Pegfilgrastim

Section: 8. Immunomodulators and antineoplastics > 8.2. Antineoplastics and supportive medicines > 8.2.3. Immunomodulators

EMLc | ATC codes: L03AA13

Indication	Acquired neutropaenia ICD11 code: 4B00.01
INN	Pegfilgrastim
Medicine type	Biological agent
List type	Complementary
Additional notes	Including quality-assured biosimilars.
Formulations	**Parenteral > General injections > SC:** 6 mg per 0.6 mL in pre-filled syringe
EML status history	First added in 2023 (TRS 1049)
Sex	All
Age	Also recommended for children
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Main patents have expired but secondary patents might remain active in some jurisdictions. For more information on specific patents and license status for developing countries visit www.MedsPal.org Read more about patents.
Tags	Biological Cancer
Wikipedia	Pegfilgrastim
DrugBank	Pegfilgrastim

Expert Committee recommendation

The Expert Committee acknowledged that the prevention of febrile neutropenia is an important aspect of cancer care in people undergoing myelosuppressive chemotherapy regimens. The Committee noted that a single dose of pegfilgrastim (once every 2 weeks) is an effective and safe alternative to daily injections of filgrastim with most of the available evidence showing no significant difference between treatments in reducing the risk of febrile neutropenia. The Committee considered that pegfilgrastim may offer advantages over filgrastim in settings where refrigerated storage outside of secondary treatment centres is limited. In these settings, patients being treated with daily injections of filgrastim face longer hospital stays or daily clinic visits and this has been associated with lower adherence to treatment and increased risk of life-threatening infections. The Committee noted that filgrastim is still a relevant treatment option for patients in whom a treatment duration of less than 2 weeks is indicated. The Committee recalled the 2015 recommendation not to include pegfilgrastim on the Model Lists because of a substantial difference in price compared to filgrastim at the time. The Committee noted that since then the patent for pegfilgrastim had expired and biosimilars had entered the market, resulting in reductions in price, often lower than the price of filgrastim. The Expert Committee therefore recommended the inclusion of pegfilgrastim (including quality-assured biosimilar products) on the complementary list of the EML and EMLc for primary prophylaxis in patients at high risk of developing febrile neutropenia associated with myelotoxic

chemotherapy, and for secondary prophylaxis in patients who have experienced neutropenia following prior myelotoxic chemotherapy.

Background

Granulocyte colony-stimulating factors (filgrastim and pegfilgrastim) were previously considered for inclusion on the Model Lists for use as supportive treatment with myelotoxic chemotherapy regimens as part of a comprehensive review of cancer medicines in 2015. The Expert Committee noted that several studies had shown comparability in effectiveness and patient outcomes of daily filgrastim and once per cycle pegfilgrastim. The Committee considered that the choice between filgrastim and pegfilgrastim was largely determined by individual preference, ease of administration and cost. At that time, pegfilgrastim was considerably more expensive than filgrastim, for which biosimilar products were available. Therefore, the Committee recommended only the inclusion of pegfilgrastim on the EML and EMLc. The Expert Committee acknowledged that avoidance of febrile neutropenia was a meaningful goal of holistic care of patients with cancer undergoing myelotoxic chemotherapy (1).

Public health relevance

Chemotherapy-induced myelotoxicity is a common and potentially life-threatening adverse event for cancer patients. The incidence of febrile neutropenia associated with myelotoxic chemotherapy varies depending on the type of cancer, the specific type and number of myelosuppressive chemotherapy agents in use, and other factors such as age and comorbidities (2,3). Febrile neutropenia is the most common life-threatening complication of cancer therapy and is an oncologic emergency. Myelosuppression continues to be a major dose-limiting toxicity for many chemotherapy regimens (4). In resource-constrained areas particularly, but also in high-income countries for many cancers, newer targeted and immunological cancer treatments might not be widely available, affordable, or feasible and myelosuppressive treatments are still the standard of care. In such settings, prevention and treatment of febrile neutropenia associated with cancer treatment is a high priority.

Benefits

Two pivotal randomized, double-blind, multicentre, phase III studies compared the efficacy of pegfilgrastim versus filgrastim in patients with solid tumours receiving chemotherapy. The first study included 157 patients who were randomized to receive a single fixed 6 mg dose of pegfilgrastim (n = 80) or filgrastim 5 micrograms/kg a day (n = 77) with each cycle of chemotherapy (doxorubicin and docetaxel) for four cycles. The results showed that a single 6 mg injection of pegfilgrastim was as effective as daily injections of filgrastim for all efficacy measures for all cycles. The mean duration of grade 4 neutropenia in cycle one was 1.8 and 1.6 days for the pegfilgrastim and filgrastim groups, respectively. Results for all efficacy endpoints in cycles two to four were consistent with the results from cycle one. A trend towards a lower incidence of febrile neutropenia was noted across all cycles with pegfilgrastim compared with filgrastim, 13% versus 20% (5). The second study included 310 patients who were randomized to receive single dose pegfilgrastim 100 micrograms/kg or filgrastim 5 micrograms/kg a day with each cycle of chemotherapy (doxorubicin and docetaxel) for four cycles. The results showed that one dose of pegfilgrastim per chemotherapy cycle was comparable to daily subcutaneous injections of filgrastim for all efficacy endpoints, including the duration of severe neutropenia and depth of the absolute neutrophil count nadir in all cycles. Febrile neutropenia in all cycles occurred less often in patients who received pegfilgrastim. The difference in the mean duration of severe neutropenia between the treatment groups was less than 1 day. Pegfilgrastim and filgrastim were similarly safe and well tolerated (6). A 2011 systematic review and meta-analysis assessed the effectiveness of granulocyte colony-stimulating factors as primary prophylaxis against febrile neutropenia in adults undergoing chemotherapy for solid tumours or lymphoma. Twenty studies compared primary prophylaxis with filgrastim (10 studies), lenograstim (five studies) or pegfilgrastim (five studies) versus no prophylaxis. A further five studies compared filgrastim and pegfilgrastim. The results showed that any primary prophylaxis with granulocyte colony-stimulating factors significantly reduced the incidence of febrile neutropenia (relative risk (RR) 0.51, 95% confidence interval (CI) 0.41 to 0.62). The RRs for each medicine were 0.30 (95% CI 0.14 to 0.65) for pegfilgrastim, 0.57 (95% CI 0.48 to 0.69) for filgrastim and 0.62 (95% CI 0.44 to 0.88) for

lenograstim. In the comparison of filgrastim and pegfilgrastim, the incidence of febrile neutropenia was significantly lower for pegfilgrastim (RR 0.66, 95% CI 0.44 to 0.98) (7). A 2007 meta-analysis of five randomized-trials (617 participants) compared the effect pegfilgrastim and filgrastim on the incidence of febrile neutropenia, grade IV neutropenia, time to absolute neutrophil count recovery and bone pain in patients with solid tumours and malignant lymphomas receiving myelosuppressive chemotherapy. Pooled estimates indicated that pegfilgrastim, administered as a single dose per cycle, was associated with a significant reduction in febrile neutropenia compared with daily filgrastim injections (risk ratio 0.64, 95% CI 0.43 to 0.97). Rates of grade IV neutropenia, time to absolute neutrophil count recovery and incidence of bone pain were similar between the treatments (8). A 2021 systematic review of 13 studies (10 non-randomized studies, three randomized trials, 4315 participants) evaluated the effectiveness and safety of pegfilgrastim in preventing febrile neutropenia in patients with non-myeloid malignancies receiving myelosuppressive chemotherapy regimens. Meta-analyses were not performed because of the heterogeneity of the studies. Six of the studies provided statistical comparisons for pegfilgrastim versus filgrastim or placebo. Three studies found a significant decrease in the incidence of febrile neutropenia with pegfilgrastim compared with filgrastim or placebo. In the remaining three, a non-significantly lower incidence of febrile neutropenia was observed with pegfilgrastim compared with filgrastim. Five of the studies reported dose delays or dose reductions, with two finding significantly lower incidences with pegfilgrastim compared with filgrastim. In one study, the incidence of dose reductions was significantly lower in patients receiving pegfilgrastim with two-weekly chemotherapy regimens compared with three-weekly chemotherapy regimens (9).

Harms

The overall safety profile of single-dose pegfilgrastim was comparable to that of standard daily filgrastim in both pivotal comparative trials (5,6). Safety data in the United States Food and Drug Administration’s product information for originator pegfilgrastim were reported from a randomized, placebo-controlled, double-blind study of pegfilgrastim plus docetaxel in 928 patients with breast cancer. Adverse events occurred in similar percentages of patients across treatment arms and were typical of those associated with docetaxel (alopecia, diarrhoea, fever, and nausea and vomiting). Most adverse events were of mild or moderate intensity. Adverse events occurring more frequently in the pegfilgrastim arm than the placebo arm were bone pain (31% versus 26%) and pain in extremities (9% versus 4%) (10).

Cost / cost effectiveness

Since the previous consideration of pegfilgrastim by the Expert Committee in 2015, the patent for pegfilgrastim has expired and biosimilar products have become available. As a result, the price of pegfilgrastim has decreased markedly. The application presented data extracted from the Eversana database (a proprietary aggregator database of public prices) comparing the price of filgrastim and pegfilgrastim, per mg and per cycle, in 21 high-income countries. Pegfilgrastim prices (per mg and per 2-week cycle) were between 5% and 68% lower than filgrastim prices in 20 of the 21 countries investigated. No information on cost–effectiveness was presented in the application. The application stated that in high-income countries, in general, pegfilgrastim was reimbursed on a cost-minimization basis to filgrastim on the basis that the efficacy and safety of pegfilgrastim and filgrastim were equivalent.

WHO guidelines

WHO guidelines for prophylaxis of febrile neutropenia are not currently available.

Other considerations

The technical team in cancer in the WHO Department of Noncommunicable Diseases reviewed and provided comments on the application. The technical team advised that it supported the inclusion of pegfilgrastim on the Model Lists, given its similar efficacy and safety compared with filgrastim, and potential indirect cost benefits and quality-of-life benefits. The EML Cancer Medicines Working Group reviewed the application and advised that it supported the inclusion of pegfilgrastim on the EML and EMLc for the prevention of febrile neutropenia in patients

receiving myelotoxic chemotherapy. The Working Group highlighted that pegfilgrastim has been shown to be a safe and effective alternative to daily filgrastim injections, which is of particular importance in settings with limited resources. Short-acting filgrastim can lead to lower adherence due to its daily administration and cold supply chain limitations in low-income countries. Shorter treatment durations are common because of these constraints, potentially leading to worse outcomes. Despite the cost of pegfilgrastim, lower costs of biosimilar products make it a viable option, which offers a single-dose administration. Pegfilgrastim is preferred for patients on shorter chemotherapy cycles, while caution is advised against routine use of granulocyte colony-stimulating factors unless the risk of neutropenia is substantial.

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