# Granulocyte Stimulating Colony Factor Criteria for Use for Hepatitis C Treatment-Related Neutropenia

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*The following recommendations are based on current medical evidence and expert opinion from clinicians. The content of the document is dynamic and will be revised as new clinical data becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. The clinician should utilize this guidance and interpret it in the clinical context of the individual patient. Additional information can be found at www.pbm.va.gov and http://vaww.pbm.va.gov*

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## Introduction

Hepatitis C virus (HCV) infection is estimated to affect several million Americans and over 170 million people worldwide. Standard treatment for chronic HCV involves an interferon-based preparation and ribavirin for 24 to 48 weeks. Sustained virologic response (SVR), defined as having undetectable virus at 6 months post-treatment, occurs in 54% to 56% of overall patients treated with peginterferon alfa and ribavirin. Moderate neutropenia is a common adverse effect of hepatitis C antiviral therapy with peginterferon alfa causing bone marrow suppression, resulting in absolute neutrophil counts (ANC) of $<750/mm^3$ in approximately 20% of those treated. Peginterferon alfa doses of <60% of target dose appears to reduce SVR. Conceptually, granulocyte colony stimulating factor use may overcome treatment-related neutropenia, maintain higher interferon doses and potentially reduce infection in high-risk patients, though clinical studies to recommend its use are lacking.

## Patient Selection

Before using a granulocyte colony stimulating factor:

- Peginterferon dose has been reduced
  - Peginterferon alfa 2a reduction from 180mcg/week to 135mcg/week
  - Peginterferon alfa 2b reduction from 1.5mcg/kg/week to 1.0mcg/kg/week

**AND**

- Persistent severe neutropenia despite at least 2 weeks of reduced dose peginterferon along with:
  - ANC $<250/mm^3$, OR
  - ANC $<500/mm^3$ with one of the following risk factors for developing infection
    1. Cirrhosis, biopsy proven or clinically evident
    2. Pre- or post-liver transplant
    3. HIV/HCV coinfection

**AND**

- Does not have known allergic or hypersensitivity reactions to filgrastim or other *E coli*-derived proteins

## Goals of Therapy

- Resolution of severe neutropenia (ANC $>500/mm^3$)
- Maintain therapeutic dose of interferon-based preparation (generally, dose reductions of up to 40% do not appear to compromise SVR)
- Reduced risk of infection and hospitalization

## Dosing and Monitoring (Refer to algorithm below)

- Filgrastim 300 mcg sq once or twice a week.

- Titrate filgrastim dose to achieve ANC 500-1000/$mm^3$.
- Check nadir ANC just prior to the next dose to evaluate response every 1-2 weeks until stable
- If ANC shows no increase or continues to decrease after at least 1 week of filgrastim, then further reduce or discontinue peginterferon and titrate filgrastim as above.
    - Investigate other potential cause for neutropenia (e.g. myelodysplasia)
- If ANC >1000/$mm^3$, stop filgrastim.

## Safety Issues

The most common adverse effects associated with filgrastim include bone pain and generalized musculoskeletal pain. Other adverse effects infrequently observed and possibly related to filgrastim use include injection site reaction, rash, hepatomegaly, and arthralgia.

Allergic reactions occurring on initial or subsequent treatment have been rarely reported (<1 in 4,000 patients), generally occurring within the first 30 minutes of administration. These have been generally characterized by systemic symptoms involving at least 2 body systems, most often skin (rash, urticaria, facial edema), respiratory (wheezing, dyspnea), and cardiovascular (hypotension, tachycardia). Symptom resolution occurred in most cases after administration of antihistamines, steroids, bronchodilators, and/or epinephrine.

Rare fatal cases of splenic rupture have been reported following administration of filgrastim in both healthy volunteers and patients. Patients reporting left upper abdominal and/or shoulder tip pain should be evaluated for an enlarged spleen or splenic rupture.

Cytopenias resulting from an antibody response to exogenous growth factors have been reported on rare occasions in patients treated with recombinant growth factors. Patients receiving filgrastim should be closely monitored for a paradoxical decrease in ANC and treatment should be discontinued in patients with evidence of neutralizing antibodies to filgrastim.

Severe sickle cell crisis resulting in death has been associated with filgrastim in patients with sickle cell disease. Risks and benefits of filgrastim use in patients with sickle cell disease must be carefully considered.

Since filgrastim single-dose vials and prefilled syringes do not contain preservatives, the vial or prefilled syringe should only be used once and any unused portion should be discarded.

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# Algorithm for use of GCSFfor Hepatitis C Treatment-Related neutropenia