Fylnetra®
(pegfilgrastim-pbbk)

Proven Similarity with Neulasta®[1]

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Fylnetra® Meets All FDA Requirements for Biosimilarity[1-4]

Fylnetra® (pegfilgrastim-pbbk) **is biosimilar** to Neulasta® based on the totality of evidence, with **no clinically meaningful differences in purity, potency, efficacy, safety, and immunogenicity** compared with Neulasta®.[1,6]

Requirements for Biosimilar Approval[2-4]

Reference Product (RP), Neulasta®[6,7]	Fylnetra®[1,5]
✓ Full CMC package	✓ Full CMC package + *In vitro* similarity
✓ Pharmacological assessment	✓ Pharmacological comparability in healthy volunteers
✓ Clinical studies:	✓ Comparative PD studies:
✓ Efficacy	✓ Efficacy (PD surrogate)
✓ Safety	✓ Safety
✓ Immunogenicity	✓ Immunogenicity
✓ Risk management plan	✓ Risk management plan

CMC = Chemistry Manufacturing and Control; PD = Pharmacodynamics; FDA: United States Food and Drug Administration

Fylnetra® robust totality of evidence proved biosimilarity with Neulasta®[1,6]

The Fylnetra® biosimilarity program was designed based on FDA guidance[2-4]

Indications

Fylnetra® is a leukocyte growth factor indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

Contraindications

Fylnetra® is contraindicated in patients with a history of serious allergic reactions to human granulocyte colony-stimulating factors such as pegfilgrastim products or filgrastim products. Reactions have included anaphylaxis.

Warnings and Precautions

Fatal splenic rupture: Evaluate patients who report left upper abdominal or shoulder pain for an enlarged spleen or splenic rupture.

Acute respiratory distress syndrome (ARDS): Evaluate patients who develop fever, lung infiltrates, or respiratory distress. Discontinue Fylnetra® in patients with ARDS.

Serious allergic reactions, including anaphylaxis: Permanently discontinue Fylnetra® in patients with serious allergic reactions.

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Fylnetra® Robust Totality of Evidence[1,5]

Multiple *in vitro* analytical similarity studies using state-of-the-art orthogonal analytical methods demonstrated similarity between Fylnetra® and Neulasta® in key features such as: primary structure, molecular conformation, charge variants, protein content, purity, and biological activity.[1,5]

Comparative stability studies between Fylnetra® and Neulasta® under accelerated and forced degradation conditions have demonstrated similar behavior and degradation pathways for the two products.[1,5]

The clinical development program for Fylnetra® (TPI-120) was comprised of a pivotal comparative PK/PD study (TPI-CL-109-A) in healthy volunteers performed with US-licensed Neulasta as the reference product and an immunogenicity and safety study (ADL-CL-112) conducted in healthy subjects[1].

Fylnetra® clinical comparability included data from 120 healthy subjects evaluated in 1 PK/PD study and 230 healthy subjects in 1 immunogenicity/safety study:[1,5]

1. Strong comparability PK package in healthy volunteer clinical study: The PK similarity of both products was established for serum filgrastim $AUC_{0\text{-}t}$; $AUC_{0\text{-}inf}$ and C_{max}.[1,5]

- Statistical analysis of the PK parameters demonstrated similarity between Fylnetra® and Neulasta®
- Secondary PK parameters included the residual area ($AUC_{\%extrap}$), T_{max}, $T_{½el}$ and K_{el} for serum
- Fylnetra® was generally well tolerated by healthy subjects

2. Strong Comparability PD package in healthy volunteer clinical study: As a surrogate for clinical efficacy, PD similarity of both products was established for baseline-corrected absolute neutrophil count (ANC) $AUEC_{0\text{-}t}$ and E_{max} for ANC:[1,5]

- Pharmacodynamic similarity of Fylnetra® versus Neulasta® was established for ANC (absolute neutrophil count) in the PK/PD study where bioequivalence was established[1]
- Secondary PD parameters included baseline-corrected $T_{max,E}$ for ANC
- The safety, tolerability, and immunogenicity profile of Fylnetra® and Neulasta® was determined to be similar

Analytical, preclinical and clinical studies have demonstrated Fylnetra® is similar to Neulasta®[1,5]

Fylnetra® ~ Neulasta®

Please see accompanying full Prescribing Information.

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Fylnetra® is FDA Approved for All Neulasta® Indications Through PK/PD Bioequivalence and Safety[1,5-7]

The Fylnetra® clinical development program was **comprised of a pivotal comparative PK/PD study** in 120 healthy volunteers performed with US-licensed Neulasta® as the reference product and a safety and tolerability study conducted on 240 healthy subjects.[1]

Fylnetra® (pegfilgrastim-pbbk) met the statutory requirements for licensure as a biosimilar product under section 351(k) of the PHS Act and has been approved by the FDA based on the totality of evidence and scientific justification for all conditions of use for which the reference product is licensed.

Fylnetra® Dosage and Administration* [5]

Indication	Dosage (per kilogram of body weight)	Route
Patients with Cancer Receiving Myelosuppressive Chemotherapy Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of febrile neutropenia.	6 mg/chemotherapy cycle	Subcutaneous injection, via a single-dose prefilled syringe for manual use. Not to administer between 14 days before and 24 hours after administration of cytotoxic chemotherapy.

Limitations of Use
Not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.

Warnings and Precautions

Fatal sickle cell crises: Discontinue Fylnetra® if sickle cell crisis occurs.

Glomerulonephritis: Evaluate and consider dose-reduction or interruption of Fylnetra® if causality is likely.

Leukocytosis: Monitor complete blood count during Fylnetra® therapy.

Thrombocytopenia: Monitor platelet counts.

Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML): Monitor patients with breast and lung cancer using Fylnetra® in conjunction with chemotherapy and/or radiotherapy for signs and symptoms of MDS/AML.

Aortitis: Discontinue Fylnetra® if aortitis is suspected.

Nuclear Imaging: When interpreting bone imaging results consider the transient positive bone imaging changes that result due to increased hematopoietic activity of the bone marrow in response to growth factor therapy.

Clinically Significant Adverse Reactions include:

- Aortitis
- Glomerulonephritis
- Serious Allergic Reactions
- Acute Respiratory Distress Syndrome
- Leukocytosis
- Thrombocytopenia
- Acute Myeloid Leukemia (AML)
- Use in Patients with Sickle Cell Disorders
- Splenic Rupture
- Capillary Leak Syndrome
- Myelodysplastic Syndrome (MDS)
- Potential for Tumor Growth Stimulatory Effects on Malignant Cells

Fylnetra® (pegfilgrastim-pbbk)

This is an abbreviated summary of the approved indications. For complete dosage and administration instructions, please see accompanying Fylnetra® full Prescribing Information.


Fylnetra® (pegfilgrastim-pbbk) is manufactured in the United States
Please see accompanying full Prescribing Information.
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Proven Similarity with Neulasta® [1,6]

Fylnetra® is a biosimilar filgrastim which has been developed in comparison with Neulasta® as the Reference Product (RP).

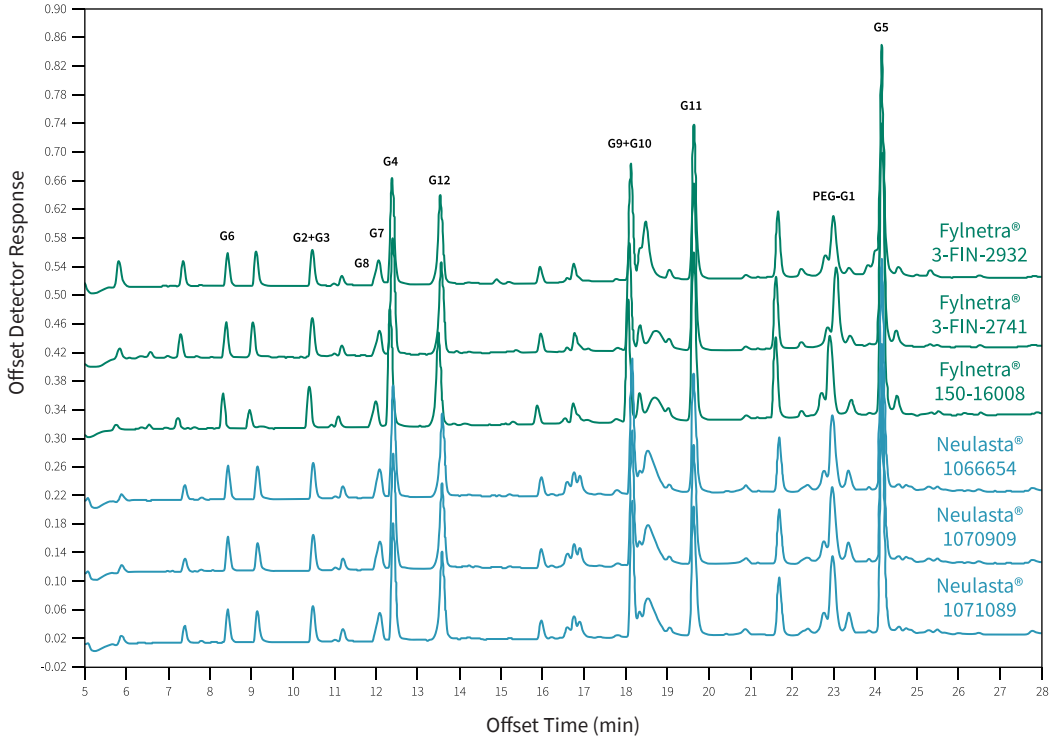
Multiple state-of-the-art analytical methods were applied to evaluate all quality attributes required of the biosimilar and confirmed analytical similarity between Fylnetra® and Neulastra®:[1]

Primary Structure

The same amino acid composition is confirmed in Fylnetra® and Neulasta®.

In the figure below, the same set of twelve (12) primary peptides G1 to G12 are seen from the digestion of Fylnetra® or Neulasta® by Glu-C for peptide mapping.

Representative Peptide Mapping Chromatograms* of Fylnetra® and Neulasta®



Charge Variants

The post-translational modification analyses demonstrated a similar relative content of acidic and basic forms between both proteins.

Protein Content and Purity

Similar protein content and high purity was found in both Fylnetra® and Neulasta®.

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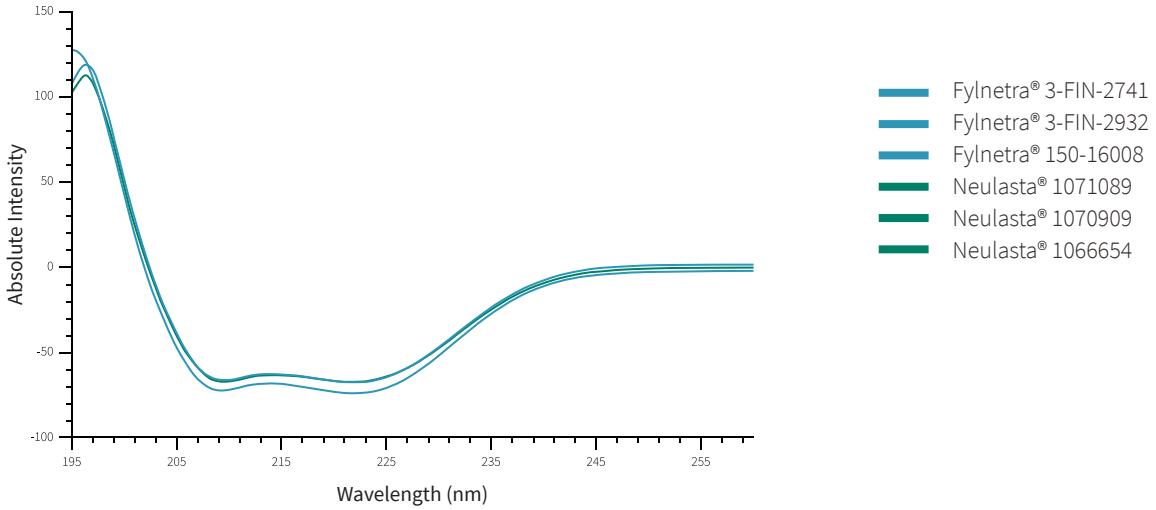
Comparative Stability

Comparative accelerated and forced degradation studies have shown a similar behavior and degradation profile of Fylnetra® and Neulasta®.

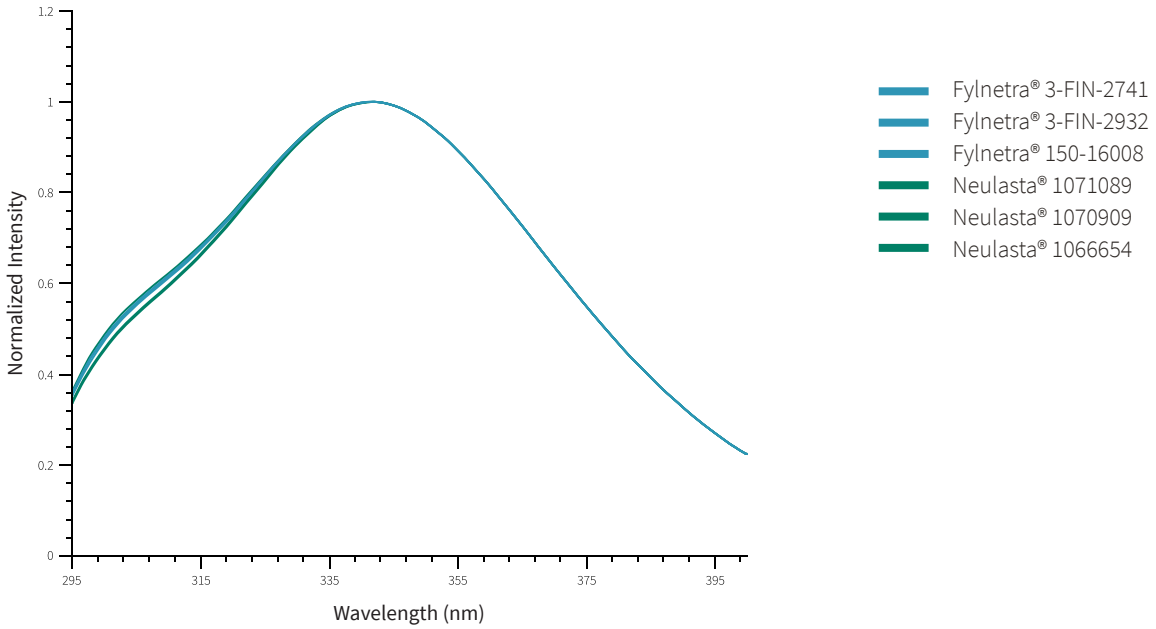
Molecular Conformation

Similarity between Fylnetra® and Neulasta® in terms of molecular conformation was demonstrated as seen by identical Far-UV Circular Dichroism Spectra, and Intrinsic Fluorescence spectra.

Representative Far-UV Circular Dichroism Spectra of Fylnetra® and Neulasta®



Overlay of Representative Intrinsic Fluorescence Spectra of Fylnetra® and Neulasta®



Biological Activity

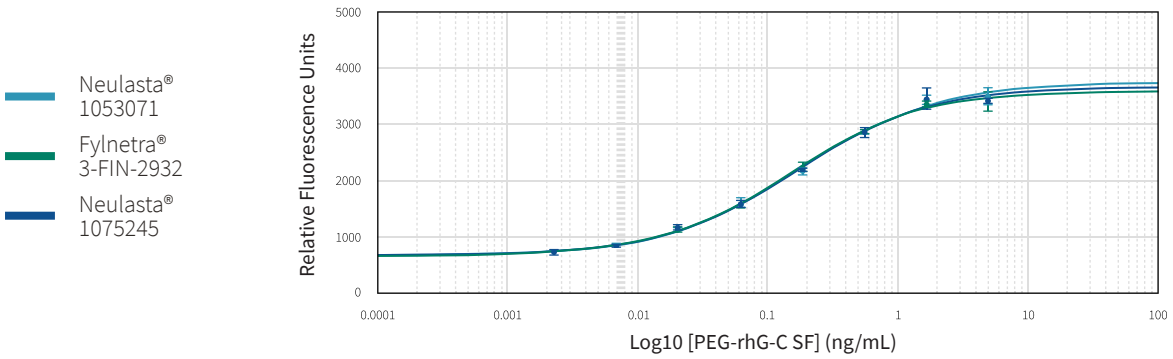
Multiple state-of-the-art orthogonal methods demonstrated the similarity of Fylnetra® to its reference product regarding biological activity.

Please see accompanying full Prescribing Information.

Biological Activity (Continued)

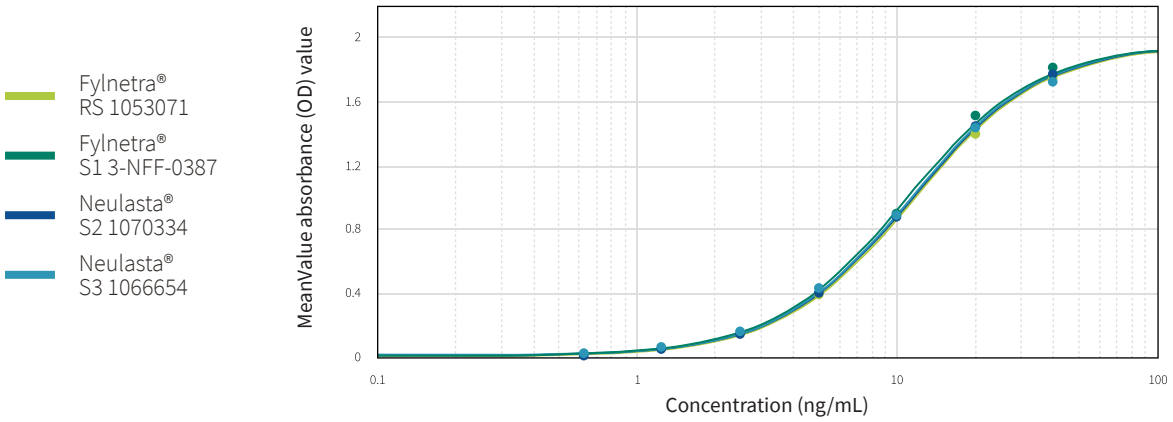
Highly similar potency of Fylnetra® and Neulasta® relative to filgrastim reference standard was seen in the M-NFS-60 Cell Proliferation Assay.

Representative Potency Dose Response Curve Showing Similar Potency of Fylnetra® and Neulasta® in M-NFS-60* Cell Proliferation Assay



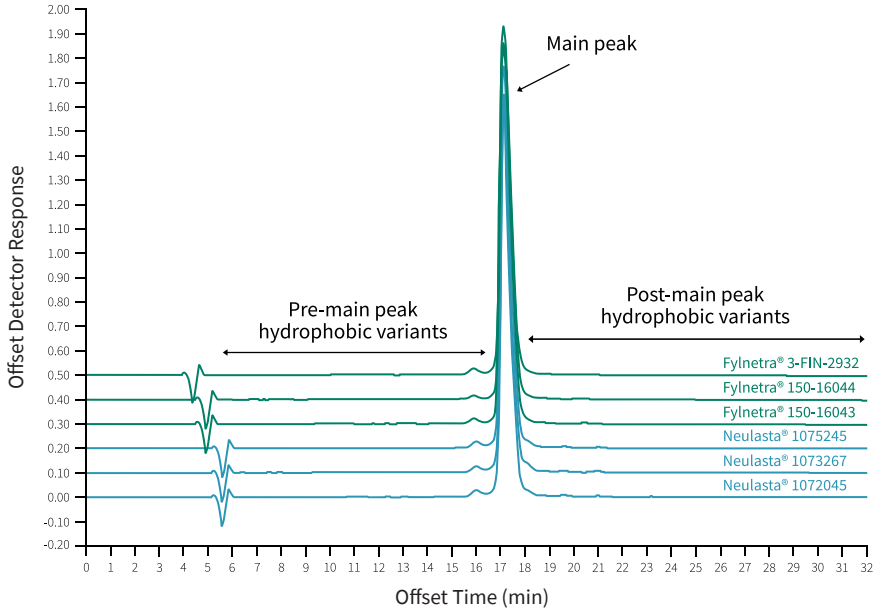
*Mouse-Myeloid Leukemia

Comparative Results of Receptor Binding by ELISA*: Representative ELISA Dose Response Curve for Fylnetra® Versus Neulasta®



*Enzyme-linked Immunoassay

Comparative Results of RP-HPLC* Chromatography of Fylnetra® and



*Reversed-phase High Performance Liquid Chromatography

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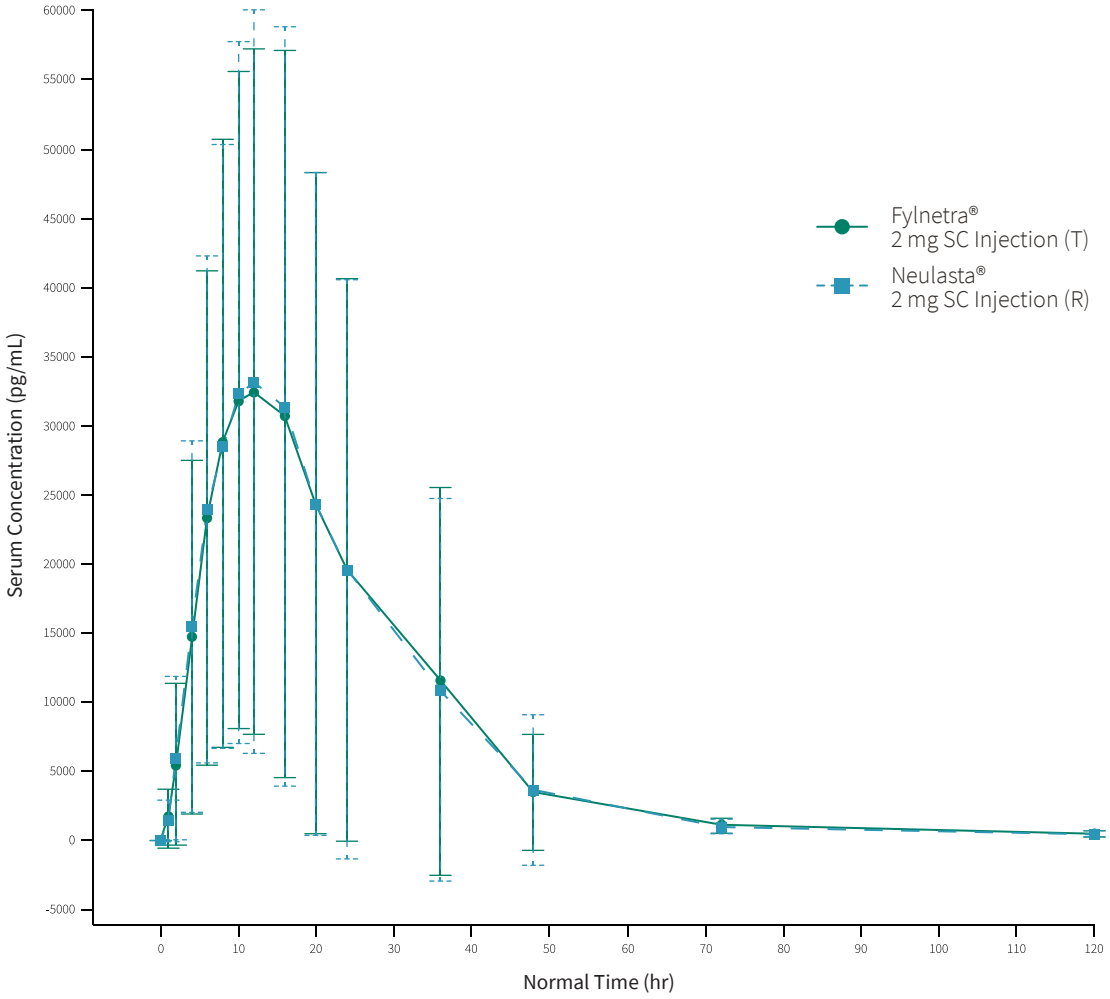
Please see accompanying full Prescribing Information.

Pharmacokinetics Demonstrate Bioequivalence to Neulasta®[1,6]

One PK/PD study was carried out in healthy volunteers' to investigate and compare the PK profiles of Fylnetra® and Neulasta® and confirm bioequivalence between both products:

The mean serum PEG-rhG-CSF* concentration versus time profiles following a single SC injection of 2mg Fylnetra (TPI-120) and Neulasta are shown in a linear scale.



**Pegylated Recombinant Human Granulocyte Colony Stimulating Factor*

It was statistically confirmed that Fylnetra® was bioequivalent to Neulasta® for the primary parameters $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}\infty)}$ and C_{max}, as the 90% CI were fully contained within the pre-defined bioequivalence limits of 0.80 - 1.25.[1,5]

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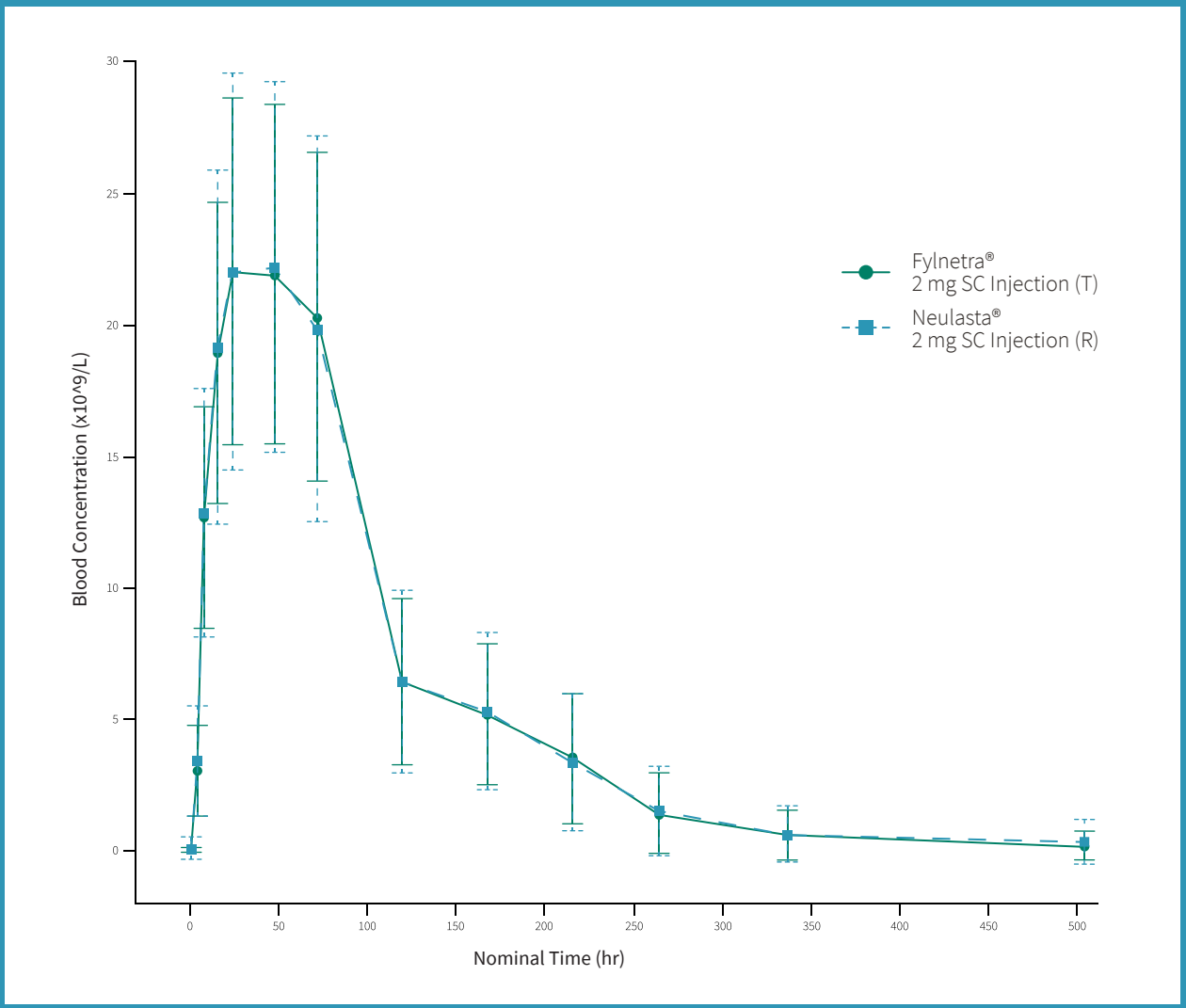
Fylnetra® was Approved Based on the Totality of Evidence, Including a Comparative PD Study as a Surrogate for Comparative Clinical Efficacy[1,5]

The PK/PD study provided the comparative PD characteristics that established PD similarity and hence comparative clinical efficacy for Fylnetra® versus Neulasta®.

PD concentration time curve shown below revealed the peak and overall baseline-corrected blood ANC (as measured by geometric mean E_{max} and $AUEC_{0-t}$) were similar following a SC injection of either Fylnetra (TPI-120) or Neulasta, as shown by the less than 10% difference in E_{max} and $AUEC_{0-t}$ between treatments.

The 90% CIs around the GMR of blood ANC E_{max} and $AUEC_{0-t}$ for TPI-120 relative to Neulasta were within the limits of the 80.00% - 125.00% boundary, and hence PD bioequivalence was demonstrated.



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Similar Efficacy Shown with Neulasta® [1,6]

The PK/PD study supported PK and PD bioequivalence and hence biosimilarity between Fylnetra® and Neulasta®. The data from these studies have established the following:

- Fylnetra® and Neulasta® display similar pharmacokinetics
- Fylnetra® and Neulasta® display similar pharmacodynamics
- Fylnetra® displays similar immunogenicity to Neulasta®
- There are no clinically meaningful differences in their safety profiles

Similar Safety and Immunogenicity to Neulasta® [1,6]

In the PK/PD study (TPI-CL-109-A) and immunogenicity study (ADL-CL-112), the safety endpoints measured included AEs, physical examinations, vital signs (heart rate, blood pressure, and temperature), 12-lead ECGs, local tolerability assessments, and clinical laboratory tests (hematology, serum chemistry, and urinalysis. ADL-CL-112 was single-blind, multi-center randomized, two cycle, parallel, repeat-dose, safety, and immunogenicity study in 230 subjects. The aggregate safety analysis across both clinical studies collectively revealed:

- Fylnetra® demonstrated similar safety and immunogenicity to Neulasta®
- There were no new or unexpected safety signals for Fylnetra® compared with Neulasta®
- Only 7% subjects had confirmed serum anti-Peg-GCSF antibodies following Fylnetra® administration compared to 15% of subjects following Neulasta® administration
- No neutralizing antibody was detected following Fylnetra® administration although one such antibody was detected in Neulasta® administered group

Multiple subcutaneous administrations of Fylnetra® and Neulasta® were generally safe and similarly tolerated in the healthy adult subjects.[1]

Most Common Adverse Reactions

Most common adverse reactions (≥ 5% difference in incidence compared to placebo) are bone pain and pain in extremity.

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Fylnetra® Product Characteristics[1,5]

Fylnetra® (pegfilgrastim-pbbk) Injection is available in the same pack size as Neulasta®[5].

NDC	Strength	Size	Form
70121-1627-1	6mg/0.6mL	1	Prefilled Syringe

HCPCS Code	Descriptor
Expected in January	Injection, pegfilgrastim-pbbk, biosimilar, (Fylnetra)

The Fylnetra® single-dose, prefilled syringe is equipped with 27 gauge, ½ inch needle with an UltraSafe Plus™ Passive Needle Guard. The needle cap on the prefilled syringe is not made with natural rubber latex.

Fylnetra® prefilled syringe does not bear graduation marks and is intended only to deliver the entire contents of the syringe (6 mg/0.6 mL) for direct administration. Use of the prefilled syringe is not recommended for direct administration for pediatric patients weighing less than 45 kg who require doses that are less than the full contents of the syringe.

Store Fylnetra® refrigerated at 2°C to 8°C (36°F to 46°F) in the original pack to protect from light. Do not shake. Discard syringes stored at room temperature [68°F to 77°F (20°C to 25°C)] for more than 72 hours. Avoid freezing; if frozen, thaw in the refrigerator before administration. Discard syringe if frozen more than once.

Fylnetra® has a shelf life of 24 months.

Amneal PATHways® Patient Support Program offering services such as:

- Benefits investigation
- Prior authorization support
- Affordability options
- Claims assistance

Amneal PATHways® Patient Access To Health

References:

1. Fylnetra® Summary Basis of Approval – Drug Approval Package https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/761084Orig1s000TOC.cfm
2. Section 7002(b)(3) of the Affordable Care Act, adding section 351(i)(2) of the PHS Act.
3. Food and Drug Administration, FDA. Scientific Considerations in Demonstrating Biosimilarity to a Reference Product. Guidance for Industry, 2015.
4. Food and Drug Administration, FDA. Draft Guidance: Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations, 2019.
5. Fylnetra® Full Prescribing Information - https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=eeadd641-573d-47fe-897a-61006e5f9e03
6. Neulasta® Summary Basis of Approval – Scientific Discussion https://www.accessdata.fda.gov/drugsatfda_docs/nda/2002/125031_0000_NeulastaTOC.cfm
7. Neulasta® Full Prescribing Information - https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=fdfe5d72-6b80-435a-afa4-c5d74dd852ce

See accompanying full Prescribing Information.

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