A.31	Pegfilgrastim – febrile neutropenia prophylaxis – EML and EMLc
Draft recommendation	☒ Recommended ☐ Not recommended Justification: I support the inclusion of pegfilgrastim and quality assured biosimilars on the EML and EMLc for the treatment and prevention of febrile neutropenia, for the same indication as the current filgrastim listing (4B00.01 Acquired neutropenia): 1. primary prophylaxis in patients at high risk for developing febrile neutropenia associated with myelotoxic chemotherapy 2. secondary prophylaxis for patients who have experienced neutropenia following prior myelotoxic chemotherapy 3. to facilitate administration of dose dense chemotherapy regimens The Expert Committee commentary noted that clinical Guidelines at the time of submission in 2015 were generally accepting of filgrastim and pegfilgrastim, depending on patient circumstances and cost considerations within the health system concerned. However, for the listing, it was decided that filgrastim alone would be recommended for addition to the EML, on the basis of existing biosimilar competition (which at the time pegfilgrastim did not have) and the impacts that had on the relative costs of regimens with comparable clinical efficacy. It was noted that biosimilars were available for filgrastim, allowing for comparable clinical efficacy at lower cost; at that time biosimilars were not available for pegfilgrastim. Pegfilgrastim costs are dropping with the approval of several biosimilars, and there is also the potential for cost-savings of using single-dose administration over daily dose administration without significantly compromising benefit. The availability of pegfilgrastim biosimilars and improved affordability is likely to correlate with increased use. While the clinical efficacy (The available evidence shows that a single dose of pegfilgrastim is an efficacious and safe alternative to daily injections of filgrastim) and safety of both medicines are comparable in a clinical trial sense, especially for low- and middle-income country contexts the comparative dosing regimen of pegfilgrastim vs filgrastim (once per two weeks vs once per day) and the concomitant reduction in cold chain storage space may be an important additional consideration for resource-poor environments. In clinical practice, particularly in low- and middle-income countries, short-acting filgrastim is associated with increased risks of lower adherence, as it can require daily administration for up to 10-14 days.

Does the proposed medicine address a relevant public health need?	☒ Yes ☐ No ☐ Not applicable Comments: Filgrastim and pegfilgrastim were both proposed for consideration on the 19th WHO Essential Medicines List by the as a part of the comprehensive review of cancer medicines undertaken by the Expert Committee. This review (and published TRS) provides a comprehensive overview of the rationale and implications for the use of G-CSF in chemotherapy regimens with curative intent. In particular, the panel of experts concluded that the prevalence of associated factors that predispose an individual to an increased risk of developing febrile neutropenia "makes febrile neutropenia outcome more pronounced." Where possible, it may increase in resource-poor settings" (WHO TRS 994). It should also be noted that new immuno-oncology agents may not be available in resource-poor centers, and myelosuppressive therapy remains the standard of care in many countries. Therefore, adequate treatment/prophylaxis of febrile neutropenia as a result of myelosuppressive chemotherapy is very important.
Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication? (this may be evidence included in the application, and/or additional evidence identified during the review process)	☒ Yes ☐ No ☐ Not applicable Comments: In general, the clinical efficacy of pegfilgrastim is comparable to that of filgrastim, given the medicine is a pegylated, long-acting version of filgrastim.
Does adequate evidence exist for the safety/harms associated with the proposed medicine? (this may be evidence included in the application, and/or additional evidence identified during the review process)	☒ Yes ☐ No ☐ Not applicable Comments: In general, the clinical safety of pegfilgrastim is comparable to that of filgrastim, given the medicine is a pegylated, long-acting version of filgrastim. Both pivotal comparative clinical trials of filgrastim vs pegfilgrastim noted that: 1. A single fixed dose of pegfilgrastim was as safe and well tolerated as standard daily filgrastim (Green et al 2002) 2. A single injection of pegfilgrastim 100 ug/kg per cycle was as safe and effective as daily injections of filgrastim 5 ug/kg/d in reducing neutropenia and its complications in patients who received four cycles of doxorubicin 60 mg/m2 and docetaxel 75 mg/m2 (Holmes et al 2003)
Are there any adverse effects of concern, or that may require special monitoring?	☐ Yes ☒ No ☐ Not applicable Comments:

Are there any special requirements for the safe, effective and appropriate use of the medicines? (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	☐ Yes ☒ No ☐ Not applicable Comments:
Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings?	☐ Yes ☐ No ☐ Not applicable Comments: Given the patents for pegfilgrastim have expired and there is now a range of biosimilar competitors to the originator medicine, the international pricing of pegfilgrastim has fallen considerably. This listing is being proposed on the basis of international per-regimen cost comparisons of filgrastim vs pegfilgrastim, where pegfilgrastim now routinely has lower costs per regimen than filgrastim. The basis of international per-regimen cost comparisons of filgrastim vs pegfilgrastim, where pegfilgrastim now routinely has lower costs per regimen than filgrastim. The major driver of the reduced comparative costs of pegfilgrastim is likely to be driven by two relevant factors: a. the expiry of the pegfilgrastim patent and the emergence of biosimilar competition, and b. the beneficial nature of the comparative dosing regimen of pegfilgrastim vs filgrastim (once per cycle vs once per day for ~2 weeks), which itself creates a competitive market opportunity and downwards pricing pressure
Are there any issues regarding the registration of the medicine by national regulatory authorities? (e.g. accelerated approval, lack of regulatory approval, off-label indication)	☐ Yes ☒ No ☐ Not applicable Comments:
Is the proposed medicine recommended for use in a current WHO guideline? (refer to: https://www.who.int/publications/who-guidelines)	☐ Yes ☒ No ☐ Not applicable Comments: