Febrile neutropenia is a serious complication of cancer chemotherapy that can require treatment delays and chemotherapy dose reductions, which compromise the efficacy of treatment. Among patients with cancer who are receiving chemotherapy, approximately 1% have febrile neutropenia. This condition affects patient morbidity and mortality and its clinical management requires significant healthcare resources.

Granulocyte colony-stimulating factor (G-CSF) is the principal cytokine that controls the development and function of neutrophils. Recognizing the clinical value of endogenous G-CSF, researchers developed recombinant G-CSF, with the goals of decreasing the duration of neutropenia and febrile neutropenia in patients with cancer who receive chemotherapy and allowing more frequent chemotherapeutic treatments. Today, G-CSFs, such as filgrastim (Neupogen), and granulocyte macrophage-colony stimulating factor, such as sargramostim (Leukine), are used to improve white blood cell production and to reduce the incidence of infections in patients with specific types of cancer who are undergoing chemotherapy.

Biosimilars
Biologic drugs, including G-CSFs, are large-molecule medicines that are produced in living organisms. Enacted in March 2010, the Biologics Price Competition and Innovation Act of 2009 (BPCIA) was passed in conjunction with the Patient Protection and Affordable Care Act. The BPCIA gives drug manufacturers an abbreviated approval process for biologic drugs that are shown to be highly similar to or interchangeable with a US Food and Drug Administration (FDA)-approved reference biologic drug. The larger objective of the BPCIA was to provide additional treatment options at reduced costs, increase access to important drugs, and potentially lower healthcare costs through competition.

The originator drug pegfilgrastim (Neulasta) was approved by the FDA in 2002 as a long-acting form of G-CSF. In June 2018, the FDA approved pegfilgrastim-jمدب (Fulphila) as the first biosimilar to Neulasta.

Biosimilars are expected to have a reduced list price compared with their reference drug. In a 2018 article, Mulcahy and colleagues discuss the potential cost-savings with biosimilars to the US healthcare system, based on information from the first biosimilar that was marketed in the United States. According to the authors, biosimilars will lead to a reduction of $54 billion (range, $24 billion-$150 billion) in direct spending on biologic drugs from 2017 to 2026, representing approximately 3% of the estimated biologic spending over that period. Mulcahy and colleagues caution, however, that the “actual savings will hinge on industry, regulatory, prescriber, and insurer decisions, as well as potential future policy changes to strengthen the biosimilar market.”

Biosimilar cost-savings can have a positive effect on healthcare payers, providers, and patients. Insurers will benefit from reduced biologic prices through lower payment rates, which can translate to lower insurance premiums for patients. Physicians may benefit from lower prices for the biologics that they administer in their offices, because they purchase the biologic drugs themselves and are reimbursed retroactively. Finally, patients are often involved in cost-sharing for biologic drugs; with increasing patient out-of-pocket costs because of deductibles and copayments, lower prices for biosimilars will clearly benefit patients.

Udenyca Second Biosimilar Approved for Febrile Neutropenia
On November 2, 2018, the FDA approved pegfilgrastim-cbqv (Udenyca; Coherus BioSciences) as a biosimilar to the reference drug Neulasta. Pegfilgrastim-cbqv is the second biosimilar to pegfilgrastim approved by the FDA. Pegfilgrastim-cbqv is approved for the same indications as the reference drug—to decrease the incidence of infection, as manifested by febrile neutropenia, in pa-
patients with nonmyeloid malignancies who are receiving myelosuppressive anticancer drugs that are associated with a clinically significant incidence of febrile neutropenia. Pegfilgrastim-cbqv is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem-cell transplantation. Pegfilgrastim-cbqv is not approved as an interchangeable drug with the originator drug, pegfilgrastim.

The FDA approval of pegfilgrastim-cbqv was based on data demonstrating that it is highly similar to its reference drug, and that there are no clinically meaningful differences between the biosimilar and its reference drug.

**Mechanism of Action**

Pegfilgrastim-cbqv is one of the colony-stimulating factors that act on specific hematopoietic cells to stimulate proliferation, differentiation, commitment, and function.

**Dosing and Administration**

Patients with cancer who are receiving myelosuppressive chemotherapy should receive a single 6-mg dose of pegfilgrastim-cbqv via subcutaneous injection once during each cycle of chemotherapy. Weight-based dosing of pegfilgrastim-cbqv is appropriate for patients who weigh less than 45 kg.

Pegfilgrastim-cbqv should not be administered between 14 days before and 24 hours after the administration of cytotoxic chemotherapy.

**Adverse Events**

The most common adverse reactions (≥5% difference between the pegfilgrastim and the placebo arms) reported in clinical studies that supported the approval of pegfilgrastim (the reference drug for pegfilgrastim-cbqv), were bone pain and pain in extremity. As with other therapeutic proteins, there is a potential for immunogenicity when using pegfilgrastim-cbqv.

**Contraindications**

The use of pegfilgrastim-cbqv is contraindicated in patients with a history of serious allergic reactions to pegfilgrastim drugs or to filgrastim drugs. Anaphylaxis can occur with these medications.

**Use in Specific Populations**

Although available data for pegfilgrastim drugs in pregnant women are insufficient to establish any risk for major birth defects, miscarriage, or adverse maternal or fetal outcomes, data from published studies in pregnant women who were exposed to filgrastim drugs have not established such an association during pregnancy.

There are no data on the effects of pegfilgrastim drugs in human milk, on the breastfed child, or on milk production. The developmental and health benefits of breastfeeding should be considered, along with the mother’s clinical need for pegfilgrastim-cbqv and any potential adverse effects on the breastfed child from this drug or from the underlying maternal condition.

The safety and effectiveness of pegfilgrastim-cbqv have not been established in children. However, the use of pegfilgrastim in children at risk for chemotherapy-induced neutropenia is based on adequate and well-controlled studies in adults, with additional pharmacokinetic and safety data in children with sarcoma.

Among 932 patients with cancer who received pegfilgrastim in clinical studies, 15% were aged ≥65 years. No overall differences in the safety or effectiveness were observed between older and younger patients.

**Warnings and Precautions**

Splenic rupture, including fatal cases, can occur after the administration of pegfilgrastim drugs. Patients who report left upper abdominal or shoulder pain after receiving pegfilgrastim-cbqv should be evaluated for splenomegaly or splenic rupture.

The potential for acute respiratory distress syndrome should be evaluated in patients who have fever and lung infiltrates or respiratory distress after receiving pegfilgrastim-cbqv.

Serious allergic reactions, including anaphylaxis, can occur in patients who receive pegfilgrastim drugs. These events typically occur with initial exposure. Pegfilgrastim-cbqv should not be administered to patients with a history of serious allergic reactions to pegfilgrastim drugs or to filgrastim drugs.

Severe sickle-cell crises can occur in patients with sickle-cell disorders who receive pegfilgrastim drugs.

Glomerulonephritis can occur with the use of pegfilgrastim drugs. Signs of glomerulonephritis include azotemia, microscopic and macroscopic hematuria, and proteinuria. In clinical trials, glomerulonephritis generally resolved after dose reduction or discontinuation of pegfilgrastim.

Aortitis can occur as early as the first week after initiating treatment with pegfilgrastim drugs. Fever, abdominal pain, malaise, back pain, and increased inflammatory markers (eg, C-reactive protein and white blood cell count) can occur.

Leukocytosis (white blood cell counts of ≥100 × 10^9/L) has been observed in patients receiving pegfilgrastim drugs.

Capillary leak syndrome has been reported after the administration of G-CSFs, including pegfilgrastim drugs. Hypotension, hypoalbuminemia, edema, and hemoconcentration are common symptoms of capillary
leak syndrome, which can be life-threatening if treatment is delayed.12

Tumor-cell lines can have the G-CSF receptor through which pegfilgrastim drugs and filgrastim drugs act. Pegfilgrastim drugs may act as a growth factor for any tumor type, including those for which pegfilgrastim drugs are not approved.12

Increased hematopoietic activity in the bone marrow in response to G-CSF therapy can result in transient positive bone imaging changes and may affect the interpretation of imaging results.12

Conclusion

Pegfilgrastim-cbqv was approved by the FDA as the second biosimilar to the reference drug Neulasta. Clinical trials demonstrate that the efficacy and safety of pegfilgrastim-cbqv are comparable to its reference drug, pegfilgrastim, in preventing febrile neutropenia in patients with nonmyeloid malignancies who are receiving myelosuppressive treatments. Pegfilgrastim-cbqv adds another treatment option for febrile neutropenia—and potentially at a reduced cost—for the treatment of patients who are receiving chemotherapy.

References