Neutrophil support for patients with cancer receiving myelosuppressive chemotherapy

**Indication**

NEUPOGEN® is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever.

*Please see Important Safety Information on page 2 and full Prescribing Information.*
NEUPOGEN Important Safety Information

Contraindication
NEUPOGEN® is contraindicated in patients with a history of serious allergic reactions to human granulocyte colony-stimulating factors, such as filgrastim or pegfilgrastim.

Splenic Rupture
Splenic rupture, including fatal cases, has been reported following the administration of NEUPOGEN®. Evaluate patients who report left upper abdominal or shoulder pain for an enlarged spleen or splenic rupture.

Acute Respiratory Distress Syndrome
Acute respiratory distress syndrome (ARDS) has been reported in patients receiving NEUPOGEN®. Evaluate patients who develop fever and lung infiltrates or respiratory distress for ARDS. Discontinue NEUPOGEN® in patients with ARDS.

Serious Allergic Reactions
Serious allergic reactions, including anaphylaxis, have been reported in patients receiving NEUPOGEN®. The majority of reported events occurred upon initial exposure. Provide symptomatic treatment for allergic reactions. Allergic reactions, including anaphylaxis, in patients receiving NEUPOGEN® can recur within days after the discontinuation of initial anti-allergic treatment. Permanently discontinue NEUPOGEN® in patients with serious allergic reactions.

Sickle Cell Disorders
Sickle cell crisis, in some cases fatal, has been reported with the use of NEUPOGEN® in patients with sickle cell trait or sickle cell disease.

Capillary Leak Syndrome
Capillary leak syndrome (CLS) has been reported after G-CSF administration, including NEUPOGEN®, and is characterized by hypotension, hypoalbuminemia, edema, and hemoconcentration. Episodes vary in frequency, 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 the need for intensive care.

Thrombocytopenia
Thrombocytopenia has been reported in patients receiving NEUPOGEN®. Monitor platelet counts.

Leukocytosis
White blood cell counts of ≥ 100,000/mm³ were observed in about 2% of patients with cancer receiving myelosuppressive chemotherapy who received NEUPOGEN® at dosages > 5 mcg/kg/day. It is recommended to monitor CBCs at least twice weekly, and adjust NEUPOGEN® dosing as clinically indicated to help mitigate risk of leukocytosis. Dosages of NEUPOGEN® that increase the absolute neutrophil count (ANC) beyond 10,000/mm³ may not result in any additional clinical benefit. Discontinuation of NEUPOGEN® therapy usually resulted in a 50% decrease in circulating neutrophils within 1 to 2 days, with a return to pretreatment levels in 1 to 7 days.

Cutaneous Vasculitis
Cutaneous vasculitis has been reported in patients treated with NEUPOGEN®. In most cases, the severity of cutaneous vasculitis was moderate or severe. Most of the reports involved patients with severe chronic neutropenia (SCN) receiving long-term NEUPOGEN® therapy. Hold NEUPOGEN® therapy in patients with cutaneous vasculitis. NEUPOGEN® may be started at a reduced dose when the symptoms resolve and the absolute neutrophil count (ANC) has decreased.

Potential Effect on Malignant Cells
The possibility that NEUPOGEN® acts as a growth factor for any tumor type, including myeloid malignancies and myelodysplasia, cannot be excluded.

Simultaneous Use with Chemotherapy and Radiation Therapy Not Recommended
The safety and efficacy of NEUPOGEN® given simultaneously with cytotoxic chemotherapy have not been established. Do not use NEUPOGEN® in the period 24 hours before or after the administration of cytotoxic chemotherapy. The safety and efficacy of NEUPOGEN® have not been evaluated in patients receiving concurrent radiation therapy. Avoid the simultaneous use of NEUPOGEN® with chemotherapy and radiation therapy.

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.

The most common adverse reactions (≥ 5% difference in incidence, compared to placebo) are pyrexia, pain, rash, cough, and dyspnea.

NEUPOGEN stimulates neutrophil proliferation, which helps reduce the risk of infection in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a significant incidence of severe neutropenia with fever.

NEUPOGEN stimulates neutrophil production

• Neutrophils are a type of granulocyte, which are important infection-fighting white blood cells produced in the bone marrow.

• Febrile neutropenia, the development of fever and associated infection due to a low number of neutrophils, is a medical emergency that can occur in patients with cancer receiving myelosuppressive chemotherapy.

NEUPOGEN requires daily dosing because of its short elimination half-life

NEUPOGEN molecules are cleared predominantly via filtration in the kidneys.

In addition, NEUPOGEN is cleared by binding to neutrophils already in circulation.

The elimination half-life of NEUPOGEN is approximately 3.5 hours. Therefore, NEUPOGEN requires daily dosing. NEUPOGEN should not be administered in the period 24 hours before through 24 hours after the administration of chemotherapy.

NEUPOGEN stimulates neutrophil proliferation and differentiation.
NEUPOGEN stimulates proliferation and decreases maturation time of neutrophils

Effect of NEUPOGEN on neutrophil proliferation and maturation

With endogenous granulocyte colony-stimulating factor (G-CSF)

MITOTIC PHASE
- Myeloblast
- Promyelocyte
- Myelocyte
- Metamyelocyte
- Band cell
- Mature segmented cell

POSTMITOTIC PHASE
- Circulating neutrophils
- 3 to 9 days
- 5 to 7 days

With exogenous G-CSF (NEUPOGEN)

MITOTIC PHASE
- Myeloblast
- Promyelocyte
- Myelocyte

POSTMITOTIC PHASE
- Metamyelocyte
- Band cell
- Mature segmented cell
- Circulating neutrophils
- 3 to 9 days
- 1 day

NEUPOGEN decreased the severity and duration of chemotherapy-induced neutropenia

- The timing and depth of neutrophil nadirs vary based on patient factors and the type of chemotherapy administered
- A longer duration of severe neutropenia (absolute neutrophil count [ANC] < 0.5 × 10^9/L) is directly related to an increased risk of febrile neutropenia

IMPORTANT SAFETY INFORMATION

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Please see additional Important Safety Information on page 2.

NEUPOGEN® Placebo

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Placebo</th>
<th>NEUPOGEN</th>
<th>Decrease</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median duration of grade 4 neutropenia in first cycle</td>
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<td>3 days</td>
<td>50%</td>
<td>&lt; .001</td>
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<tr>
<td>Median duration of fever with neutropenia in first cycle</td>
<td>5 days</td>
<td>4 days</td>
<td>—</td>
<td>NS</td>
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</tbody>
</table>
Less-than-labeled doses of NEUPOGEN were associated with a greater incidence of febrile neutropenia

NEUPOGEN used for $\geq 7$ days decreased the rate of febrile neutropenia by 65% compared with dosing of $< 7$ days.

Therapeutic dosing of NEUPOGEN helps reduce the incidence of febrile neutropenia.

**IMPORTANT SAFETY INFORMATION**

**Splenic Rupture**

Splenic rupture, including fatal cases, has been reported following the administration of NEUPOGEN. Evaluate patients who report left upper abdominal or shoulder pain for an enlarged spleen or splenic rupture.

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Dose NEUPOGEN based on weight, and with proper scheduling and administration, to help reduce the risk of febrile neutropenia

Recommended dosage and administration provide neutrophil support for patients with cancer receiving myelosuppressive chemotherapy:

- Starting dosage of 5 mcg/kg/day, administered as a single daily injection by subcutaneous injection, by short intravenous infusion (15 to 30 minutes), or by continuous intravenous infusion
- Obtain a CBC and platelet count before instituting therapy and monitor twice weekly during therapy
- Consider dose escalation in increments of 5 mcg/kg for each chemotherapy cycle, according to the duration and severity of ANC nadir
- Recommend stopping NEUPOGEN if ANC increases > 10,000/mm³
- Administer ≥ 24 hours after cytotoxic chemotherapy; do not administer within the 24-hour period prior to chemotherapy
- Administer daily for up to 2 weeks or until the ANC has reached 10,000/mm³ following the expected chemotherapy-induced neutrophil nadir

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Acute Respiratory Distress Syndrome

Acute respiratory distress syndrome (ARDS) has been reported in patients receiving NEUPOGEN®. Evaluate patients who develop fever and lung infiltrates or respiratory distress for ARDS. Discontinue NEUPOGEN® in patients with ARDS.

References

Help reduce the risk of febrile neutropenia

Use NEUPOGEN at the appropriate dose and duration

- NEUPOGEN helps stimulate neutrophil production
- NEUPOGEN helps decrease the severity and duration of chemotherapy-induced neutropenia for patients with cancer receiving myelosuppressive chemotherapy
- Dose NEUPOGEN based on weight and with proper scheduling and administration to help reduce the risk of febrile neutropenia
- Efficacy has been shown to be compromised when NEUPOGEN was dosed at less than the label-indicated dose
- The most common adverse reactions (≥ 5% difference in incidence, compared to placebo) are pyrexia, pain, rash, cough, and dyspnea

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NEUPOGEN weight-based dosing

Dosing information in patients receiving myelosuppressive chemotherapy

Recommended dosing by patient weight

<table>
<thead>
<tr>
<th>Patient Weight</th>
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<th>NEUPOGEN Starting Dose (5 mcg/kg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 50 kg</td>
<td>&lt; 110 lb</td>
<td>&lt; 250 mcg</td>
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<tr>
<td>55 kg</td>
<td>121 lb</td>
<td>275 mcg</td>
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<td>110 kg</td>
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1. NEUPOGEN® (filgrastim) prescribing information, Amgen.
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