count (leukocytosis).**Your healthcare provider will check your blood during treatment with RYZNEUTA.
- **Decreased platelet count (thrombocytopenia).**Your healthcare provider will check your blood during treatment with RYZNEUTA.
- **Capillary Leak Syndrome.**RYZNEUTA can cause fluid to leak from blood vessels into your body's tissues. This condition is called "Capillary Leak Syndrome" (CLS). CLS can quickly cause you to have symptoms that may become life-threatening. Get emergency medical help right away if you develop any of the following symptoms:
  - swelling or puffiness and urinating less than usual
  - trouble breathing
  - swelling of your stomach area (abdomen) and feeling of fullness
  - dizziness or feeling faint
  - a general feeling of tiredness
- **Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML).**If you have breast cancer or lung cancer, when RYZNEUTA is used with chemotherapy and radiation therapy, or with radiation therapy alone, you may have an increased risk of developing a precancerous blood condition called myelodysplastic syndrome (MDS) or a blood cancer called acute myeloid leukemia (AML). Symptoms of MDS and AML may include tiredness, fever, and easy bruising or bleeding. Call your healthcare provider if you develop these symptoms during treatment with RYZNEUTA.
- **Inflammation of the aorta (aortitis).**Inflammation of the aorta (the large blood vessel that transports blood from the heart to the body) has been reported in patients who received products like RYZNEUTA. Symptoms may include fever, abdominal pain, feeling tired, and back pain. Call your healthcare provider if you experience these symptoms.
- **The most common side effects of RYZNEUTA**are nausea, anemia, and thrombocytopenia.
- These are not all the possible side effects of RYZNEUTA.
- Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of RYZNEUTA.
Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. You can ask your pharmacist or healthcare provider for information about RYZNEUTA that is written for health professionals.

What are the ingredients in RYZNEUTA?
Active ingredient:efbemalenograstim alfa-vuxw
Inactive ingredients:acetate, EDTA, polysorbate 20, sodium, and sorbitol in water for injection.
Manufactured by: EVIVE BIOTECHNOLOGY SINGAPORE PTE. LTD., Singapore, 189720

Distributed by: Acrotech Biopharma Inc, East Windsor, NJ 08520 USA
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For more information, go to www.ryzneuta.com or call 1-888-292-9617.

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 12/2024