Medical Policy

Healthcare Services Department

Policy Name	Policy Number	Scope
efbemalenograstim alfa-vuxw (Ryzneuta®)	MP-RX-FP-139-24	☒ MMM MA ☒ MMM Multihealth

Service Category

☐ Anesthesia
☐ Surgery
☐ Radiology Procedures
☐ Pathology and Laboratory Procedures
☐ Medicine Services and Procedures
☐ Evaluation and Management Services
☐ DME/Prosthetics or Supplies
☒ Part B Drugs

Service Description

This document addresses the use of efbemalenograstim alfa-vuxw (Ryzneuta®), a leukocyte growth factor approved by the Food and Drug Administration (FDA) 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.

Background Information

Ryzneuta is a leukocyte growth factor FDA 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. Ryzneuta is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation

Ryzneuta, a granulocyte colony-stimulating factor (G-CSF) used to modulate the immune system by targeting white blood cell growth factors, commonly referred to as colony stimulating factors (CSF). These CSFs play a pivotal role in regulating the production, differentiation, and maturation of specific types of white blood cells crucial for immune function. Ryzneuta primarily targets two distinct categories of CSFs: granulocyte colony stimulating factors (G-CSF) and granulocyte-macrophage colony stimulating factor (GM-CSF).

1. Granulocyte Colony Stimulating Factors (G-CSF): G-CSFs are glycoproteins that serve as critical regulators in the proliferation and maturation of granulocytes, a subtype of white blood cells essential for combating infections. These glycoproteins exert precise control over the reproduction and differentiation of granulocytes, thereby bolstering the body's innate immune response against microbial threats.
2. Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF): GM-CSF functions as a hematopoietic growth factor, stimulating the proliferation and differentiation of hematopoietic progenitor cells into a broader spectrum of immune cells, including granulocytes and macrophages. By influencing the development of both granulocytes and macrophages, GM-CSF plays a pivotal role in enhancing immune surveillance and response mechanisms against various pathogens.

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Ryzneuta leverages the targeted modulation of these essential white blood cell growth factors to optimize immune function and bolster the body's ability to combat infections, particularly in individuals with compromised immune systems or those undergoing certain medical treatments.

Primary prophylaxis of chemotherapy-induced febrile neutropenia

Neutropenia with fever (febrile neutropenia [FN]) is a serious consequence of myelosuppressive chemotherapy that usually results in hospitalization and the need for intravenous antibiotics (Lyman 2014). FN may result in dose reductions, delays, or even discontinuation of chemotherapy, which, in turn, may compromise patient outcomes. It is important to identify which patients are at high risk for developing FN so that patients can receive optimal chemotherapy while their risk for FN is appropriately managed. There are many factors that need to be evaluated to determine a patient's risk of developing FN, which includes type of chemotherapy regimen, type of cancer being treated, and other patient-specific risk factors.

A review of the literature was performed to gain a comprehensive and updated understanding of FN risk associated with chemotherapy regimens and patient-specific FN risk factors. Studies that have analyzed FN risk factors, often have several limitations, including their retrospective nature and small sample sizes. Our assessment of the following patient risk factors and chemotherapy regimens (see **appendix** below) is after a review of published literature and guidelines from the American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN).
The patient risk factors for the development of febrile neutropenia include:

- Age greater than 65 years (Lyman 2014; Aagaard 2018); **OR**
- Poor performance status (Eastern Cooperative Oncology Group 3 or 4) or HIV infection (in particular, those with low CD4 counts (≤ 450/µL)) but chemotherapy still indicated (Lyman 2014); **OR**
- Prior radiation therapy (within previous 1 year) (Terbuch 2018) (Fujiwara 2017) (Shigeta 2015); **OR**
- Bone marrow involvement by tumor producing cytopenias (Lyman 2014); **OR**
- Persistent neutropenia (absolute neutrophil count [ANC] less than 1500mm3) (Lyman 2014); **OR**
- Poor renal function (glomerular filtration rate [GFR] less than 60mL/min) (Lyman 2014; Aagaard 2018); **OR**
- Liver dysfunction (liver function tests at least 2X upper limit of normal or bilirubin > 2.0 mg/dL) (Lyman 2014; Aagaard 2018); **OR**
- Recent surgery performed as part of cancer management within previous 30 days (not to include a procedure such as port placement, drain placement, IVC filter, etc.) (Lyman 2014; Aagaard 2018); **OR**
- History of active infection within previous 60 days (Lyman 2014; Aagaard 2018); **OR**
- Current open wound and chemotherapy cannot be delayed (Lyman 2014; Aagaard 2018).

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Definitions

- **Absolute neutrophil count (ANC):** A measure of the number of neutrophils (a type of white blood cell) in the blood. Acute Radiation Syndrome (ARS): Also known as radiation sickness.
- **Adjuvant or adjunctive treatment:** Treatment given after the primary treatment to increase the chances of a cure and may include chemotherapy, radiation, hormone or biological therapy.
- **Febrile neutropenia:** Febrile neutropenia can occur as a result of severe neutropenia; defined as the occurrence of fever (greater than or equal to 38.3°C for more than 1 hour) in association with an ANC less than 0.5 x 10^9/L or ANC less than 1.0 x 10^9/L and a predicted decline to less than or equal to 0.5 x 109/L over the subsequent 48 hours.
- **ECOG or Eastern Cooperative Oncology Group Performance Status:** A scale and criteria used by doctors and researchers to assess how an individual's disease is progressing, assess how the disease affects the daily living abilities of the individual, and determine appropriate treatment and prognosis. This scale may also be referred to as the WHO (World Health Organization) or Zubrod score which is based on the following scale:
  - 0 = Fully active, able to carry on all pre-disease performance without restriction
  - 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light housework, office work
  - 2 = Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
  - 3 = Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
  - 4 = Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
  - 5 = Dead
- **Neutropenia:** A decrease in the number of neutrophils (white blood cells that respond quickly to infection) in the blood. Neutrophils less than 1,500/mm3 is considered to be neutropenic and at risk for infection. Neutrophils fewer than 500 cells/mm3 is considered at high risk of infection.
- **Neutrophil:** A type of white blood cell that helps fight infection.
- Primary prophylaxis: Prevention of febrile neutropenia with the first cycle of a specified chemotherapy regimen.
- **Secondary prophylaxis:** Prevention of febrile neutropenia given with the second and/or subsequent cycle of a given regimen of chemotherapy for individuals who had a neutropenic complication from the preceding cycle of chemotherapy and there is no plan to reduce the dose intensity.

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Approved Indications

Ryzneuta is approved by the FDA 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. Ryzneuta is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.

Other Uses

None

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Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS	Description
J3490	Unclassified drugs (when specified as [Ryzneuta] (efbemalenograstim alfa-vuxw))
J3590	Unclassified biologics (when specified as [Ryzneuta] (efbemalenograstim alfa-vuxw))

ICD-10	Description
D70.1	Agranulocytosis secondary to drugs
D70.8	Other Neutropenia
D70.9	Neutropenia, unspecified
C00 – D49	Neoplasms (malignant) of any site

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Medical Necessity Guidelines

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

efbemalenograstim alfa-vuxw (Ryzneuta®)

A. Criteria For Initial Approval *(Provider must submit documentation [such as office chart notes, lab results, pathology reports, imaging studies, and any other pertinent clinical information] supporting the patient's diagnosis for the drug and confirming that the patient has met **all** approval criteria.)*

i. Individual with nonmyeloid malignancy is using for primary prophylaxis of Febrile Neutropenia (FN); **AND**
ii. Individual has a risk of FN of 20% or greater based on chemotherapy regimen (NCCN 2A);

OR

iii. Individual with nonmyeloid malignancy is using for primary prophylaxis of FN; **AND**
iv. Individual has a risk of developing FN is greater than or equal to 10% and less than 20% based on chemotherapy regimen and individuals have any of the following risk factors for FN:
   A. Age greater than 65 years (Lyman 2014; Aagaard 2018); **OR**
   B. Poor performance status (Eastern Cooperative Oncology Group 3 or 4) or HIV infection (in particular, those with low CD4 counts (≤ 450/µL)) but chemotherapy still indicated (Lyman 2014); **OR**
   C. Prior radiation therapy (within previous 1 year) (Terbuch 2018) (Fujiwara 2017) (Shigeta 2015); **OR**
   D. Bone marrow involvement by tumor producing cytopenias (Lyman 2014); **OR**
   E. Persistent neutropenia (absolute neutrophil count [ANC] less than 1500mm^3) (Lyman 2014); **OR**
   F. Poor renal function (glomerular filtration rate [GFR] less than 60mL/min) (Lyman 2014; Aagaard 2018); **OR**
   G. Liver dysfunction (liver function tests at least 2X upper limit of normal or bilirubin > 2.0 mg/dL) (Lyman 2014) (Aagaard 2018); **OR**
   H. Recent surgery performed as part of cancer management within the previous 30 days

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(not to include a procedure such as port placement, drain placement, IVC filter, etc.) (Lyman 2014; Aagaard 2018); **OR**

I. History of active infection within previous 60 days (Lyman 2014; Aagaard 2018); **OR**
J. Current open wound and chemotherapy cannot be delayed (Lyman 2014; Aagaard 2018).

OR

v. Individual with nonmyeloid malignancy is using for secondary prophylaxis of FN; **AND**
vi. Individual has experienced a neutropenic complication from a prior cycle of chemotherapy (for which prophylaxis was not received), in which a reduced dose may compromise disease-free or overall survival or treatment outcome (NCCN 2A)

OR

vii. Individual is using as adjunctive treatment for FN; **AND**
viii. Individual has not received prophylactic therapy with pegfilgrastim (NCCN 2A); **AND**
ix. Individual has a high risk for infection-associated complications as demonstrated by any of the following:

A. Expected prolonged (greater than 10 days) and profound (less than 0.1 x 109/L) neutropenia; **OR**
B. Age greater than 65 years; **OR**
C. Pneumonia or other clinically documented infections; **OR**
D. Hypotension and multi organ dysfunction (sepsis syndrome); **OR**
E. Invasive fungal infection; **OR**
F. Prior episode of febrile neutropenia; **OR**
G. Hospitalized at the time of the development of fever.

B. Criteria For Continuation of Therapy

MMM considers continuation of efbemalenograstim alfa-vuxw (Ryzneuta®) therapy medically necessary in members requesting reauthorization for an indication listed in Section A above (Criteria for Initial Approval). Provider must submit documentation [such as office chart notes, lab results, pathology reports, imaging studies, and any other pertinent clinical information] supporting confirming that the patient continues to met **all** approval criteria.

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C. Authorization Duration

i. Initial Approval Duration: Up to 6 months
ii. Reauthorization Approval Duration: Up to 6 months

D. Conditions Not Covered

Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive):

I. Individual is using as prophylaxis for febrile neutropenia, except when above criteria are met; **OR**
II. Individual using as treatment for neutropenia in those who are afebrile, except when above criteria are met; **OR**
III. Individual is using as adjunctive therapy in those with uncomplicated febrile neutropenia, defined as a fever less than 10 days duration, no evidence of pneumonia, cellulitis, abscess, sinusitis, hypotension, multi-organ dysfunction, or invasive fungal infection, and no uncontrolled malignancies; **OR**
IV. Individual is using for chemo sensitization of myeloid leukemias; **OR**
V. Individual is continuing use if no response is seen within 28-42 days (individuals who have failed to respond within this time frame are considered non-responders); **OR**
VI. Individual is using as a technique to increase the numbers of circulating hematopoietic stem cells as treatment of damaged myocardium.

Limits or Restrictions

A. Therapeutic Alternatives

The list below includes preferred alternative therapies recommended in the approval criteria and may be subject to prior authorization.

i. N/A

B. Quantity Limitations

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. The chart below includes dosing recommendations as per the FDA-approved prescribing information.

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Drug	Recommended Dosing Schedule
Ryzneuta	20 mg sc once per chemotherapy cycle.
Exceptions	
• Should be administered approximately 24 hours after cytotoxic chemotherapy. • Not to be administered between 14 days before and 24 hours after administration of cytotoxic chemotherapy.	

Appendix

Febrile Neutropenia Risk of Selected Chemotherapy Regimens

The following table represents selected chemotherapy regimens requiring further examination in their disease setting and the associated risk for development of febrile neutropenia. This is not a comprehensive list, as there are other regimens that are associated with risk for the development of FN. The FN risk of these other regimens will follow the guidance within the NCCN Guidelines Management of Neutropenia. A high-risk chemotherapy regimen is defined as a ≥ 20% probability of developing febrile neutropenia, an intermediate-risk chemotherapy regimen is associated with ≥10 to ≤ 20% incidence of developing FN, and a low-risk chemotherapy regimen is associated with <10% incidence of developing FN.

Table 1

Disease State	Chemotherapy Regimen	Risk of developing FN	References
Breast Cancer	Adjuvant TC in an older adult	Intermediate	Do 2015; Jones 2009; Jones 2006; Kosaka 2015; Younis 2012
Breast Cancer (Metastatic)	Fam-trastuzuamab deruxtecan-nxki	Low	Modi S et al. 2020; Modi S et al. 2022; Cortes J et al 2022;
Breast cancer (Neoadjuvant)	Pembrolizumab, paclitaxel, and carboplatin	Intermediate	Schmid P, et al. 2022

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Breast Cancer (Metastatic)	Pembrolizumab, and chemotherapy	Low	Cortes J, et al 2022; Tolaney SM et al 2021; Tolaney SM et al 2020; Perez-Garcia JM et al 2021; Shah AN et al 2020; de la Cruz-Merino L et al 2022
Breast Cancer	Metastatic Sacituzumab govitecan-hziy	Low	Bardia A et al 2021; Bardia A et al 2019; Rugo HS et al 2022; Kathpalia M et al. 2023
Breast Cancer	Neoadjuvant TCHP (docetaxel, carboplatin, trastuzumab, and pertuzumab)	High	Gilbar 2014; Hurvitz 2018
Breast Cancer (Advanced)	Docetaxel (dosing of less than 75 mg/m2)	Low	Harvey V 2006; Mauri D 2010; Rivera E 2008; Sparano JA 2008; Tabernero J 2004
Breast Cancer (Advanced)	Docetaxel (dosing of 75 mg/m2)	Intermediate	Andersson M 2011; Baselga J 2012; Burris HA 1999; Harvey V 2006; Jones SE 2005; Marty M 2005;
Castrate-Resistant Prostate Cancer (CRPC) (Advanced)	Cabazitaxel	Intermediate	De Bono JS. 2010; Eisenberger M 2017; Oudard S 2017
Cervical Cancer (Advanced)	Cisplatin and paclitaxel ± bevacizumab	Intermediate	Angioli R 2015; Lissoni AA 2009; Lorusso D 2014; Monk BJ 2009; Moore DH 2004; Tewari KS 2014, 2017; Yang Z 2016
	Topotecan	Intermediate	Bookman MA 2000; Coronel J 2009; Lorusso D 2011; Muderspach LI 2001;
	Pembrolizumab and platinum- based chemotherapy ± bevacizumab	Low	Colombo N et al. 2021
Gastroesophageal Cancer	Cisplatin and irinotecan	Intermediate	Ajani JA 2002; Enzinger PC 2016; Ilson DH 2004, 2012;

			Knox JJ 2010; Newman E 2005
	Nivolumab and FOLFOX or XELOX	Low	Janjigian YY et al. 2021
Germ Cell Tumors (Advanced)	Bleomycin, etoposide, and cisplatin	Intermediate	de Wit R 2012; Fizazi K 2014; Garcia del Muro X 2008; Nichols CR 1991
	Etoposide and cisplatin	Intermediate	Arranz A 2001; Horwich A 2000; Motzer RJ 1995
Head and Neck Cancer (Recurrent/Metastatic)	EGFR-inhibitor (cetuximab or panitumumab) and platinum- based chemotherapy	Low	Burtness B 2005; Vermorken JB 2008; Vermorken JB 2013;
	Pembrolizumab plus platinum- based chemotherapy	Low	Burtness B 2019;
Non-Hodgkin Lymphoma	Gemcitabine, dexamethasone, and cisplatin ± rituximab	Intermediate	Baetz T 2003; Crump M 2004, 2014
Non-Small Cell Lung Cancer	Cisplatin and vinorelbine	Intermediate	Douillard JY 2006; Fossella F 2003; Gebbia V 2008; Georgoulias V 2005; Kenmotsu H 2020; Pujol JL 2005; Winton T 2005
Non-Small Cell Lung Cancer (Advanced)	Docetaxel	Intermediate	Abe T 2015; Barlesi F 2018; Camps C 2006; Georgoulias V 2004; Gridelli C 2004; Hanna N 2004; Herbst RS 2010; Karampeazis A 2011; Kudoh S 2006; Okamoto I 2020; Paz-Ares L 2008
Non-Small Cell Lung Cancer (Advanced)	Docetaxel and cisplatin	Low	Abe T 2015; Fossella F 2003; Kubota K 2015; Schiller JH 2002
Non-Small Cell Lung Cancer (Advanced)	Docetaxel and ramucirumab	Intermediate	Garon 2014; Yoh 2016

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Non-Small Cell Lung Cancer (Metastatic)	Carboplatin/cisplatin, pemetrexed, and pembrolizumab	Low	Gandhi 2018; Langer 2016; Rodrigues-Pereira 2011; Scagliotti 2008
Non-Small Cell Lung Cancer (Metastatic, non-squamous)	Carboplatin, paclitaxel, and atezolizumab ± bevacizumab	Low	Lilenbaurm 2005; Ohe 2007; Socinski 2018; Williamson 2005
Non-Small Cell Lung Cancer (Metastatic, squamous)	Carboplatin, paclitaxel/nab- paclitaxel, and pembrolizumab	Low	Gadgeel 2018; Lilenbaum 2005; Ohe 2007; Paz-Ares 2018; Williamson 2005
Ovarian Cancer	Carboplatin and paclitaxel	Low	Clamp 2019; Coleman 2017; Katsumata 2009, 2013; Lhomme 2008; Pignata 2014; Sugiyama 2016; Vasey 2004
Ovarian Cancer (Advanced)	Topotecan	Intermediate	Aoki 2011; Gordon 2001, 2004; Gore 2002; McGonigle 2011; Meier 2009; Sehouli J 2008; Spannuth WA 2007; Swisher 1997
Ovarian Cancer (Advanced)	Carboplatin and docetaxel	Intermediate	Vasey 2004; Vorobiof 2003; Wang 2014
Pancreatic Cancer	FOLFIRINOX	Intermediate	Chlorean 2019; Conroy 2011; Conroy 2005; Hosein 2012; Okusaka 2014; Peddi 2012; Suker 2016; Thibodeau 2018; Tong 2018
Small Cell Lung Cancer (Extensive Stage)	Carboplatin, etoposide, and atezolizumab	Low	Horn 2018; Kosmidis 1994; Socinski 2009
Soft Tissue Sarcoma (Advanced)	Doxorubicin	High	Judson I 2014; Lorigan P 2007; Nielsen OS 1998; Seddon B 2017; Tap WD 2017; Tap WD 2020

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Policy History

Revision Type	Summary of Changes	P&T Approval Date	UM/CMPC Approval Date
Policy Inception	Elevance Health's Medical Policy adoption	N/A	6/28/2024

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