

# Colony Stimulating Factors

Overrides	Approval Duration
Prior Authorization Quantity Limit	1 year

Medications	Quantity Limit
Fulphila (pegfilgrastim-jmdb)	May be subject to quantity limit
Fylnetra (pegfilgrastim-pbbk)	May be subject to quantity limit
Granix (tbo-Filgrastim)	N/A
Leukine (sargramostim)	N/A
Neulasta/Neulasta Onpro (pegfilgrastim)	May be subject to quantity limit
Neupogen (filgrastim)	N/A
Nypozi (filgrastim-txid)	N/A
Nivestym (filgrastim-aafi)	N/A
Nyvepria (pegfilgrastim-apgf)	May be subject to quantity limit
Releuko (filgrastim-ayow)	N/A
Rolvedon (eflapegastim-xnst)	May be subject to quantity limit
Ryzneuta (efbemalenograstim alfa-vuxw)	May be subject to quantity limit
Stimufend (pegfilgrastim-fpgk)	May be subject to quantity limit
Udenyca/Udenyca Onbody (pegfilgrastim-cbqv)	May be subject to quantity limit
Zarxio (filgrastim-sndz)	N/A
Ziextenzo (pegfilgrastim-bmez)	May be subject to quantity limit

## APPROVAL CRITERIA

- I. Requests for filgrastim (Neupogen), filgrastim-aafi (Nivestym), filgrastim-txid (Nypozi), filgrastim-ayow (Releuko), or filgrastim-sndz (Zarxio) may be approved if the following criteria are met:
  - A. Individual with nonmyeloid malignancy is using for primary prophylaxis of febrile neutropenia (FN); **AND**
  - B. Individual has a risk of FN of 20% or greater based on chemotherapy regimen ([see Appendix](#), Table 1);

### **OR**

- C. Individual with nonmyeloid malignancy is using for primary prophylaxis of FN; **AND**
- D. Individual's risk of developing FN is greater than or equal to 10% and less than 20% based on chemotherapy regimen ([see Appendix](#), Table 1) and individual has any of the following risk factors for :
  1. Age greater than 65 years (Lyman 2014; Aagaard 2018); **OR**
  2. Poor performance status (Eastern Cooperative Oncology Group 3 or 4) or HIV infection (in particular, those with low CD4 counts ( $\leq 450/\mu\text{L}$ ) but chemotherapy still indicated (Lyman 2014); **OR**

3. Prior radiation therapy (within the previous 1 year) (Terbuch 2018; Fujiwara 2017; Shigeta 2015); **OR**
4. Bone marrow involvement by tumor producing cytopenias (Lyman 2014); **OR**
5. Persistent neutropenia (absolute neutrophil count [ANC] less than 1500mm<sup>3</sup>) (Lyman 2014); **OR**
6. Poor renal function (glomerular filtration rate [GFR] less than 60mL/min) (Lyman 2014; Aagaard 2018); **OR**
7. Liver dysfunction (liver function tests at least 2X upper limit of normal or bilirubin > 2.0 mg/dL) (Lyman 2014; Aagaard 2018); **OR**
8. Recent surgery performed as part of cancer management within the previous 30 days (not to include a procedure such as port placement, drain placement, IVC filter, etc.) (Lyman 2014; Aagaard 2018); **OR**
9. History of active infection within the previous 60 days (Lyman 2014; Aagaard 2018); **OR**
10. Current open wound and chemotherapy cannot be delayed (Lyman 2014; Aagaard 2018);

**OR**

E. Individual with nonmyeloid malignancy is using for secondary prophylaxis of FN;

**AND**

F. Individual has experienced a neutropenic complication from a prior cycle of chemotherapy (for which primary prophylaxis was not received), in which a reduced dose may compromise disease-free or overall survival or treatment outcome (NCCN 2A);

**OR**

G. Individual is using as adjunctive treatment for FN (NCCN 2A); **AND**

H. Individual has been on prophylactic therapy with filgrastim;

**OR**

I. Individual has not received prophylactic therapy with granulocyte colony stimulating factor (NCCN Guidelines Myeloid Growth Factors); **AND**

J. Individual has a high risk for infection-associated complications as demonstrated by any of the following (NCCN 2A):

1. Expected prolonged (greater than 10 days) and profound (less than 0.1 x 10<sup>9</sup>/L) neutropenia; **OR**
2. Age greater than 65 years; **OR**
3. Pneumonia or other clinically documented infections; **OR**
4. Hypotension and multi organ dysfunction (sepsis syndrome); **OR**
5. Invasive fungal infection; **OR**
6. Prior episode of febrile neutropenia; **OR**
7. Hospitalized at the time of the development of fever;

**OR**

K. Individual is 18 years of age or older and has a diagnosis of acute myeloid leukemia (AML); **AND**

L. Individual is using shortly after the completion of induction or repeat induction chemotherapy or after the completion of consolidation chemotherapy for AML;

**OR**

M. Individual has a diagnosis of hairy cell leukemia with severe neutropenia (AHFS, NCCN Guidelines Hairy Cell Leukemia);

**OR**

N. Individual has a diagnosis of myelodysplastic syndromes (MDS) (NCCN 2A); **AND**

O. Individual has severe neutropenia (ANC less than or equal to 500 mm<sup>3</sup>) or experiencing recurrent infection or resistant infections;

**OR**

P. Individual has a diagnosis of myelodysplastic syndrome with ring sideroblasts (MDS-RS) or MDS/MPN-RS-T; **AND**

Q. Individual is using in combination with Reblozyl;

**OR**

R. Individual has IPSS-R (Very Low, Low, Intermediate) risk myelodysplastic syndrome associated with symptomatic anemia (NCCN 2A); **AND**

S. Individual does not have a del(5q) chromosomal abnormality; **AND**

T. Individual has serum erythropoietin ≤ 500 mU/ML; **AND**

U. Individual will use in combination with an erythropoiesis-stimulating agent (ESA) following no response to either an ESA alone or luspatercept-aamt (Reblozyl);

V. **OR** Individual is receiving dose dense therapy (treatment given more frequently, such as every 2 weeks instead of every 3 weeks) for adjuvant treatment of breast cancer (ASCO Smith 2015);

**OR**

W. Individual is using for chronic administration to reduce the incidence and duration of sequelae of neutropenia (for example, fever, infections, oropharyngeal ulcers) in symptomatic individuals with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia;

**OR**

X. Individual is using for the treatment of (non-chemotherapy) drug-induced neutropenia (AHFS);

**OR**

Y. Individual is less than 21 years of age and has a diagnosis of glycogen storage disease type 1b; **AND**

Z. Individual is using for the treatment of low neutrophil counts (AHFS);

**OR**

AA. Individual is using for the treatment for neutropenia associated with human immunodeficiency virus infection and antiretroviral therapy (AHFS);

**OR**

BB. Individual is using after accidental or intentional total body radiation of myelosuppressive doses (greater than 2 Grays [Gy]) (such as Hematopoietic Syndrome of Acute Radiation Syndrome);

**OR**

CC. Individual is using after a hematopoietic progenitor stem cell transplant (HPCT/HSCT) to promote myeloid reconstitution or when engraftment is delayed or has failed;

**OR**

DD. Individual is using to mobilize progenitor cells into peripheral blood for collection by leukapheresis, as an adjunct to peripheral blood/hematopoietic stem cell transplantation (PBSCT/PHSCT);

**OR**

EE. Individual is using as an alternate or adjunct to donor leukocyte infusions (DLI) in individuals with leukemic relapse after an allogeneic hematopoietic stem cell transplant (DrugPoints B IIa);

**OR**

FF. Individual is using to reduce the duration of neutropenia and neutropenia related clinical sequelae in those with nonmyeloid malignancies undergoing myeloblastic chemotherapy followed by bone marrow transplant (BMT) (Label);

**OR**

GG. Individual is using for treatment for hematopoietic cell mobilization for autologous donors (NCCN 2A);

**OR**

HH. Individual is using for additional therapy for insufficient collection of stem cells in combination with plerixafor following treatment with filgrastim alone (or its biosimilars) or filgrastim (or its biosimilars) and disease-specific chemotherapy (NCCN 2A);

**OR**

II. Individual is using for Wilms Tumor (Nephroblastoma) (NCCN 2A); **AND**

JJ. Using with Regimen M and Regimen I for one of the following courses:

1. Cyclophosphamide and etoposide; **OR**
2. Cyclophosphamide, doxorubicin, and vincristine;

**OR**

KK. Individual is using for autologous hematopoietic stem cell (HSC) mobilization as part of the development of an FDA-approved ex vivo gene therapy (e.g. Zynteglo (betibeglogene autotemcel)) (NCCN 2A);

**OR**

LL. Individual is using for hematopoietic cell mobilization for allogeneic donors as a single agent (NCCN 2A);

**OR**

MM. Individual is using as supportive management of neutropenic events due to immunotherapy related toxicities from CAR T-cell therapy (NCCN 2A).

- II. Requests for sargramostim (Leukine) may be approved if the following criteria are met:
- A. Individual is using as adjunctive treatment for FN: **AND**
  - B. Individual has not previously received prophylactic granulocyte colony-stimulating factors (NCCN 2A); **AND**
  - C. Individual has a high risk for infection-associated complications as demonstrated by any of the following (NCCN 2A):
    - 1. Expected prolonged (greater than 10 days) and profound (less than  $0.1 \times 10^9/L$ ) neutropenia; **OR**
    - 2. Age greater than 65 years; **OR**
    - 3. Pneumonia or other clinically documented infections; **OR**
    - 4. Hypotension and multi organ dysfunction (sepsis syndrome); **OR**
    - 5. Invasive fungal infection; **OR**
    - 6. Prior episode of febrile neutropenia; **OR**
    - 7. Hospitalized at the time of the development of fever;

**OR**

- D. Individual is receiving dose dense therapy (treatment given more frequently, such as every 2 weeks instead of every 3 weeks) for adjuvant treatment of breast cancer (ASCO Smith 2015);

**OR**

- E. Individual has a diagnosis of acute myeloid leukemia (AML); **AND**
- F. Individual is 55 years and older **AND**
- G. Individual is using shortly after the completion of induction or repeat induction of chemotherapy of AML;

**OR**

- H. Individual has a diagnosis of myelodysplastic syndromes (MDS); **AND**
- I. Individual has severe neutropenia (ANC less than or equal to  $500 \text{ mm}^3$ ) or experiencing recurrent or resistant infections (NCCN Guidelines Myelodysplastic Syndromes; AHFS);

**OR**

- J. Individual is 18 years or older; **AND**
- K. Individual is using for the mobilization of hematopoietic progenitor cells into peripheral blood for collection by leukapheresis and autologous transplantation

**OR**

- L. Individual is 2 years of age and older; **AND**
- M. Individual is using for the acceleration of myeloid reconstitution following autologous or allogenic bone marrow transplantation or peripheral blood progenitor cell transplantation;

**OR**

- N. Individual is 2 years of age and older; **AND**
- O. Individual is using for the treatment of delayed neutrophil recovery or graft failure after autologous or allogenic bone marrow transplantation;

**OR**

- P. Individual is using for treatment for hematopoietic cell mobilization for autologous donors (NCCN 2A);

**OR**

Q. Individual is using to increase survival in adult and pediatric individuals (from birth to 17 years of age) acutely exposed to myelosuppressive doses of radiation (such as Hematopoietic Syndrome of Acute Radiation Syndrome (H-ARS));

**OR**

R. Individual is 18 years of age or younger; **AND**

S. Individual is diagnosed with relapsed/refractory high-risk neuroblastoma; **AND**

T. Individual is using in combination with dinutuximab (Unituxin) (NCCN 1,2A); **AND**

U. Individual achieved a partial response to first-line multi-agent, multi-modality therapy (i.e. induction combination chemotherapy, or myeloablative consolidation chemotherapy followed by autologous stem cell transplant);

**OR**

V. Individual is diagnosed with relapsed/refractory high-risk neuroblastoma; **AND**

W. Individual is using in combination with Danyelza (naxitamab-gqgk).

III. Requests for tbo-filgrastim (Granix) may be approved if the following criteria are met:

A. Individual with non-myeloid malignancy is using for primary prophylaxis of FN; **AND**

B. Individual has a risk of FN of 20% or greater based on chemotherapy regimen ([see Appendix](#), Table 1);

**OR**

C. Individual with nonmyeloid malignancy is using for primary prophylaxis of FN; **AND**

D. Individual's risk of developing FN is greater than or equal to 10% and less than 20% based on chemotherapy regimen and individual has any risk factors for FN:

1. Age greater than 65 years (Lyman 2014; Aagaard 2018); **OR**
2. Poor performance status (Eastern Cooperative Oncology Group 3 or 4) or HIV infection (in particular, those with low CD4 counts ( $\leq 450/\mu\text{L}$ )) but chemotherapy still indicated (Lyman 2014); **OR**
3. Prior radiation therapy (within previous 1 year) (Terbuch 2018) (Fujiwara 2017) (Shigeta 2015); **OR**
4. Bone marrow involvement by tumor producing cytopenias (Lyman 2014); **OR**
5. Persistent neutropenia (absolute neutrophil count [ANC] less than  $1500\text{mm}^3$ ) (Lyman 2014); **OR**
6. Poor renal function (glomerular filtration rate [GFR] less than  $60\text{mL/min}$ ) (Lyman 2014; Aagaard 2018); **OR**
7. Liver dysfunction (liver function tests at least 2X upper limit of normal or bilirubin  $> 2.0\text{ mg/dL}$ ) (Lyman 2014; Aagaard 2018); **OR**
8. 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**
9. History of active infection within previous 60 days (Lyman 2014; Aagaard 2018); **OR**
10. Current open wound and chemotherapy cannot be delayed (Lyman 2014; Aagaard 2018);

**OR**

- E. Individual with nonmyeloid malignancy is using for secondary prophylaxis of FN; **AND**
- F. 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**

- G. Individual is using as an adjunctive treatment for FN;

**AND**

- H. Individual was previously using Granix (tbo-filgrastim) prophylactically (NCCN 2A);
- OR**
- I. Individual has not received prophylactic therapy with a granulocyte colony stimulating factor (NCCN Guidelines Myeloid Growth Factors);
- AND**
- J. Individual has a high risk for infection-associated complications as demonstrated by any of the following:
    - 1. Expected prolonged (greater than 10 days) and profound (less than  $0.1 \times 10^9/L$ ) neutropenia (NCCN 2A); **OR**
    - 2. Age greater than 65 years; **OR**
    - 3. Pneumonia or other clinically documented infections; **OR**
    - 4. Hypotension and multi organ dysfunction (sepsis syndrome); **OR**
    - 5. Invasive fungal infection; **OR**
    - 6. Prior episode of febrile neutropenia; **OR**
    - 7. Hospitalized at the time of the development of fever;

**OR**

- K. Individual is using after a hematopoietic progenitor stem cell transplant (HPCT/HSCT) to promote myeloid reconstitution or when engraftment is delayed or has failed (NCCN 2A);

**OR**

- L. Individual has a diagnosis of myelodysplastic syndrome (MDS); **AND**
- M. Individual has severe neutropenia (ANC less than or equal to  $500\text{mm}^3$ ) or experiencing recurrent or resistant infections (NCCN 2A);

**OR**

- N. Individual has a diagnosis of myelodysplastic syndrome with ring sideroblasts (MDS-RS) or MDS/MPN-RS-T; **AND**
- O. Individual is using in combination with Reblozyl;

**OR**

- P. Individual has IPSS-R (Very Low, Low, Intermediate) risk myelodysplastic syndrome associated with symptomatic anemia (NCCN 2A); **AND**
- Q. Individual does not have a del(5q) chromosomal abnormality; **AND**
- R. Individual has serum erythropoietin  $\leq 500$  mU/ML; **AND**
- S. Individual will use in combination with an erythropoiesis-stimulating agent (ESA) following no response to either an ESA alone or luspatercept-aamt (Reblozyl);

**OR**

T. Individual is using to mobilize progenitor cells into peripheral blood for collection by leukapheresis, as an adjunct to peripheral blood/hematopoietic stem cell transplantation (PBSCT/PHSCT) (AHFS);

**OR**

U. Individual is using for treatment of hematopoietic cell mobilization for autologous donors (NCCN 2A);

**OR**

V. Individual is using for additional therapy for insufficient collection of stem cells in combination with plerixafor following treatment with tbo-filgrastim alone or tbo-filgrastim and disease-specific chemotherapy (NCCN 2A);

**OR**

W. Individual is using for autologous hematopoietic stem cell (HSC) mobilization as part of the development of an FDA-approved ex vivo gene therapy (e.g. Zynteglo (betibeglogene autotemcel));

**OR**

X. Individual is using for hematopoietic cell mobilization for autologous donors in combination with Aphexda (motixafortide) (Aphexda Label).

IV. In addition to criteria outlined below, requests for Fulphila, Fylnetra, Nyvepria, Rolvedon, Ryzneuta, Stimufend, Ziextenzo must also meet the following criteria:

A. Individual has had a trial and inadequate response or intolerance to Neulasta/Neulasta Onpro;

V. Requests for pegfilgrastim (Neulasta/Neulasta Onpro), pegfilgrastim-jmdb (Fulphila), pegfilgrastim-pbbk (Fylnetra), pegfilgrastim-fpgk (Stimufend), pegfilgrastim-cbqv (Udenyca/Udenyca Onbody), pegfilgrastim-apgf (Nyvepria) or pegfilgrastim-bmez (Ziextenzo) may be approved if the following criteria are met:

A. Individual with nonmyeloid malignancy is using for primary prophylaxis of FN; **AND**

B. Individual has a risk of FN of 20% or greater based on chemotherapy regimen ([see Appendix](#), Table 1);

**OR**

C. Individual with nonmyeloid malignancy is using for primary prophylaxis of FN; **AND**

D. Individual's risk of developing FN is greater than or equal to 10% and less than 20% based on chemotherapy regimen (see Appendix, Table 1) and individual has any of the following risk factors for FN:

1. Age greater than 65 years (Lyman 2014; Aagaard 2018); **OR**
2. Poor performance status (Eastern Cooperative Oncology Group 3 or 4) or HIV infection (in particular, those with low CD4 counts  $\leq 450/\mu\text{L}$ ) but chemotherapy still indicated (Lyman 2014); **OR**
3. Prior radiation therapy (within previous 1 year) (Terbuch 2018; Fujiwara 2017; Shigeta 2015); **OR**
4. Bone marrow involvement by tumor producing cytopenias (Lyman 2014); **OR**



5. Persistent neutropenia (absolute neutrophil count [ANC] less than 1500mm<sup>3</sup>) (Lyman 2014); **OR**
6. Poor renal function (glomerular filtration rate [GFR] less than 60mL/min) (Lyman 2014; Aagaard 2018); **OR**
7. Liver dysfunction (liver function tests at least 2X upper limit of normal or bilirubin > 2.0mg/dL) (Lyman 2014); **OR**
8. 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**
9. History of active infection within the previous 60 days (Lyman 2014; Aagaard 2018); **OR**
10. Current open wound and chemotherapy cannot be delayed (Lyman 2014; Aagaard 2018);

**OR**

- E. Individual with nonmyeloid malignancy is using for secondary prophylaxis of FN; **AND**
- F. 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**

- G. Individual is using as adjunctive treatment for FN; **AND**
- H. Individual has not received prophylactic therapy with pegfilgrastim (NCCN 2A); **AND**
- I. Individual has a high risk for infection-associated complications as demonstrated by any of the following:
1. Expected prolonged (greater than 10 days) and profound (less than 0.1 x 10<sup>9</sup>/L) neutropenia; **OR**
  2. Age greater than 65 years; **OR**
  3. Pneumonia or other clinically documented infections; **OR**
  4. Hypotension and multi organ dysfunction (sepsis syndrome); **OR**
  5. Invasive fungal infection; **OR**
  6. Prior episode of febrile neutropenia; **OR**
  7. Hospitalized at the time of the development of fever;

**OR**

- J. Individual is receiving dose dense therapy (treatment given more frequently, such as every 2 weeks instead of every 3 weeks) for adjuvant treatment of breast cancer (ASCO Smith 2015);

**OR**

- K. Individual is using after accidental or intentional total body radiation of myelosuppressive doses (greater than 2 Grays [Gy]) (such as Hematopoietic Syndrome of Acute Radiation Syndrome);

**OR**

L. Individual is using after a hematopoietic progenitor stem cell transplant (HPCT/HSCT) to promote myeloid reconstitution or when engraftment is delayed or has failed (NCCN 2A);

**OR**

M. Individual is using for treatment for hematopoietic cell mobilization in combination with plerixafor (NCCN 2A);

**OR**

N. Individual is using for Wilms Tumor (Nephroblastoma) (NCCN 2A); **AND**

O. Using with Regimen M and Regimen I for one of the following courses:

1. Cyclophosphamide and etoposide; **OR**
2. Cyclophosphamide, doxorubicin, and vincristine;

**OR**

P. Individual is using for autologous hematopoietic stem cell (HSC) mobilization as part of the development of an FDA-approved ex vivo gene therapy (e.g. Zynteglo (betibeglogene autotemcel)).

VI. Requests for Rolvedon (eflapegastim-xnst) may be approved if the following criteria are met:

A. Individual with nonmyeloid malignancy is using for primary prophylaxis of FN; **AND**

B. Individual has a risk of FN of 20% or greater based on chemotherapy regimen (NCCN 2A) ([see Appendix](#), Table1);

**OR**

C. Individual with nonmyeloid malignancy is using for primary prophylaxis of FN; **AND**

D. Individual's risk of developing FN is greater than or equal to 10% and less than 20%

based on chemotherapy regimen ([see Appendix](#), Table 1) and individual has any of the following risk factors for FN:

1. Age greater than 65 years (Lyman 2014; Aagaard 2018); **OR**
2. Poor performance status (Eastern Cooperative Oncology Group 3 or 4) or HIV infection (in particular, those with low CD4 counts ( $\leq 450/\mu\text{L}$ ) but chemotherapy still indicated) (Lyman 2014); **OR**
3. Prior radiation therapy (within previous 1 year) (Terbuch 2018) (Fujiwara 2017) (Shigeta 2015); **OR**
4. Bone marrow involvement by tumor producing cytopenias (Lyman 2014); **OR**
5. Persistent neutropenia (absolute neutrophil count [ANC] less than  $1500\text{mm}^3$ ) (Lyman 2014); **OR**
6. Poor renal function (glomerular filtration rate [GFR] less than  $60\text{mL/min}$ ) (Lyman 2014; Aagaard 2018); **OR**
7. Liver dysfunction (liver function tests at least 2X upper limit of normal or bilirubin  $> 2.0\text{ mg/dL}$ ) (Lyman 2014; Aagaard 2018); **OR**
8. 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**

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

**OR**

E. Individual with nonmyeloid malignancy is using for secondary prophylaxis of FN;

**AND**

F. 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**

G. Individual is using as adjunctive treatment for FN; **AND**

H. Individual has not received prophylactic therapy with pegfilgrastim (NCCN 2A);

**AND**

I. Individual has a high risk for infection-associated complications as demonstrated by any of the following:

1. Expected prolonged (greater than 10 days) and profound (less than  $0.1 \times 10^9/L$ ) neutropenia; **OR**
2. Age greater than 65 years; **OR**
3. Pneumonia or other clinically documented infections; **OR**
4. Hypotension and multi organ dysfunction (sepsis syndrome); **OR**
5. Invasive fungal infection; **OR**
6. Prior episode of febrile neutropenia; **OR**
7. Hospitalized at the time of the development of fever.

VII. Requests for Ryzneuta (efbemalenograstim alfa-vuxw) may be approved if the following criteria are met:

A. Individual with nonmyeloid malignancy is using for primary prophylaxis of Febrile Neutropenia (FN); **AND**

B. Individual has a risk of FN of 20% or greater based on chemotherapy regimen (NCCN 2A) ([see Appendix](#), Table 1);

**OR**

C. Individual with nonmyeloid malignancy is using for primary prophylaxis of FN;

**AND**

D. Individual has a risk of developing FN is greater than or equal to 10% and less than 20% based on chemotherapy regimen ([see Appendix](#), Table 1) and individuals have any of the following risk factors for FN:

1. Age greater than 65 years (Lyman 2014; Aagaard 2018); **OR**
2. Poor performance status (Eastern Cooperative Oncology Group 3 or 4) or HIV infection (in particular, those with low CD4 counts ( $\leq 450/\mu L$ )) but chemotherapy still indicated (Lyman 2014); **OR**
3. Prior radiation therapy (within previous 1 year) (Terbuch 2018) (Fujiwara 2017) (Shigeta 2015); **OR**
4. Bone marrow involvement by tumor producing cytopenias (Lyman 2014); **OR**

5. Persistent neutropenia (absolute neutrophil count [ANC] less than 1500mm<sup>3</sup>) (Lyman 2014); **OR**
6. Poor renal function (glomerular filtration rate [GFR] less than 60mL/min) (Lyman 2014; Aagaard 2018); **OR**
7. Liver dysfunction (liver function tests at least 2X upper limit of normal or bilirubin > 2.0 mg/dL) (Lyman 2014) (Aagaard 2018); **OR**
8. 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**
9. History of active infection within previous 60 days (Lyman 2014; Aagaard 2018); **OR**
10. Current open wound and chemotherapy cannot be delayed (Lyman 2014; Aagaard 2018).

**OR**

E. Individual with nonmyeloid malignancy is using for secondary prophylaxis of FN; **AND**

F. 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**

G. Individual is using as adjunctive treatment for FN; **AND**

H. Individual has not received prophylactic therapy with pegfilgrastim (NCCN 2A);

**AND**

I. Individual has a high risk for infection-associated complications as demonstrated by any of the following:

1. Expected prolonged (greater than 10 days) and profound (less than 0.1 x 10<sup>9</sup>/L) neutropenia; **OR**
2. Age greater than 65 years; **OR**
3. Pneumonia or other clinically documented infections; **OR**
4. Hypotension and multi organ dysfunction (sepsis syndrome); **OR**
5. Invasive fungal infection; **OR**
6. Prior episode of febrile neutropenia; **OR**
7. Hospitalized at the time of the development of fever.

**OR**

J. Individual is using after accidental or intentional total body radiation of myelosuppressive doses (greater than 2 Grays [Gy]) (such as Hematopoietic Syndrome of Acute Radiation Syndrome) (NCCN 2A).

Colony Stimulating Factors (efbmalenograstim alfa-vuxw, eflapegrastim-xnst, filgrastim and their biosimilars, pegfilgrastim and their biosimilars, sargramostim, and tbo-filgrastim) may not be approved for any of the following:

- I. Individual is using as prophylaxis for FN, except when criteria above are met; **OR**
- II. Individual is using as treatment in neutropenia in those who are afebrile, except when criteria above are met; **OR**

- III. Individual is using as adjunctive therapy in those with uncomplicated febrile neutropenia, defined as: 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 as 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.

### **Key References:**

1. Aagaard T, Roen A, Reekie J., et.al. Development and Validation of a Risk Score for Febrile Neutropenia After Chemotherapy in Patients With Cancer: The FENCE Score. *JNCI Cancer Spectrum*. 2018; 2(4):1-8.
2. Abe T, Takeda K, Ohe Y, et al. Randomized phase III trial comparing weekly docetaxel plus cisplatin versus docetaxel monotherapy every 3 weeks in elderly patients with advanced non-small-cell lung cancer: the intergroup trial JCOG0803/WJOG4307L. *J Clin Oncol*. 2015;33(6):575-81.
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### 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  $\geq 20\%$  probability of developing febrile neutropenia, an intermediate-risk chemotherapy regimen is associated with  $\geq 10$  to  $\leq 20\%$  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	Intermediate	Do 2015; Jones 2009; Jones 2006; Kosaka 2015; Younis 2012
Breast Cancer (Advanced)	Docetaxel (dosing of less than 75 mg/m <sup>2</sup> )	Low	Harvey V 2006; Mauri D 2010; Rivera E 2008; Sparano JA 2008; Tabernero J 2004
Breast Cancer (Advanced)	Docetaxel (dosing of 100 mg/m <sup>2</sup> every 3 weeks or less)	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 $\pm$ 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;
Gastroesophageal Cancer	Cisplatin and irinotecan	Intermediate	Ajani JA 2002; Enzinger PC 2016; Ilson DH 2004, 2012; Knox JJ 2010; Newman E 2005
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	Burtneess B 2005; Vermorken JB 2008; Vermorken JB 2013;
	Pembrolizumab plus platinum-based chemotherapy	Low	Burtneess B 2019;
Lymphoma	Gemcitabine, dexamethasone, and cisplatin $\pm$ 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; Georgoulas 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; Georgoulas 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 (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	Lilenbaum 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
Pancreatic Cancer	FOLFIRINOX	Intermediate	Chloreaan 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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