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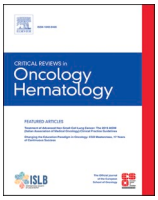

Filgrastim biosimilar (EP2006): A review of 15 years' post-approval evidence

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ABSTRACT

Filgrastim is approved for several indications, including reduction of the incidence and duration of chemotherapy-induced neutropenia and for stem cell mobilization. The filgrastim biosimilar, EP2006, has been available in Europe since 2009, and in the United States since 2015. In this time, preclinical and clinical data used to support the approval of EP2006 have been published. These data established the biosimilarity of EP2006 to reference filgrastim in terms of structure, pharmacokinetics, pharmacodynamics, efficacy, safety, and immunogenicity. Additional real-world evidence studies have also demonstrated equivalent efficacy and safety of EP2006 compared with reference filgrastim, both in the reduction of neutropenia and in stem cell mobilization in clinical practice. This review summarizes these preclinical, clinical, and real-world data, as well as the available cost-effectiveness data, for EP2006 since its approval 15 years ago.

1. Introduction

Filgrastim – a biological medicine – is a recombinant human granulocyte colony-stimulating factor (G-CSF), which stimulates the proliferation and maturation of neutrophils, and facilitates their release into the blood (Aghedo and Gupta, 2022). The G-CSF receptor is a member of the cytokine receptor superfamily and exerts its influence through various signaling molecules, including components of the Janus kinase/signal transducer and activator of transcription pathway, and the p21Ras/Raf/mitogen-activated protein kinase pathway (Hermans et al., 2003).

Filgrastim is approved for several indications, including reduction in the incidence and duration of chemotherapy-induced neutropenia (CIN), and stem cell mobilization (US Food and Drug Administration, 2023). The European Society for Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN) recommend filgrastim for prophylaxis of febrile neutropenia at a dose of 5 μg/kg/day, 24–72 hours after the last day of chemotherapy until post-nadir absolute neutrophil count recovery (Crawford et al., 2010). ESMO also recommends the use of filgrastim for peripheral blood stem cell mobilization at a dose of 10 μg/kg/day, for 7–10 days before apheresis, with or without chemotherapy (Crawford et al., 2010), while the NCCN's recommendation is for 4–5 days, continued until apheresis and collection goals are met (National Comprehensive Cancer Network, 2023a). However, variations exist between different clinicians from different hospitals and countries regarding the preferred method of administration and optimal timing of filgrastim therapy, while prior to the emergence of biosimilars, high drug costs may have reduced the uptake of filgrastim (Cornes and Krendyukov, 2019).

Biosimilars are biologic medicines that match the reference medicine in terms of biological activity, efficacy, safety, immunogenicity, and quality. These medicines are approved via abbreviated yet robust regulatory processes in Europe and the United States (US), which rely on establishing comparability of the biosimilar to the reference medicine across all relevant parameters in sensitive indications (European Medicines Agency, 2019; US Food and Drug Administration, 2022b). Over the last 15 years, routine pharmacovigilance has confirmed the safety profiles of biosimilars compared to their reference medicines, and the lower

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production cost of biosimilars has expanded patient access to treatment and reduced healthcare costs, thus contributing to the sustainability of healthcare (Aapro et al., 2018; Goldsmith et al., 2018). Since the approval of reference filgrastim (Neupogen®; Amgen) in 1991 (US Food and Administration, 2023), several biosimilars have been approved in Europe and/or the US (Table 1), with the first two biosimilars, XM02 and EP2006, approved within six months of each other (European Medicines Agency, 2023d; European Medicines Agency, 2023e; European Medicines Agency, 2023f; US Food and Administration, 2021a).

This review will discuss the approval process and key post-approval data acquired for filgrastim biosimilar EP2006 (Zarzio®/ Zarxio®; Sandoz), focusing on data that pertain to the indications for CIN and stem cell mobilization.

1.1. Development of EP2006 (biosimilar filgrastim)

EP2006 was approved by the European Medicines Agency (EMA) in 2009 (Table 1) (European Medicines Agency, 2023d). In 2015, EP2006 (Zarxio®, Sandoz) became the first biosimilar to be approved in the US by the Food and Drug Administration (FDA) (Colwell, 2015; US Food and Administration, 2021a). Regulatory approval of biosimilar drugs is granted by the EMA or FDA if quality characteristics, structure, biological activity, clinical safety, efficacy, and immunogenicity match those of the licensed reference biologic medicine (Gascon et al., 2019). Approval of EP2006 was based on the totality of evidence from analytical, preclinical, and clinical studies demonstrating that EP2006 matched reference filgrastim in terms of safety, efficacy, and quality (Weise et al., 2014).

Analytical and preclinical studies showed that EP2006 had an identical primary structure and matching post-translational modifications, purity, G-CSF receptor binding affinity, and *in vitro* biological activity compared with the European Union (EU)-approved and US-approved reference filgrastim medicine (Sörgel et al., 2010; Sörgel et al., 2015). Preclinical studies have shown the physicochemical properties and biological characteristics of EP2006 to match those of the reference medicine, and studies in healthy volunteers have established the biosimilarity of EP2006 and the reference medicine in terms of pharmacodynamics, pharmacokinetics, and safety profiles (Gascon et al., 2010; Sörgel et al., 2015). The clinical development program for EP2006 also included two Phase III studies, one in the EU and one in the US, establishing the biosimilarity of EP2006 to the reference medicine in terms of efficacy, safety, and immunogenicity (Blackwell et al., 2015; Gascon et al., 2010).

1.2. Indications

Based on the totality of evidence establishing the biosimilarity of EP2006 with the reference medicine (Gascon et al., 2019; Holzmann et al., 2016), EP2006 was approved for the indications for which the reference medicine was approved in the EU and the US (Table 2).

2. EP2006 in chemotherapy-induced neutropenia

2.1. Indication

Febrile neutropenia (FN) is a potential complication of myelosuppressive chemotherapy and can lead to patients receiving delayed or reduced doses of chemotherapy, and compromise clinical outcomes (Campbell et al., 2022). FN has been associated with an increased risk of infection and increased mortality (Aagaard et al., 2020; Dulisse et al., 2013; Lyman et al., 2010; Nordvig et al., 2018). Emergency treatment is often needed, with more than 90% of patients requiring hospitalization (Averin et al., 2021; Baugh et al., 2019). Thus, FN can reduce patients' quality of life and lead to increased medical costs (Campbell et al., 2022; Dulisse et al., 2013). FN has been observed in 13–21% of patients receiving myelosuppressive chemotherapy regimens for metastatic solid tumors, of which 10–22% received primary prophylaxis with G-CSF (Weycker et al., 2015). G-CSF has been shown to increase neutrophil counts by expanding the pool of hematopoietic stem cells available and by facilitating their maturation and mobilization. G-CSF has also been shown to improve the activity of mature neutrophils. Therefore, G-CSF has greatest impact in increasing the supply and activity of neutrophils before the full effect of myelosuppressive chemotherapy is achieved, by which time the numbers of G-CSF-responsive progenitor and circulating neutrophils are at their lowest (Crea et al., 2009).

The risk of FN is known to vary depending on the chemotherapy regimen used, disease setting, and patient characteristics; the predicted risk of developing FN determines the need for prophylaxis with G-CSFs, which are typically recommended in patients with a high risk of developing FN (≥20% probability, based on disease setting and

Table 1
Summary of the known filgrastim medicines, including biosimilars.

Marketing authorization holder	Brand name	Non-branded descriptor	EMA approval	FDA approval
Reference medicine				
Amgen	Neupogen®	–	National approvals prior to formation of EMA	Feb 1991 (US Food and Administration, 2023)
Biosimilars				
Teva Generics	Tevagrastim®	XM02	Sept 2008 (European Medicines Agency, 2023e)	–
RatioPharm	Ratiograstim®			
CT Arzneimittel	Biograstim®	XM02	Sept 2008; withdrawn in Sept 2015 (European Medicines Agency, 2017)	–
Sandoz	Zarzio®/Zarxio®	EP2006/Filgrastim-sndz	Feb 2009 (European Medicines Agency, 2023 f, d)	Mar 2015 (US Food and Drug Administration, 2021a)
Hexal	Filgrastim Hexal®			–
Hospira	Nivestim®/ Nivestym®	Pliva/Mayne filgrastim/ Filgrastim-aafi	June 2010 (European Medicines Agency, 2023c)	July 2018 (US Food and Drug Administration, 2021b)
Apotex	Grastofil	Apo-Filgrastim	Oct 2013 (European Medicines Agency, 2023b)	–
Accord Healthcare	Accofil®		Sept 2014 (European Medicines Agency, 2023a)	–
Kashiv Biosciences	Releuko®	Filgrastim-ayow	–	Feb 2022 (US Food and Drug Administration, 2022a)

Abbreviations: European Medicines Agency (EMA); Food and Drug Administration (FDA).

Table 2
Indications for EP2006.

EU indication *(European Medicines Agency, 2023d)*
• Reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with established cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukemia and myelodysplastic syndromes) • Reduction in the duration of neutropenia in patients undergoing myeloablative therapy followed by bone marrow transplantation considered to be at increased risk of prolonged severe neutropenia o The safety and efficacy of filgrastim are similar in adults and children receiving cytotoxic chemotherapy • Mobilization of peripheral blood progenitor cells • In patients with severe congenital, cyclic, or idiopathic neutropenia with an ANC of $\leq 0.5 \times 10^9$/L, and a history of severe or recurrent infections, long-term administration of filgrastim is indicated to increase neutrophil counts, and to reduce the incidence and duration of infection-related events • Treatment of persistent neutropenia (ANC $\leq 1.0 \times 10^9$/L) in patients with advanced HIV infection, in order to reduce the risk of bacterial infections when other options to manage neutropenia are inappropriate
US indication *(US Food and Administration, 2021a)*
• Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever • Reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia • Reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with non-myeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation • Mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis • Reduce the incidence and duration of sequelae of severe neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia

Abbreviations: absolute neutrophil count (ANC); European Union (EU); human immunodeficiency virus (HIV); United States (US).

treatment regimen), or in special high-risk situations (Crawford et al., 2010; National Comprehensive Cancer Network, 2023b). G-CSF primary prophylaxis has also been shown to reduce FN incidence in patients receiving regimens with intermediate risk of FN (10–20% probability). G-CSF has also been associated with a lower incidence of FN-related dose delays and reductions, and fewer hospitalization days for patients at intermediate risk of FN. Furthermore, data from clinical trials and economic models have demonstrated that prophylaxis with G-CSF reduces medical treatment and hospitalization costs (Aslam et al., 2023). Despite this, G-CSF usage rates for these patients vary widely across published studies (Campbell et al., 2022), indicating a need for broader access to G-CSF prophylaxis for FN. For example, among 1457 patients with metastatic cancer in the US, 20.5% of patients were at high risk of FN, and over half (51.5%) of these patients did not receive G-CSF prophylaxis (Averin et al., 2021), in contrast to clinical guideline recommendations (Crawford et al., 2010; National Comprehensive Cancer Network, 2023b).

2.2. Clinical trial data for EP2006 in chemotherapy-induced neutropenia

Two Phase III confirmatory studies were conducted, one in the EU (Gascon et al., 2010) and one in the US (Blackwell et al., 2015), in which EP2006 was used as prophylaxis for neutropenia in adult patients with breast cancer (Fig. 1A; Table 3). The EU registration study was a single-arm, Phase III study involving 170 female patients with breast cancer (stage II–IV) undergoing four cycles of doxorubicin and docetaxel chemotherapy. EP2006 was effective, with a mean duration of severe neutropenia comparable to previously observed results for reference filgrastim; no new safety signals or issues relating to immunogenicity were observed (Gascon et al., 2010). The US registration study was a randomized, double-blind, multicenter, Phase III study (PIONEER; NCT01519700) designed to compare EP2006 with reference filgrastim in 218 patients with breast cancer receiving six cycles of (neo)adjuvant myelosuppressive chemotherapy. Patients were randomized 1:1:1:1 into four arms, two in which patients received either EP2006 or reference filgrastim at all six cycles, and two in which patients alternated between reference filgrastim and EP2006 at each cycle. EP2006 was shown to be non-inferior to reference filgrastim in terms of duration of severe neutropenia, and no clinically meaningful differences in safety or immunogenicity were observed (Blackwell et al., 2015).

In a sub-analysis of PIONEER, no clinically meaningful differences were observed in efficacy, safety, or immunogenicity when switching from reference filgrastim to EP2006, or vice versa, compared with patients who received only reference filgrastim (Blackwell et al., 2018). An analysis of safety data from 277 patients who received EP2006 in both Phase III trials showed a safety profile consistent with that observed in previous filgrastim studies (Harbeck et al., 2018a).

Results from these Phase III studies demonstrated therapeutic equivalence and a similar safety profile for EP2006 and reference filgrastim, with no differences in the incidence of drug-related or serious adverse events (AEs), and no patients in either study developing neutralizing antibodies (Blackwell et al., 2018; Harbeck et al., 2018a).

2.3. Real-world evidence for EP2006 in chemotherapy-induced neutropenia

Several large real-world studies and meta-analyses have added to the continually growing evidence supporting the effectiveness and acceptable tolerability of EP2006 in patients with cancer receiving chemotherapy (Fig. 1A; Table 3).

MONITOR-GCSF (NCT01459653) was an international, multicenter, prospective, observational, open-label study of 1496 patients with stage III–IV cancer treated with myelosuppressive chemotherapy across 6213 cycles and receiving prophylaxis with EP2006. Effectiveness outcomes for 1447 evaluable patients and safety outcomes for 1496 patients were within the range of reported data for the reference medicine, even though many patients were under- (17.4%) or over-prophylacted (26.0%) (Gascon et al., 2016). However, subsequent analysis of MONITOR-GCSF data suggested that providing G-CSF support at doses above guideline recommendations (i.e., over-prophylaxis) may yield improved results in terms of incidence of CIN, FN, and CIN/FN-related hospitalization (Bokemeyer et al., 2017). Another analysis compared efficacy and safety results from 217 and 466 patients in the PIONEER and MONITOR-GCSF studies, respectively, which evaluated outcomes in a clinical trial and real-world setting. While the reported frequencies of FN were similar in patients with breast cancer (5.1% vs. 6.2%), respectively, the incidence of all-grade AEs was higher in the Phase III PIONEER study compared with the real-world MONITOR-GCSF study, likely due to differences in the study settings and designs (Harbeck et al., 2018b).

When comparing results between elderly and non-elderly patients included in MONITOR-GCSF, no significant differences were found between these patient groups in terms of prophylaxis initiation or duration, as well as the associated outcomes. However, more elderly patients received CIN/FN prophylaxis, in line with guidelines, and fewer were over-prophylacted compared to non-elderly patients (Aapro et al.,

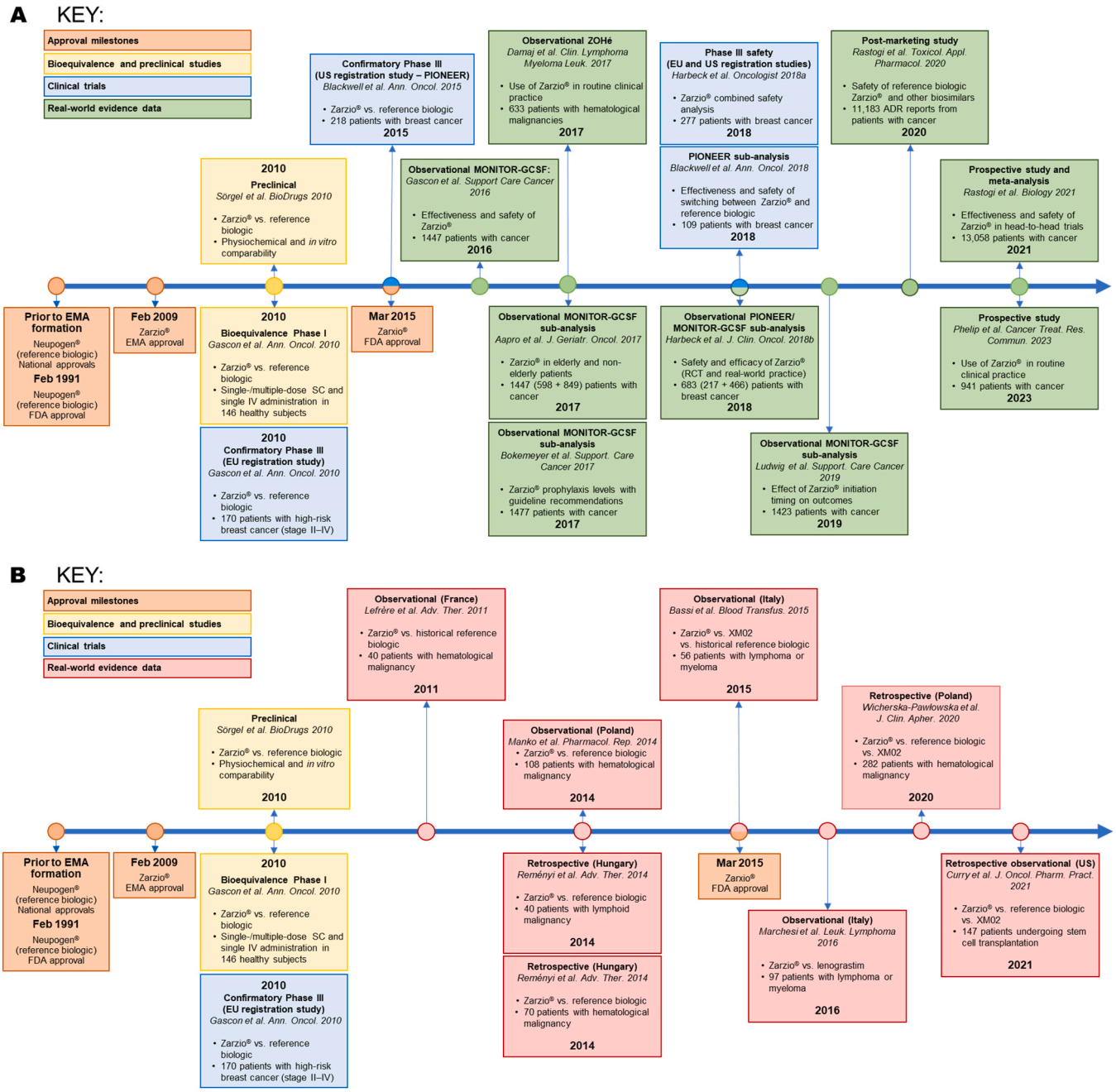

Fig. 1. A timeline highlighting the key data across the clinical development for EP2006 in chemotherapy-induced neutropenia (A) and hematopoietic stem cell mobilization (B). Abbreviations: adverse drug reaction (ADR); European Medicines Agency (EMA); Food and Drug Administration (FDA); intravenous (IV); randomized controlled trial (RCT); subcutaneous (SC).

2017). Further analysis of results from 1423 patients in MONITOR-GCSF suggest that filgrastim prophylaxis on the day of chemotherapy resulted in a similar safety profile and outcomes to per-guideline prophylaxis (24–72 hours after chemotherapy), indicating that same-day administration may be appropriate in some patients with low or moderate FN risk who have been treated mainly with chemotherapy regimens (Ludwig et al., 2019).

ZOHé was a prospective, observational, multicenter study undertaken in France, designed to assess the use of EP2006 in routine clinical practice in patients undergoing prophylaxis for CIN. In 633 patients with hematological malignancies, the use of EP2006 followed the label indication for 96.7% of patients, and the incidences of FN and AEs were low and consistent with previous studies of EP2006, with chemotherapy dose intensity maintained in 85.2% of patients (Damaj et al., 2017).

Another French, multicenter, prospective, non-interventional study included 941 patients; 84.8% had solid tumor cancer and 15.2% had lymphoid hemopathy. These patients were prescribed EP2006 for primary or secondary prophylaxis. FN was reported in 1.5% of patients with a solid tumor and 12.6% of patients with lymphoma. Overall, EP2006 was well tolerated and effective in preventing FN, allowing the dose intensity of chemotherapy to be maintained (Phelip et al., 2023).

A retrospective, post-marketing study of data acquired between 1991 and May 2018 using VigiBase®, a World Health Organization global database, analyzed 11,183 adverse drug reaction reports for reference filgrastim (n = 5764) and several filgrastim biosimilars, including EP2006 (n = 622), filgrastim-aafi (Nivestim®, Hospira; n = 359), and XM02 (Tevagrastim®, Teva Generics; n = 152). Compared with reference filgrastim, EP2006 was associated with a higher rate of arthralgia

Table 3
Key clinical and real-world evidence studies of EP2006 in chemotherapy-induced neutropenia.

Study	Phase/type	Study design	Patients	Indication	Main safety outcome for EP2006
Gascon et al. Ann. Oncol. 2010 **EU registration**	Confirmatory Phase III	EP2006 vs. reference biologic	170	Breast cancer (stage II–IV)	No neutralizing or anti-rhG-CSF antibodies; TEAE incidence was similar in both arms
Blackwell et al. Ann. Oncol. 2015 **US registration**	Confirmatory Phase III	EP2006 vs. reference biologic	218	Breast cancer	No neutralizing or anti-rhG-CSF antibodies; TEAE incidence was similar in both arms
Gascon et al. Support. Care Cancer 2016 **MONITOR-GCSF**	Observational	EP2006	1447 (1496 for safety)	Cancer	Bone pain (mostly mild to moderate) in 24.7% (n = 357); 148 ADRs (four serious) in 76 patients
Damaj et al. Clin. Lymphoma Myeloma Leuk. 2017 **ZOHé**	Observational	EP2006	633	Hematological malignancy	Mild or moderate AEs; typically, musculoskeletal/connective tissue disorders (50.9%, n = 27)
Aapro et al. J. Geriatr. Oncol. 2017 **MONITOR-GCSF (sub-analysis)**	Observational	EP2006	1447 (598 + 849)	Elderly + non-elderly patients with cancer	NR
Bokemeyer et al. Support. Care Cancer. 2017 **MONITOR-GCSF (sub-analysis)**	Observational	EP2006	1447	Cancer	No differences in safety (including ADRs); although fewer headaches with under-prophylaxis
Harbeck et al. Oncologist 2018a **EU/US study analysis**	Phase III safety	EP2006	277	Breast cancer	Most common AEs: musculoskeletal/connective tissue disorders (overall 15.2%, n = 34; bone pain 7.2%, n = 16) no neutralizing antibodies; one death (not related to treatment)
Blackwell et al. Ann. Oncol. 2018 **PIONEER (sub-analysis)**	Observational	EP2006 vs. reference biologic (switch)	107	Breast cancer	Most common AEs: musculoskeletal/connective tissue disorders (overall 35.5%, n = 38 with EP2006; bone pain 30.8%, n = 33 with EP2006); no neutralizing antibodies
Harbeck et al. J. Clin. Oncol. 2018b **PIONEER/ MONITOR-GCSF (sub-analysis)**	Observational	EP2006	683 (217 + 466)	Breast cancer	Higher AE rate in PIONEER vs. MONITOR-GCSF, including musculoskeletal/connective tissue disorders (261 vs. 20) events
Ludwig et al. Support. Care Cancer 2019 **MONITOR-GCSF (sub-analysis)**	Observational	EP2006	1423	Cancer	Proportions of events were similar for same-day or per-guideline prophylaxis
Rastogi et al. Toxicol. Appl. Pharmacol 2020 **Post-marketing study**	Post-marketing	EP2006, reference biologic and other biosimilars	11,183 ADR reports	Cancer	5.6% (n = 622) ADRs with EP2006, most frequently arthralgia (4.5%) and neutropenia (11.4%)
Rastogi et al. Biology 2021 **Meta-analysis**	Prospective	EP2006 vs. placebo/ comparator	13,058	Cancer	No significant difference between EP2006 and reference; the most common AE was bone pain
Phelip et al. Cancer Treat. Res. Commun. 2023	Prospective	EP2006	937	Cancer	TEAEs in <1%; the most frequent was bone pain, (2.8% with Hodgkin lymphoma and 1.3% with a solid tumor)

Abbreviations: adverse drug reaction (ADR); adverse event (AE); European Union (EU); not reported (NR); recombinant human granulocyte colony-stimulating factor (rhG-CSF); treatment-emergent adverse event (TEAE); United States (US).

(4.5% vs. 2.9%, reporting odds ratio [ROR] 1.59, information component $[IC]_{025}$ 1.25) and neutropenia (11.4% vs. 4%, ROR 2.59, IC_{025} 3.07), while filgrastim-aafi was associated with a higher rate of bone pain (14.4% vs. 8.3%, ROR 1.87, IC_{025} 5.30) (Rastogi et al., 2020). This may reflect differences in the patient demographics and in safety reporting standards of countries in which filgrastim biosimilars have become available.

A meta-analysis was carried out to explore efficacy and safety data of filgrastim and biosimilars versus placebo/no treatment in 13,058 patients with cancer using various chemotherapy regimens across 56 studies in approved indications. Filgrastim was effective in reducing FN and related complications compared with placebo/no treatment, with a 42% reduction in risk of FN in favor of filgrastim, and demonstrated a good safety profile. The duration of severe neutropenia was comparable with reference filgrastim and its biosimilars, with a risk ratio of 1.03 (95% confidence interval 0.93–1.13). EP2006 was not compared to reference filgrastim separately (Rastogi et al., 2021). The key safety outcomes are presented in Table 3.

Several smaller real-world studies have also provided insights into the efficacy and safety of EP2006 across centers in several countries.

A retrospective, single-center chart review in Germany included 77 patients with cancer who were gradually switched to EP2006 and 25 patients who were maintained on reference filgrastim prophylaxis over 2.5 years. EP2006 was comparable to reference filgrastim in terms of prevention of neutropenia-induced chemotherapy dose reductions (6.5% vs. 8%, respectively) and dose discontinuation (2.5% vs. 8%, respectively). The authors reported a trend for increased use of G-CSF as primary prophylaxis in the patients switched to EP2006 versus the historic cohort treated with reference filgrastim (52% vs. 36% of patients) (Verpoort and Möhler, 2012).

In an Italian observational, single-center study, 48 patients with solid tumors were treated with EP2006 for 4–14 days at the end of chemotherapy. A total of 37 patients (77%) received EP2006 as primary prophylaxis. Three cases of FN were reported, and these patients were treated with antibiotics and improved within 24 hours without the need for hospitalization. Non-febrile Grade 4 neutropenia was observed in a further six patients (Salesi et al., 2012).

A single-center study in Poland evaluated 23 patients with hematological malignancies receiving EP2006 after myeloablative chemotherapy, followed by peripheral blood stem cell transplantation (PBSCT), compared to a historical cohort of 23 patients who received reference filgrastim. This study, one of the first to report the use of

EP2006 for neutrophil recovery after PBSCT, reported that hematopoietic recovery parameters were similar between patients who received EP2006 or reference filgrastim, with no significant differences. There was a similar occurrence of neutropenic fever (five vs. six patients) and bone pain (seven patients each) in the EP2006 and reference filgrastim groups, respectively (Cioch et al., 2014).

An observational, prospective, longitudinal, multicenter study carried out in France reported efficacy and safety data for 184 patients with solid tumors (89.7%) or non-Hodgkin lymphoma (NHL, 10.3%) receiving EP2006. No cases of FN or serious AEs related to EP2006 treatment were reported in this high-risk population. Study discontinuations were typically associated with disease progression (Nahon et al., 2016).

In a retrospective Italian real-world study, 67 patients with soft-tissue tumors treated with epirubicin and ifosfamide received EP2006, reference filgrastim, or lenograstim as primary prophylaxis for a total of 260 cycles of therapy. The frequencies of FN ($p = 0.935$), all-grade neutropenia ($p = 0.272$), and Grade 4 neutropenia ($p = 0.080$) were similar across the three treatment groups, with similar safety profiles observed (Bongiovanni et al., 2017).

In a single-center, 1-year, retrospective chart review from the US of hospitalized adults who received either EP2006 ($n = 100$) or reference filgrastim ($n = 100$) for prophylaxis of CIN or neutrophil recovery post-autologous hematopoietic stem cell transplantation (HSCT), efficacy and safety were similar between the treatments (Zecchini et al., 2018).

A further retrospective claims analysis in the US evaluated data for patients with non-myeloid cancer who received EP2006 or reference filgrastim during ≥1 treatment cycles (EP2006, $n = 162$; reference filgrastim, $n = 3297$). The treatments were statistically equivalent in preventing FN across chemotherapy cycles 1–6 (Schwartzberg et al., 2018b).

Overall, these real-world, post-approval data confirm the expected effectiveness and safety profile of EP2006 in patients with CIN. Although not all studies reported specific cost-effectiveness data, the known additional costs of delaying treatment doses or reducing dose intensity, and the potential negative impact on clinical outcomes, reinforce the importance of using filgrastim to optimize reductions in hospitalization and medical costs. The use of filgrastim biosimilars will further enhance potential cost-effectiveness and will facilitate wider access of filgrastim to patients.

3. EP2006 in hematopoietic stem cell mobilization

3.1. Indication and overview of approval

G-CSF is used in HSCT to mobilize CD34+ stem cells and to speed neutrophil recovery following HSCT (Link, 2022; National Comprehensive Cancer Network, 2023a). Approval of EP2006 for this indication was based on data from Phase III confirmatory studies in patients with breast cancer undergoing myelosuppressive chemotherapy, considered to be a sensitive population (Harbeck et al., 2018a). Approval of EP2006 in hematopoietic stem cell mobilization was based on extrapolation of indications. Extrapolation of data is considered valid when a biosimilar has the same mechanism of action as the reference medicine, and the same mechanism of action is applicable in different indications (Gascon et al., 2013). In the decade following the approval of EP2006, the extrapolation of indications from reference filgrastim was validated by real-world evidence, demonstrating both equivalent safety and efficacy of EP2006 and reference filgrastim, along with the validity of the concept of extrapolation of indications in the approval of biosimilars generally (Krendyukov and Schiestl, 2019). Real-world evidence for EP2006 continues to accumulate.

3.2. Real-world evidence for EP2006 in hematopoietic stem cell mobilization

Accumulating real-world data have demonstrated the effectiveness and safety of EP2006 in patients undergoing hematopoietic stem cell mobilization (Fig. 1B; Table 4).

In a French single-center study, outcomes were compared between 40 patients with a hematological malignancy who received EP2006 and a historical cohort treated with reference filgrastim. No significant differences were observed between the groups in the median number of CD34+ cells mobilized and collected, the number of G-CSF injections and leukapheresis treatment required to obtain the minimal CD34+ cell count, or the proportion of failures in both groups (Lefrère et al., 2011).

In a single-center study from Poland, patients with hematological malignancies received EP2006 ($n = 54$) or reference filgrastim ($n = 54$) for stem cell mobilization. EP2006 demonstrated similar effectiveness and safety to reference filgrastim, while CD34+ cell counts and AEs were similar between the EP2006 and reference filgrastim groups, with the most common events being bone pain (17 vs. 19 patients) and neutropenic fever (11 vs. 10 patients) (Manko et al., 2014).

In two retrospective studies carried out in Hungary, 70 patients with hematological malignancies and 40 patients with lymphoid malignancies received EP2006 for stem cell mobilization. EP2006 demonstrated similar effectiveness and safety compared with previous reports for reference filgrastim in this setting (Reményi et al., 2014).

In an Italian single-center, retrospective study, 56 patients with lymphoma or myeloma received filgrastim biosimilars (EP2006 or XM02) for engraftment after autologous stem cell transplantation. Outcomes for the biosimilars were similar to published data for reference filgrastim, in terms of time to engraftment, median number of vials injected, and duration of hospitalization (Bassi et al., 2015).

A non-randomized, single-center study from Italy was designed to assess stem cell mobilization outcomes and safety in 97 consecutive patients with lymphoma ($n = 54$) or myeloma ($n = 43$). Patients were administered EP2006 or the G-CSF lenograstim. No differences were observed between the two treatment groups in terms of drug-related AEs, with no reported serious AEs. Effectiveness was similar for both groups among myeloma patients; however, some stem cell mobilization parameters were higher for lenograstim versus EP2006 among patients with lymphoma (Marchesi et al., 2016).

In a retrospective analysis of 282 patients with hematological tumors undergoing stem cell mobilization in Poland, 95 patients received EP2006, 92 received biosimilar filgrastim-aafi, and 95 received the filgrastim biosimilar XM02. All three biosimilars demonstrated similar effectiveness and safety profiles: effective mobilizations occurred in 88.2% of patients treated with EP2006, 86.2% with filgrastim-aafi, and 84.9% with XM02 (Wicherska-Pawłowska et al., 2020).

A US retrospective, observational cohort study from North Carolina evaluated the efficacy of EP2006 and reference filgrastim in 147 patients with multiple myeloma or NHL who underwent mobilization prior to HSCT. EP2006 was non-inferior to reference filgrastim in terms of the mean number of CD34+ cells mobilized and the median number of days of apheresis needed (2 days in both groups) (Curry et al., 2021). The key safety outcomes are presented in Table 4.

A prospective cohort study in Italy compared data from 56 patients with multiple myeloma who received biosimilar pegfilgrastim for stem cell mobilization with historical cohorts who received either EP2006 ($n=102$) or reference pegfilgrastim ($n=73$). Neutrophil engraftment was achieved after a median of 10 days with reference and biosimilar reference pegfilgrastim and 11 days with EP2006. FN incidence was higher and Grade 2–3 diarrhea and mucositis were more common with EP2006 versus reference or biosimilar pegfilgrastim (Martino et al., 2023). This study partly contrasts with results from a prospective cohort study in Italy that compared outcomes for patients with lymphoma and myeloma undergoing HSCT who received biosimilar pegfilgrastim with historical control groups who received biosimilar filgrastim, reference

Table 4
Key clinical and real-world evidence studies of EP2006 in hematopoietic stem cell mobilization.

Study	Phase/type	Study design	Patients	Indication	Main safety outcome for EP2006
Lefrère et al. Adv. Ther. 2011 **France**	Prospective	EP2006 vs. historical reference biologic	40	Hematological malignancy	Bone pain and/or headache were reported in 14 patients
Manko et al. Pharmacol. Rep. 2014 **Poland**	Prospective	EP2006 vs. reference biologic	108	Hematological malignancy	The AE profile was similar between groups
Reményi et al. Adv. Ther. 2014 **Hungary**	Retrospective	EP2006	70 40	Hematological malignancy Lymphoid malignancy	The AE profile was similar to previous reports for reference biologic NR
Bassi et al. Blood Transfus. 2015 **Italy**	Retrospective	EP2006 vs. XM02 (vs. historical reference biologic)	56	Lymphoma or myeloma	AEs were similar to the reference biologic; no severe AEs and no cases required treatment interruption
Marchesi et al. Leuk. Lymphoma 2016 **Italy**	Retrospective	EP2006 vs. lenograstim	97	Lymphoma or myeloma	No differences in terms of TEAEs, with no serious AEs
Wicherska-Pawłowska et al. J. Clin. Apher. 2020 **Poland**	Retrospective	EP2006 vs. filgrastim-aafi vs. XM02	282	Hematological malignancy	Most frequently reported AEs were bone pain (10%, n = 9) and headache (9%, n = 8)
Curry et al. J. Oncol. Pharm. Pract. 2021 **US**	Retrospective, observational	EP2006 vs. reference biologic	147	Patients undergoing SCT	NR
Martino et al. Ann. Hematol. 2023 **Italy**	Prospective	Pefilgrastim-bmez vs. historical EP2006 vs. historical reference pegfilgrastim	231	Multiple myeloma	Lower incidence of FN, diarrhea, and mucositis with pegfilgrastim groups vs. EP2006

Abbreviations: adverse event (AE); not reported (NR); stem cell transplant (SCT); treatment-emergent adverse event (TEAE).

pegfilgrastim, or lenograstim. In propensity score matching analysis, biosimilar and reference pegfilgrastim demonstrated similar neutropenia prophylaxis outcomes, a shorter time to transplant engraftment, and a lower mean number of transfusions compared with biosimilar filgrastim. The four groups were similar in terms of mortality, mucositis, and diarrhea. The biosimilars used are not named (Marchesi et al., 2024). Further research is warranted to compare clinical outcomes between EP2006 and pegfilgrastim in hematopoietic stem cell mobilization.

Several studies have also assessed the use of EP2006 for stem cell mobilization in healthy donors.

A meta-analysis of clinical studies from public databases included data for 1892 individuals, most of whom had hematological malignancies, and 351 healthy donors who received either EP2006 or XM02, with no significant differences between the treatments in stem cell mobilization outcomes. Bioequivalence was observed between the medicines for the yield of CD34+ stem cells and for the rate of transplant engraftment (Schmitt et al., 2016).

In a two-center safety surveillance study (NCT01766934), 244 healthy donors underwent mobilization with EP2006. Safety and efficacy were consistent with previous reports for filgrastim (Becker et al., 2016). After 5 years of follow-up, no long-term adverse health outcomes were noted after hematopoietic stem and progenitor cell donation. Superior physical and mental health compared with the general healthy non-donor population was maintained over time (Heyn et al., 2022).

A comparison of the effectiveness of EP2006, reference filgrastim, and lenograstim was performed in 313 consecutive, unrelated donors in Poland. EP2006 was as effective as filgrastim and lenograstim in the mobilization of CD34+ cells (Farhan et al., 2017).

A retrospective study in Spain evaluated the use of EP2006 and reference filgrastim in 216 patients and 56 healthy donors in a setting where G-CSF was used alone to mobilize stem cells, with no prior chemotherapy treatment. This study found that EP2006 had a similar efficacy for stem cell mobilization versus reference filgrastim, but a lower efficacy in patients defined as poor mobilizers and needing the immunostimulant plerixafor; however, the number of patients needing plerixafor was low (n = 45) (Parody et al., 2020).

In a single-center study from Saudi Arabia, 97 patients with cancer and 17 healthy donors underwent stem cell mobilization with EP2006 or reference filgrastim. There was no difference between EP2006 and reference filgrastim in the number of CD34+ stem cells collected at leukapheresis (Islami et al., 2023).

The collective data from these studies confirm the expected effectiveness and safety profile of EP2006 in patients undergoing stem cell mobilization.

4. Cost-effectiveness and access data for EP2006

Biosimilars have the potential to improve treatment access via price competition (Car et al., 2023). Several studies have evaluated cost-effectiveness and access data for EP2006 across multiple healthcare markets (Table 5).

A cost-efficiency study analyzed the direct costs of EP2006, reference filgrastim, or pegfilgrastim for managing one patient during one cycle of chemotherapy across the European G5 countries. Prophylaxis or treatment of FN with EP2006 was cost-efficient under all possible treatment scenarios relative to the comparators (Aapro et al., 2012).

The introduction of filgrastim biosimilars in New Zealand, starting with EP2006 in late 2012, resulted in savings of NZ$5 million by 2014 due to price competition, and in that time, usage of filgrastim increased by 25% (Pharmaceutical Management Agency, 2014).

In the previously mentioned single-center, retrospective study from Italy, a cost analysis demonstrated that the use of EP2006 and XM02 was associated with reductions in medical costs of 86% and 56% versus reference filgrastim, respectively. In this study, the total cost of EP2006 treatment corresponded to one day of treatment with reference filgrastim (Bassi et al., 2015).

A cost-efficiency analysis was also conducted for managing one patient during one chemotherapy cycle in the US. Prophylaxis with EP2006 was consistently associated with significant cost savings over prophylaxis with reference filgrastim, and pegfilgrastim, across various administration scenarios (McBride et al., 2017).

In an Italian real-world study, the use of EP2006 resulted in cumulative cost savings versus reference filgrastim and lenograstim (€225.25

Table 5
Key cost-effectiveness and access data for EP2006.

Study	Study type	Study design	Patients	Indication	Main cost-effectiveness or access outcomes
Aapro et al. J. Oncol. Pharm. Pract. 2012 **France, Germany, Italy, Spain, UK**	Cost-efficiency analysis	EP2006 vs. reference biologic or pegfilgrastim	NR	CIN	Cost savings: €32.70–€457.84 vs. reference; no savings with pegfilgrastim vs. EP2006
Pharmaceutical Management Agency, 2014 **New Zealand**	Cost analysis (annual review)	EP2006 vs. reference biologic	NR	Cancer	Cost savings: NZ$5 million per year with >25% increase in usage
Bassi et al. Blood Transfus. 2015 **Italy**	Retrospective	EP2006 vs. XM02 (vs. historical reference biologic)	56	Lymphoma or myeloma	Cost savings: EP2006 86% (€10.85) and XM02 56% (€34.10) vs. reference (€77.53) of one vial
McBride et al. J. Med. Econ. 2017 **US**	Cost-efficiency analysis	EP2006 vs. reference biologic, pegfilgrastim, or pegfilgrastim injector	NR	CIN/FN	Cost savings: $65 (1 day) to $916 (14 days) vs. reference; $284 to $3666 vs. pegfilgrastim, and $257 to $3692 vs. pegfilgrastim injector
Bongiovanni et al. Support. Care Cancer. 2017 **Italy**	Retrospective	EP2006 vs. reference biologic or lenograstim	67	CIN	Cost savings; €225.25 vs. reference filgrastim and €262.00 vs. lenograstim over 5 days
Schwartzberg et al. J Manag. Care. Spec. Pharm. 2018a **US**	Retrospective claims analysis	EP2006 and reference biologic	3542 (172 + 3370)	Non-myeloid cancer or FN	Total medical costs across all patients: $8040–$30,003 depending on FN definition
Karaca-Mandic et al. Health Aff. (Millwood) 2019 **US**	Retrospective claims analysis	EP2006 vs. reference biologic and tbo-filgrastim	16,323 episodes (2778 + 11,207 + 2338)	FN prophylaxis	Average costs (2018): $641 vs. $835 and vs. $628 (commercially insured); $258 vs. $347 and vs. $223 (Medicare Advantage)
McBride et al. J. Med. Econ. 2020 **US**	Cost-simulation analysis	Pegfilgrastim injector vs. EP2006, reference biologic, or pegfilgrastim single injection	20,000 (10,000 each)	Lung cancer or NHL	Total costs: $6,691,969–$31,765,299 vs. reference and $18,901,969–$36,538,299 vs. EP2006 (lung cancer); $6,794,984–$30,361,345 vs. reference and $19,004,984–$35,911,345 vs. EP2006 (NHL)
Socal et al. Value Health. 2020 **US**	Retrospective claims analysis	EP2006 vs. reference biologic or tbo-filgrastim	NR	NR	30% decrease in Medicare spending from $12.5 million in January 2015 to $8.8 million in December 2017
Qian et al. J. Manag. Care Spec. Pharm. 2021 **US**	Retrospective claims analysis	EP2006 vs. reference biologic or tbo-filgrastim	263,766/27,037 (2015 claims) 252,749/28,199 (2018 claims)	FN prophylaxis	Rapid uptake during the first 3 years of marketing accounted for 49.1%, 46.0%, and 38.7% of filgrastim Medicare Part B, Part D, and Medicaid claims, respectively
Li et al. JCO Oncol. Pract. 2021 **US**	Cost-effectiveness analysis	EP2006 primary and secondary prophylaxis	NR	Breast cancer, NSCLC, or NHL	ICERs were: $5660–$20,806 per FN event avoided, and $7213–$35,563 per QALY gained
Yousef et al. J. Med. Econ. 2023 **Saudi Arabia**	Cost-efficiency analysis	EP2006 and filgrastim-aaf vs. reference filgrastim or pegfilgrastim	4000	Breast cancer	Cost savings: $3,460,800 and $3,086,400 vs. reference filgrastim; $12,086,640 and $11,712,240 vs. reference pegfilgrastim
Aapro et al. Support. Care Cancer 2023 **Austria, France, Germany**	Cost-effectiveness analysis	EP2006 or pegfilgrastim-bmez for primary vs. secondary prophylaxis	NR	Breast cancer, NSCLC, or NHL	ICERs (€/FN event avoided, €/life year, €/QALY) consistently below the €30,000 WTP for primary vs. secondary prophylaxis for EP2006 across all three cancers and all three countries

Abbreviations: chemotherapy-induced neutropenia (CIN); febrile neutropenia (FN); incremental cost-effectiveness ratio (ICER); non-Hodgkin lymphoma (NHL); not reported (NR); non-small cell lung cancer (NSCLC); quality-adjusted life-year (QALY); willingness-to-pay threshold (WTP).

vs. reference filgrastim and €262.00 vs. lenograstim) over the course of a single chemotherapy cycle (Bongiovanni et al., 2017).

In an analysis of 3542 patients (172 treated with EP2006 and 3370 treated with reference filgrastim) included in a retrospective claims analysis from the US, mean FN-related healthcare resource utilization and medical costs among patients who developed FN were substantial ($8040–$30,003), with inpatient costs accounting for at least 73.5–93.4% (Schwartzberg et al., 2018a).

Retrospective analyses of claims data in the US found that due to lower costs, EP2006 had rapid uptake following launch in 2015, accounting for 47% of filgrastim administrations among commercially insured and 42% among Medicare Advantage beneficiaries by March 2018 (Karaca-Mandic et al., 2019). In another analysis of US Medicare data, utilization of EP2006 in Medicare Part B increased sharply between January and August 2016, surpassing that of reference filgrastim by November 2017, and contributing to a 30% decrease in overall spending on filgrastim since 2015 (Socal et al., 2020). A separate analysis of US Medicare Part B, Part D, and Medicaid reimbursement data also showed a rapid uptake of EP2006 in the first three years of marketing, with EP2006 accounting for 49.1%, 46.0%, and 38.7% of filgrastim Medicare Part B, Part D, and Medicaid claims, respectively, in 2018 (Qian, 2021). In cost simulations of 10,000 patients with lung cancer and 10,000 patients with NHL in the US, EP2006 offered the greatest cost-efficiency among several different FN prophylaxis options (McBride et al., 2020).

A cost-effectiveness analysis was performed to assess primary versus secondary prophylaxis with EP2006 for patients receiving curative chemotherapy who were at intermediate risk of FN. In patients with breast cancer, non-small cell lung cancer (NSCLC), and NHL, primary prophylaxis with EP2006 was cost-effective versus secondary prophylaxis (Li et al., 2021).

Another study compared the use of EP2006 versus reference filgrastim and pegfilgrastim in 4000 patients undergoing six cycles of cancer treatment in Saudi Arabia. The simulation demonstrated significant potential cost savings from biosimilar conversion, and suggested savings could provide budget-neutral increased access to supportive and therapeutic cancer care (Yousef et al., 2023).

A final cost-effectiveness analysis was performed to assess primary prophylaxis versus secondary prophylaxis with EP2006 or biosimilar pegfilgrastim for patients receiving therapy for breast cancer, NSCLC,

and NHL and who were at intermediate risk of FN. Model inputs were based on data from Austria, France, and Germany. EP2006 was consistently more cost-effective for each cancer and in each country when used as primary prophylaxis versus secondary prophylaxis, and EP2006 generally achieved lower incremental cost-effectiveness ratios than pegfilgrastim (Aapro et al., 2023).

Since approval, a good uptake of EP2006 has been observed; EP2006 has also been shown to be cost-effective and is associated with cost savings across multiple different markets, as summarized in Table 5.

5. Post-launch storage changes

Following launch, the EMA summary of product characteristics for EP2006 (Zarzio®) has been amended to show that EP2006 can be kept at room temperature (up to 25°C) for a single period of up to 8 days (European Medicines Agency, 2023d), and the US prescribing information for EP2006 (Zarxio®) now states that EP2006 can be kept at room temperature for up to 4 days (NIH National Library of Medicine - DailyMed database, 2022). This is in contrast to the reference medicine (Neupogen®), which can be stored at room temperature for up to 24 hours (US Food and Administration, 2023). This change is clinically important as improved temperature stability is more convenient for patients who do not have access to accurate and reliable refrigeration storage at home or when traveling (Vlieland et al., 2016; Vlieland et al., 2018). Improved stability also helps prevent drug degradation and subsequent wastage in the event of a cold chain breakdown or an unforeseen power outage at the hospital pharmacy (Kosari et al., 2018).

6. Conclusions

Filgrastim plays a crucial role in helping eligible patients undergoing certain treatments for cancer to receive the correct dose intensity of chemotherapy within an optimal time frame. It also facilitates optimal cell harvesting for various stem cell and HSCT procedures, and aids recovery in patients who are experiencing FN. It would, therefore, be clinically relevant for those patients most likely to benefit to receive this supportive treatment when indicated. However, publications show that often this is not the case, despite the reported lower individual medication costs and cost-effectiveness analyses confirming that filgrastim biosimilar EP2006 results in cost savings in the clinical setting. Although the reasons for this are not fully understood, it has been suggested that there may be a gap in current knowledge or awareness that needs to be addressed to improve uptake in clinical practice.

Clinical data collected in the 15 years post-approval of the filgrastim biosimilar EP2006 highlight its continued safety and effectiveness in all approved indications. In addition, real-world evidence demonstrates that EP2006 is a well-tolerated treatment option that results in cost savings through reductions in hospitalizations and medical treatment costs. These data can help to reassure healthcare professionals that EP2006 is effective and has repeatedly demonstrated an acceptable and consistent safety profile across all indications, in both clinical studies and real-world settings. Indeed, since the release of EP2006, numerous other biosimilars have become available in oncology, indicating clinicians' increasing willingness to use biosimilars.

Given reports that there are eligible patients who do not receive filgrastim for FN prophylaxis, cost-effectiveness data accumulated over the last 15 years complement both clinical and real-world data, underlining that EP2006 represents an affordable treatment option to increase earlier patient access to filgrastim. With increasing healthcare costs and guideline-recommended disease management, these findings are likely to have particular importance for future clinical management, especially as cytotoxic chemotherapy will remain the standard of care worldwide for the foreseeable future for patients with cancer who are ineligible for, or lack access to, other therapies.

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References

Aagaard, T., Reekie, J., Jørgensen, M., et al., 2020. Mortality and admission to intensive care units after febrile neutropenia in patients with cancer. Cancer Med. 9 (9), 3033–3042.

Aapro, M., Cornes, P., Abraham, I., 2012. Comparative cost-efficiency across the European G5 countries of various regimens of filgrastim, biosimilar filgrastim, and pegfilgrastim to reduce the incidence of chemotherapy-induced febrile neutropenia. J. Oncol. Pharm. Pract. 18 (2), 171–179.

Aapro, M., Bokemeyer, C., Ludwig, H., et al., 2017. Chemotherapy-induced (febrile) neutropenia prophylaxis with biosimilar filgrastim in elderly versus non-elderly cancer patients: patterns, outcomes, and determinants (MONITOR-GCSF study). J. Geriatr. Oncol. 8 (2), 86–95.

Aapro, M., Krendyukov, A., Höbel, N., et al., 2018A. Development and 10-year history of a biosimilar: the example of Binocrit®. Ther. Adv. Med. Oncol. 10, 1758835918768419 https://doi.org/10.1200/JCO.2018.36.15_suppl.111.

Aapro, M.S., Chaplin, S., Cornes, P., et al., 2023E. Cost-effectiveness of granulocyte colony-stimulating factors (G-CSFs) for the prevention of febrile neutropenia (FN) in patients with cancer. Support. Care Cancer 31 (10), 581.

Aghedo, B.O., Gupta, V., 2022. Filgrastim. [Updated 2023 Jul 3]. In: StatPearls [Internet]. https://www.ncbi.nlm.nih.gov/books/NBK559282/ (Accessed 27 November 2023).

Aslam, S., Li, E., Bell, E., et al., 2023. Risk of chemotherapy-induced febrile neutropenia in intermediate-risk regimens: clinical and economic outcomes of granulocyte colony-stimulating factor prophylaxis. J. Manag. Care Spec. Pharm. 29 (2), 128–138.

Averin, A., Silvia, A., Lamerato, L., et al., 2021. Risk of chemotherapy-induced febrile neutropenia in patients with metastatic cancer not receiving granulocyte colony-stimulating factor prophylaxis in US clinical practice. Support. Care Cancer 29 (4), 2179–2186.

Bassi, S., Stroppa, E.M., Moroni, C.F., et al., 2015. Safety and efficacy of granulocyte colony-stimulating factor biosimilars in engraftment after autologous stem cell transplantation for haematological malignancies: a 4-year, single institute experience with different conditioning regimens. Blood Transfus. 13 (3), 478–483.

Baugh, C.W., Faridi, M.K., Mueller, E.L., et al., 2019. Near-universal hospitalization of US emergency department patients with cancer and febrile neutropenia. PLoS One 14 (5), e0216835.

Becker, P., Schwebig, A., Brauninger, S., et al., 2016. Healthy donor hematopoietic stem cell mobilization with biosimilar granulocyte-colony-stimulating factor: safety, efficacy, and graft performance. Transfusion 56 (12), 3055–3064.

Blackwell, K., Semiglazov, V., Krasnozhon, D., et al., 2015. Comparison of EP2006, a filgrastim biosimilar, to the reference: a phase III, randomized, double-blind clinical study in the prevention of severe neutropenia in patients with breast cancer receiving myelosuppressive chemotherapy. Ann. Oncol. 26 (9), 1948–1953.

Blackwell, K., Gascon, P., Krendyukov, A., et al., 2018. Safety and efficacy of alternating treatment with EP2006, a filgrastim biosimilar, and reference filgrastim: a phase III, randomised, double-blind clinical study in the prevention of severe neutropenia in patients with breast cancer receiving myelosuppressive chemotherapy. Ann. Oncol. 29 (1), 244–249.

Bokemeyer, C., Gascón, P., Aapro, M., et al., 2017. Over- and under-prophylaxis for chemotherapy-induced (febrile) neutropenia relative to evidence-based guidelines is associated with differences in outcomes: findings from the MONITOR-GCSF study. Support. Care Cancer 25 (6), 1819–1828.

Bongiovanni, A., Monti, M., Foca, F., et al., 2017. Recombinant granulocyte colony-stimulating factor (rG-CSF) in the management of neutropenia induced by anthracyclines and ifosfamide in patients with soft tissue sarcomas (NEUSAR). Support. Care Cancer 25 (1), 111–117.
Campbell, K., Chadha, N., Dimri, S., et al., 2022. G-CSF primary prophylaxis use and outcomes in patients receiving chemotherapy at intermediate risk for febrile neutropenia: a scoping review. Expert Rev. Hematol. 15 (7), 619–633.
Car, E., Vulto, A.G., Houdenhoven, M.V., et al., 2023. Biosimilar competition in European markets of TNF-alpha inhibitors: a comparative analysis of pricing, market share and utilization trends. Front. Pharmacol. 14, 1151764.
Cioch, M., Jawniak, D., Kotwica, K., et al., 2014. Biosimilar granulocyte colony-stimulating factor is effective in reducing the duration of neutropenia after autologous peripheral blood stem cell transplantation. Transplant. Proc. 46 (8), 2882–2884.
Colwell, J., 2015. FDA approves first biosimilar, zarxio. Cancer Discov. 5 (5), 460.
Cornes, P., Krendyukov, A., 2019. The evolution of value with filgrastim in oncology. Future Oncol. 15 (13), 1525–1533.
Crawford, J., Caserta, C., Roila, F., 2010. Hematopoietic growth factors: ESMO clinical practice guidelines for the applications. Ann. Oncol. 21 (Suppl 5), v248–v251.
Crea, F., Giovannetti, E., Zinzani, P.L., et al., 2009. Pharmacologic rationale for early G-CSF prophylaxis in cancer patients and role of pharmacogenetics in treatment optimization. Crit. Rev. Oncol. Hematol. 72 (1), 21–44.
Curry, L.D., Anders, B., Dressler, E.V., et al., 2021. Efficacy of a conversion from filgrastim to filgrastim-sndz in stem cell transplant patients undergoing mobilization. J. Oncol. Pharm. Pract. 27 (4), 871–876.
Damaj, G.L., Benbrahim, O., Hacini, M., et al., 2017. ZOHé: a prospective study of the use of biosimilar filgrastim Zarzio in clinical practice in patients treated with chemotherapy for lymphoid malignancies. Clin. Lymphoma Myeloma Leuk. 17 (6), 362–369. e362.
Dulisse, B., Li, X., Gayle, J.A., et al., 2013. A retrospective study of the clinical and economic burden during hospitalizations among cancer patients with febrile neutropenia. J. Med. Econ. 16 (6), 720–735.
European Medicines Agency, 2017. Biograstim Summary of Product Characteristics. ⟨https://www.ema.europa.eu/en/medicines/human/EPAR/biograstim#product-information-section (Accessed 23 August 2023).
European Medicines Agency, 2019. Biosimilars in the EU: Information guide for healthcare professionals. ⟨https://www.ema.europa.eu/en/documents/leaflet/biosimilars-eu-information-guide-healthcare-professionals_en.pdf⟩ (Accessed 27 November).
European Medicines Agency, 2023a. Accofil Summary of Product Characteristics. ⟨https://www.ema.europa.eu/en/medicines/human/EPAR/accofil#product-information-section⟩ (Accessed 27 November 2023).
European Medicines Agency, 2023b. Grastofil Summary of Product Characteristics. ⟨https://www.ema.europa.eu/en/medicines/human/EPAR/grastofil#product-information-section⟩ (Accessed 27 November 2023).
European Medicines Agency, 2023c. Nivestim Summary of Product Characteristics. ⟨https://www.ema.europa.eu/en/medicines/human/EPAR/nivestim#product-information-section⟩ (Accessed 27 November 2023).
European Medicines Agency, 2023d. Zarzio Summary of Product Characteristics. ⟨https://www.ema.europa.eu/en/medicines/human/EPAR/zarzio#product-information-section⟩ (Accessed 27 November 2023).
European Medicines Agency, 2023e. Tevagrastim Summary of Product Characteristics. ⟨https://www.ema.europa.eu/en/medicines/human/EPAR/tevagrastim#product-information-section⟩ (Accessed 27 November 2023).
European Medicines Agency, 2023f. Filgrastim Hexal Summary of Product Characteristics. ⟨https://www.ema.europa.eu/en/medicines/human/EPAR/filgrastim-hexal#product-information-section⟩ (Accessed 27 November 2023).
Farhan, R., Urbanowska, E., Zborowska, H., et al., 2017. Biosimilar G-CSF versus filgrastim and lenograstim in healthy unrelated volunteer hematopoietic stem cell donors. Ann. Hematol. 96 (10), 1735–1739.
Gascon, P., Fuhr, U., Sorgel, F., et al., 2010. Development of a new G-CSF product based on biosimilarity assessment. Ann. Oncol. 21 (7), 1419–1429.
Gascon, P., Tesch, H., Verpoort, K., et al., 2013. Clinical experience with Zarzio® in Europe: what have we learned? Support. Care Cancer 21 (10), 2925–2932.
Gascon, P., Aapro, M., Ludwig, H., et al., 2016. Treatment patterns and outcomes in the prophylaxis of chemotherapy-induced (febrile) neutropenia with biosimilar filgrastim (the MONITOR-GCSF study). Support. Care Cancer 24 (2), 911–925.
Gascon, P., Krendyukov, A., Mathieson, N., et al., 2019. Extrapolation in practice: lessons from 10 years with biosimilar filgrastim. BioDrugs 33 (6), 635–645.
Goldsmith, D., Dellanna, F., Schiestl, M., et al., 2018. Epoetin biosimilars in the treatment of renal anemia: what have we learned from a decade of European experience? Clin. Drug Investig. 38 (6), 481–490.
Harbeck, N., Gascon, P., Krendyukov, A., et al., 2018a. Safety profile of biosimilar filgrastim (Zarzio/Zarxio): a combined analysis of phase III studies. Oncologist 23 (4), 403–409.
Harbeck, N., Yau, L., Mathieson, N., et al., 2018b. Comparison of efficacy and safety of biosimilar filgrastim in a RCT (PIONEER) and real-world practice (MONITOR-GCSF). J. Clin. Oncol. 36 (15_suppl), 111.
Hermans, M.H., van de Geijn, G.J., Antonissen, C., et al., 2003. Signaling mechanisms coupled to tyrosines in the granulocyte colony-stimulating factor receptor orchestrate G-CSF-induced expansion of myeloid progenitor cells. Blood 101 (7), 2584–2590.
Heyn, J., Bräuninger, S., Dimova-Dobreva, M., et al., 2022. Superior physical and mental health of healthy volunteers before and five years after mobilized stem cell donation. J. Transl. Med. 20 (1), 121.
Holzmann, J., Balser, S., Windisch, J., 2016. Totality of the evidence at work: the first U. S. biosimilar. Expert. Opin. Biol. Ther. 16 (2), 137–142.
Islami, M.M., Khan, M.A., Aseeri, M.A., et al., 2023. Comparison of biosimilar filgrastim with innovator fligrastim for peripheral blood stem cells mobilization, collection of CD34+ stem cells, and engraftment in patients undergoing autologous and allogeneic stem cell transplantation: a single-center experience. Ann. Transplant. 28, e938585.
Karaca-Mandic, P., Chang, J., Go, R., et al., 2019. Biosimilar filgrastim uptake and costs among commercially insured, medicare advantage. Health Aff. (Millwood) 38 (11), 1887–1892.
Kosari, S., Walker, E.J., Anderson, C., et al., 2018. Power outages and refrigerated medicines: the need for better guidelines, awareness and planning. J. Clin. Pharm. Ther. 43 (5), 737–739.
Krendyukov, A., Schiestl, M., 2019. Biosimilars in oncology: a decade of experience with granulocyte colony-stimulating factor and its implications for monoclonal antibodies. Crit. Rev. Oncol. Hematol., 102785
Lefrère, F., Brignier, A.C., Elie, C., et al., 2011. First experience of autologous peripheral blood stem cell mobilization with biosimilar granulocyte colony-stimulating factor. Adv. Ther. 28 (4), 304–310.
Li, E., Mezzio, D.J., Campbell, D., et al., 2021. Primary prophylaxis with biosimilar filgrastim for patients at intermediate risk for febrile neutropenia: a cost-effectiveness analysis. JCO Oncol. Pract. 17 (8), e1235–e1245.
Link, H., 2022. Current state and future opportunities in granulocyte colony-stimulating factor (G-CSF). Support. Care Cancer 30 (9), 7067–7077.
Ludwig, H., Gascón, P., Bokemeyer, C., et al., 2019. Outcomes of chemotherapy-induced (febrile) neutropenia prophylaxis with biosimilar filgrastim (Zarzio®) initiated "same-day" (< 24h), "per-guidelines" (24–72 h), and "late" (> 72h): findings from the MONITOR-GCSF study. Support. Care Cancer 27 (6), 2301–2312.
Lyman, G.H., Michels, S.L., Reynolds, M.W., et al., 2010. Risk of mortality in patients with cancer who experience febrile neutropenia. Cancer 116 (23), 5555–5563.
Manko, J., Walter-Croneck, A., Jawniak, D., et al., 2014. A clinical comparison of the efficacy and safety of biosimilar G-CSF and originator G-CSF in haematopoietic stem cell mobilization. Pharmacol. Rep. 66 (2), 239–242.
Marchesi, F., Vacca, M., Gumenyuk, S., et al., 2016. Biosimilar filgrastim (Zarzio®) vs. lenograstim (Myelostim®) for peripheral blood stem cell mobilization in adult patients with lymphoma and myeloma: a single center experience. Leuk. Lymphoma 57 (2), 489–492.
Marchesi, F., Terrenato, I., Papa, E., et al., 2024. Efficacy and safety of biosimilar Peg-filgrastim after autologous stem cell transplant in myeloma and lymphoma patients: a comparative study with biosimilar Filgrastim, Lenograstim, and originator Peg-filgrastim. Ann. Hematol. 103, 947–956.
Martino, M., Gori, M., Porto, G., et al., 2023. Effectiveness of biosimilar pegfilgrastim in patients with multiple myeloma after high-dose melphalan and autologous stem cell transplantation. Ann. Hematol. 102 (7), 1915–1925.
McBride, A., Campbell, K., Bikkina, M., et al., 2017. Cost-efficiency analyses for the US of biosimilar filgrastim-sndz, reference filgrastim, pegfilgrastim, and pegfilgrastim with on-body injector in the prophylaxis of chemotherapy-induced (febrile) neutropenia. J. Med. Econ. 20 (10), 1083–1093.
McBride, A., Krendyukov, A., Mathieson, N., et al., 2020. Febrile neutropenia hospitalization due to pegfilgrastim on-body injector failure compared to single-injection pegfilgrastim and daily injections with reference and biosimilar filgrastim: US cost simulation for lung cancer and non-Hodgkin lymphoma. J. Med. Econ. 23 (1), 28–36.
Nahon, S., Rastkhah, M., Ben Abdelghani, M., et al., 2016. Zarzio®, biosimilar of filgrastim, in prophylaxis of chemotherapy-induced neutropenia in routine practice: a French prospective multicentric study. Support. Care Cancer 24 (5), 1991–1998.
National Comprehensive Cancer Network, 2023a. NCCN Clinical Practice Guidelines in Oncology – Hematopoietic Cell Transplantation v1. ⟨https://www.nccn.org/guidelines/guidelines-detail?category=3&id=1501⟩ (Accessed 27 November 2023).
National Comprehensive Cancer Network, 2023b. NCCN Clinical Practice Guidelines in Oncology – Hematopoietic Growth Factors v1. ⟨https://www.nccn.org/guidelines/guidelines-detail?category=3&id=1493⟩ (Accessed 27 November 2023).
NIH National Library of Medicine - DailyMed database Zarxio Prescribing Information 2022.accessed 27 November 2023⟨https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=c0d1c22b-566b-4776-bdbf-00f96dad0cae⟩.
Nordvig, J., Aagaard, T., Daugaard, G., et al., 2018a. Febrile neutropenia and long-term risk of infection among patients treated with chemotherapy for malignant diseases. Open Forum Infect. Dis. 5 (10), ofy255.
Parody, R., Sánchez-Ortega, I., Ferrá, C., et al., 2020. Mobilization of hematopoietic stem cells into peripheral blood for autologous transplantation seems less efficacious in poor mobilizers with the use of a biosimilar of filgrastim and plerixafor: a retrospective comparative analysis. Oncol. Ther. 8 (2), 311–324.
Pharmaceutical Management Agency, 2014. Annual Review. https://pharmac.govt.nz/assets/annual-review-2014.pdf (Accessed 27 November 2023).
Phelip, J.M., Souquet, P.J., Hacini, M., et al., 2023. G-CSF filgrastim biosimilar-Sandoz reduces the incidence of febrile neutropenia in patients receiving chemotherapy regimens with rest periods not exceeding 14 days: a French, multicenter, prospective, non-interventional study. Cancer Treat. Res. Commun. 35, 100690.
Qian, J., 2021. Uptake and cost of biosimilar filgrastim among Medicare and Medicaid populations in 2015-2018. J. Manag. Care Spec. Pharm. 27 (5), 660–666.
Rastogi, S., Shukla, S., Sharma, A.K., et al., 2020. Towards a comprehensive safety understanding of granulocyte-colony stimulating factor biosimilars in treating chemotherapy associated febrile neutropenia: trends from decades of data. Toxicol. Appl. Pharmacol. 395, 114976.

Rastogi, S., Kalaiselvan, V., Ali, S., et al., 2021. Efficacy and safety of filgrastim and its biosimilars to prevent febrile neutropenia in cancer patients: a prospective study and meta-analysis. Biology (Basel) 10 (10), 1069.
Reményi, P., Gopcsa, L., Marton, I., et al., 2014. Peripheral blood stem cell mobilization and engraftment after autologous stem cell transplantation with biosimilar rhG-CSF. Adv. Ther. 31 (4), 451–460.
Salesi, N., Di Cocco, B., Colonna, M., et al., 2012. Biosimilar medicines in oncology: single-center experience with biosimilar G-CSF. Future Oncol. 8 (5), 625–630.
Schmitt, M., Hoffmann, J.M., Lorenz, K., et al., 2016. Mobilization of autologous and allogeneic peripheral blood stem cells for transplantation in haematological malignancies using biosimilar G-CSF. Vox. Sang. 111 (2), 178–186.
Schwartzberg, L.S., Lal, L.S., Balu, S., et al., 2018a. Clinical outcomes of treatment with filgrastim versus a filgrastim biosimilar and febrile neutropenia-associated costs among patients with nonmyeloid cancer undergoing chemotherapy. J. Manag. Care Spec. Pharm. 24 (10), 976–984.
Schwartzberg, L.S., Lal, L.S., Balu, S., et al., 2018b. Incidence of febrile neutropenia during chemotherapy among patients with nonmyeloid cancer receiving filgrastim vs a filgrastim biosimilar. Clinicoecon. Outcomes Res. 10, 493–500.
Socal, M.P., Anderson, K.E., Sen, A., et al., 2020. Biosimilar uptake in Medicare Part B varied across hospital outpatient departments and physician practices: the case of filgrastim. Value Health 23 (4), 481–486.
Sörgel, F., Lerch, H., Lauber, T., 2010. Physicochemical and biologic comparability of a biosimilar granulocyte colony-stimulating factor with its reference product. BioDrugs 24 (6), 347–357.
Sörgel, F., Schwebig, A., Holzmann, J., et al., 2015. Comparability of biosimilar filgrastim with originator filgrastim: protein characterization, pharmacodynamics, and pharmacokinetics. BioDrugs 29 (2), 123–131.
U.S. Food and Drug Administration, 2021a. Zarxio Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125553s023lbl.pdf (Accessed 27 November 2023).
U.S. Food and Drug Administration, 2021b. Nivestym Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761080s007lbl.pdf (accessed 27 November 2023).
U.S. Food and Drug Administration, 2022a. Releuko Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761082s003lbl.pdf (accessed 27 November 2023).
U.S. Food and Drug Administration, 2022b. Biosimilars – review and approval. https://www.fda.gov/drugs/biosimilars/review-and-approval (accessed 27 November 2023).
U.S. Food and Drug Administration, 2023. Neupogen Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/103353s5198lbl.pdf (Accessed 27 November 2023).
Verpoort, K., Möhler, T.M., 2012. A non-interventional study of biosimilar granulocyte colony-stimulating factor as prophylaxis for chemotherapy-induced neutropenia in a community oncology centre. Ther. Adv. Med. Oncol. 4 (6), 289–293.
Vlieland, N.D., Gardarsdottir, H., Bouvy, M.L., et al., 2016. The majority of patients do not store their biologic disease-modifying antirheumatic drugs within the recommended temperature range. Rheumatology (Oxford) 55 (4), 704–709.
Vlieland, N.D., van den Bemt, B.J.F., Bekker, C.L., et al., 2018. Older patients' compliance with drug storage recommendations. Drugs Aging 35 (3), 233–241.
Weise, M., Kurki, P., Wolff-Holz, E., et al., 2014. Biosimilars: the science of extrapolation. Blood 124 (22), 3191–3196.
Weycker, D., Li, X., Edelsberg, J., et al., 2015. Risk and consequences of chemotherapy-induced febrile neutropenia in patients with metastatic solid tumors. J. Oncol. Pract. 11 (1), 47–54.
Wicherska-Pawłowska, K., Rybka, J., Prajs, I., et al., 2020. The comparison of effectiveness and safety between different biosimilars of G-CSF in the mobilization of peripheral blood stem cells (PBSCs) for autologous transplantation (autologous peripheral blood stem cell transplantation, auto-PBSCT). J. Clin. Apher. 35 (1), 4–8.
Yousef, C.C., Khan, M.A., Almodaimegh, H., et al., 2023. Cost-efficiency analysis of conversion to biosimilar filgrastim for supportive cancer care and resultant expanded access analysis to supportive care and early-stage HER2+ breast cancer treatment in Saudi Arabia: simulation study. J. Med. Econ. 26 (1), 394–402.
Zecchini, J., Yum, K., Steinberg, A., et al., 2018. A single-center, retrospective analysis to compare the efficacy and safety of filgrastim-sndz to filgrastim for prophylaxis of chemotherapy-induced neutropenia and for neutrophil recovery following autologous stem cell transplantation. Support. Care Cancer 26 (3), 1013–1016.

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