Supported by the totality of evidence for biosimilarity and the expertise of Sandoz, a Novartis Division

- Approved in the US in 2015
- Approved in Europe in 2009
- More than 7.5 million patient-exposure days outside of the US
- Confirmed biosimilarity to Neupogen® (filgrastim)

ZARXIO shares the following 5 indications with Neupogen®
(See full indications on page 10.)

- Patients with Cancer Receiving Myelosuppressive Chemotherapy
- Patients with Acute Myeloid Leukemia Receiving Induction or Consolidation Chemotherapy
- Patients with Cancer Undergoing Bone Marrow Transplantation
- Patients Undergoing Autologous Peripheral Blood Progenitor Cell Collection and Therapy
- Patients with Severe Chronic Neutropenia

Important Safety Information

CONTRAINDICATIONS

- ZARXIO is contraindicated in patients with a history of serious allergic reactions to human granulocyte colony-stimulating factors such as filgrastim or pegfilgrastim products.

WARNINGS AND PRECAUTIONS

- Splenic rupture, including fatal cases, has been reported following the administration of filgrastim products. Patients who report left upper abdominal or shoulder pain should be evaluated.
- Acute respiratory distress syndrome (ARDS) has been reported in patients receiving filgrastim products. Patients who develop fever and lung infiltrates or respiratory distress should be evaluated. Discontinue ZARXIO in patients with ARDS.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.

ZARXIO is a registered trademark of Novartis AG.
Neupogen is a registered trademark of Amgen Inc.
The Role of Biosimilars

What are biosimilars?

Biosimilars are biologic medicines that are highly similar to their reference biologic, as they have demonstrated no clinically meaningful differences in safety, purity, and potency compared to that of the reference biologic.7

Because biologics are larger, more complex, and of higher molecular weight than small-molecule medicines, biosimilars are subject to a step-wise, multifaceted regulatory approval pathway.7

Biosimilars are not generics8

In order to prove biosimilarity and gain FDA approval, biosimilar data must include analytical studies, pre-clinical testing, and clinical trials, which typically include an equivalence design study or studies which are sufficient to demonstrate safety, purity, and potency.7

INCREASING level of complexity

Small-chemical molecule8,10

For example: Salicylic acid
• Chemically synthesized
• Well-defined structure
• Low molecular weight

Biologic molecule8,10

For example: Filgrastim
• Derived from living material
• Larger, more complex structure
• High molecular weight

Complex biologic10,12,13

For example: Monoclonal antibody
• Derived from living material
• Most complex structure
• Very high molecular weight

Biosimilarity Based on a “Totality of Evidence”7

The FDA established an approval pathway for sponsors of a biological product seeking approval as a biosimilar to a reference biologic based on a totality of evidence.

• To gain approval, a biosimilar must be comparable to the reference biologic in terms of structure, function, animal toxicity, human pharmacokinetics (PK) and pharmacodynamics (PD), immunogenicity, clinical safety, and efficacy7

Biosimilar development goal: Demonstrate biosimilarity to reference biologic7,14

*The nature and scope of the clinical study or studies will depend on the nature and extent of residual uncertainty about biosimilarity after conducting structural and functional characterization and, where relevant, animal studies.

Note: Illustrations are not to scale.
**Sandoz: the US Biosimilar Pathway Pioneer**

The efforts of Sandoz led to the development of the first biosimilar to receive FDA approval. Sandoz selected comprehensive methods to fully characterize and evaluate ZARXIO in order to meet all FDA requirements.1

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### Biosimilar Requirements and ZARXIO

<table>
<thead>
<tr>
<th>Statutory requirement</th>
<th>ZARXIO fulfillment of requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DEMONSTRATE HIGH SIMILARITY</strong></td>
<td></td>
</tr>
<tr>
<td>Analytical data</td>
<td>• Physiochemical and functional analytical data demonstrated that ZARXIO is highly similar to Neupogen® (filgrastim)2</td>
</tr>
<tr>
<td>Animal studies*</td>
<td>• Five animal studies confirmed that the pharmacologic and toxicological profiles of ZARXIO and Neupogen® are similar2</td>
</tr>
<tr>
<td>Clinical studies</td>
<td>• Study to evaluate PD, PK, and safety2</td>
</tr>
<tr>
<td>Mechanism of action</td>
<td>• The mechanism of action of filgrastim is mediated by selective binding to the G-CSF receptor and is similar across all labeled indications2,3</td>
</tr>
<tr>
<td>Route of administration, dosage form, and strength</td>
<td>• ZARXIO has the same route of administration, dosage form, and strengths as Neupogen®3,6</td>
</tr>
</tbody>
</table>

**SAME AS REFERENCE BIOSIMILAR**

- **Statutory requirement**
- **ZARXIO fulfillment of requirement**
- **Analytical data**
  - Physiochemical and functional analytical data demonstrated that ZARXIO is highly similar to Neupogen® (filgrastim)2
- **Animal studies***
  - Five animal studies confirmed that the pharmacologic and toxicological profiles of ZARXIO and Neupogen® are similar2
- **Clinical studies**
  - Study to evaluate PD, PK, and safety2
  - Study to evaluate comparative efficacy and safety of ZARXIO and Neupogen® (The PIONEER study)3
- **Mechanism of action**
  - The mechanism of action of filgrastim is mediated by selective binding to the G-CSF receptor and is similar across all labeled indications2,3
- **Route of administration, dosage form, and strength**
  - ZARXIO has the same route of administration, dosage form, and strengths as Neupogen®3,6

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### Important Safety Information

**WARNINGS AND PRECAUTIONS (cont’d)**

- Serious allergic reactions, including anaphylaxis, have been reported in patients receiving filgrastim products. The majority of reported events occurred upon initial exposure. Provide symptomatic treatment for allergic reactions. Allergic reactions, including anaphylaxis, in patients receiving filgrastim products can recur within days after the discontinuation of initial anti-allergic treatment. Permanently discontinue ZARXIO in patients with serious allergic reactions.
- Sickle cell crisis, in some cases fatal, has been reported with the use of filgrastim products in patients with sickle cell trait or sickle cell disease.
- Glomerulonephritis has occurred in patients receiving filgrastim products. The diagnoses were based upon azotemia, hematuria (microscopic and macroscopic), proteinuria, and renal biopsy. Generally, events of glomerulonephritis resolved after dose reduction or discontinuation of filgrastim products. If glomerulonephritis is suspected, evaluate for cause. If causality is likely, consider dose-reduction or interruption of ZARXIO.
- Alveolar hemorrhage manifesting as pulmonary infiltrates and hemoptysis requiring hospitalization have been reported in healthy donors treated with filgrastim products undergoing peripheral blood progenitor cell (PBPC) collection mobilization. Hemoptysis resolved with discontinuation of filgrastim. The use of ZARXIO for PBPC mobilization in healthy donors is not an approved indication.

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**Confirmed Biosimilarity of ZARXIO to Neupogen® (filgrastim)2,5**

Biosimilarity was confirmed by the PIONEER study and a PK/PD study that demonstrated equivalence with regard to ANC* and CD34+ cell counts.2,5

**PIONEER** was a randomized, double-blind, comparative study of efficacy and safety between ZARXIO and Neupogen® in 218 breast cancer patients treated with myelosuppressive chemotherapy.2,5

- **Study duration:** 24 weeks1
- **All patients received 6 cycles (3 weeks per cycle) of TAC‡ combination chemotherapy administered on Day 1 of each cycle5**
  - Starting on Day 2 of each chemotherapy cycle, ZARXIO or Neupogen® was administered daily and continued until the ANC recovered to 10 x 10^9/L after the nadir or up to a maximum of 14 days (whichever occurred first)
- **The study included 4 arms in total2**
  - –2 arms received treatment with either ZARXIO or Neupogen® across all cycles
  - –2 arms started with either ZARXIO or Neupogen® in Cycle 1, then alternated treatment in each subsequent cycle

**Primary endpoint equivalence analysis:** Comparative equivalency assessment of mean duration of severe neutropenia between ZARXIO and Neupogen® in Cycle 1.5

**ZARXIO** is not interchangeable with Neupogen®. Sandoz did not seek a designation of interchangeability for ZARXIO.

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### Important Safety Information

**WARNINGS AND PRECAUTIONS (cont’d)**

- Capillary leak syndrome (CLS) has been reported after G-CSF administration, including filgrastim products, and is characterized by hypotension, hypoaalbuminemia, edema and hemococoncentration. Episodes vary in frequency, severity and may be life-threatening if treatment is delayed. Patients who develop symptoms of capillary leak syndrome should be closely monitored and receive appropriate treatment.

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Please see additional Important Safety Information throughout and accompanying full Prescribing Information.

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*ANC is absolute neutrophil count.*

*A total of 218 patients were randomized in the study of which 204 were included in the primary prophylaxis (PP) population for the primary analysis. A total of 34 patients did not complete the study as planned or discontinued study treatment prematurely. The PP patients were on average 49.0 years old with an overall range between 23 and 76 years. The median duration since breast cancer diagnosis was 2.0 months (range from 0 to 171 months) and the majority of patients had stage II cancer (51.4%) or stage III cancer (41.6%). A total of 163 patients (76.2%) had an ECOG status of 0 and 51 patients (23.8%) had an ECOG status of 1.2

**PIONEER Study Design**

- **CYCLE 1 - PRIMARY ENDPOINT**
  - Primary endpoint equivalence analysis: Comparative equivalency assessment of mean duration of severe neutropenia between ZARXIO and Neupogen® in Cycle 1.5
  - **ZARXIO**
    - n=109
  - **Neupogen®**
    - n=109

- **CYCLES 2-6**
  - **ZARXIO**
    - n=109
  - **Neupogen®**
    - n=109

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Confirmed Biosimilarity of ZARXIO to Neupogen® (filgrastim)\textsuperscript{5}

PIONEER was a randomized, double-blind, comparative study of efficacy and safety between ZARXIO and Neupogen\textsuperscript{a} in 218 breast cancer patients treated with myelosuppressive chemotherapy.\textsuperscript{3}

**Primary endpoint for equivalence (in Cycle 1): mean duration of severe neutropenia (DSN)\textsuperscript{2,4**}

<table>
<thead>
<tr>
<th></th>
<th>Cycle 1 Mean DSN (SD)</th>
<th>ZARXIO N=101</th>
<th>Neupogen\textsuperscript{a} N=103</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1.17 days (1.11)</td>
<td>1.20 days (1.02)</td>
</tr>
<tr>
<td>DSN Difference for Neupogen\textsuperscript{a} minus ZARXIO (90% CI)\textsuperscript{†}</td>
<td>0.04 days (-0.21, 0.28)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Tested using 90\% confidence interval for DSN difference
- Upper and lower margins for this trial would be 1 day
- Equivalence was demonstrated

**Secondary endpoints (in Cycle 1)\textsuperscript{2,4**}

- Incidence of febrile neutropenia (FN)\textsuperscript{b} (n [\%])
- Time to ANC recovery\textsuperscript{c} (days) (mean + SD)
- Depth of ANC nadir\textsuperscript{d} (x10\textsuperscript{9}) (mean ± SD)
- Number of days of fever\textsuperscript{e} (days) (median, range)
- Frequency of infections (n [\%])
- Incidence of hospitalizations due to FN (n)

<table>
<thead>
<tr>
<th></th>
<th>ZARXIO N=101</th>
<th>Neupogen\textsuperscript{a} N=103</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of febrile neutropenia (FN)\textsuperscript{b} (n [%])</td>
<td>4 (4.0%)</td>
<td>2 (1.9%)</td>
</tr>
<tr>
<td>Time to ANC recovery\textsuperscript{c} (days) (mean + SD)</td>
<td>1.8 ± 0.97</td>
<td>1.7 ± 0.81</td>
</tr>
<tr>
<td>Depth of ANC nadir\textsuperscript{d} (x10\textsuperscript{9}) (mean ± SD)</td>
<td>0.734 ± 1.1388</td>
<td>0.757 ± 1.3131</td>
</tr>
<tr>
<td>Number of days of fever\textsuperscript{e} (days) (median, range)</td>
<td>0 (0-2)</td>
<td>0 (0-2)</td>
</tr>
<tr>
<td>Frequency of infections (n [%])</td>
<td>2 (2.0%)</td>
<td>2 (1.9%)</td>
</tr>
<tr>
<td>Incidence of hospitalizations due to FN (n)</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

- Secondary endpoints were not adjusted for multiplicity.\textsuperscript{2}

**Important Safety Information**

**WARNINGS AND PRECAUTIONS (cont’d)**

- Leukocytosis:
  - Patients with Cancer Receiving Myelosuppressive Chemotherapy: White blood cell counts of 100,000/mm\textsuperscript{3} or greater were observed in approximately 2\% of patients receiving filgrastim at dosages above 5 mcg/kg/day. In patients with cancer receiving ZARXIO as an adjunct to myelosuppressive chemotherapy, to avoid the potential risks of excessive leukocytosis, it is recommended that ZARXIO therapy be discontinued if the ANC surpasses 10,000/mm\textsuperscript{3} after the chemotherapy-induced ANC nadir has occurred. Monitor CBCs at least twice weekly during therapy.
  - Peripheral Blood Progenitor Cell (PBPC) Collection and Therapy: During the period of administration of ZARXIO for PBPC mobilization in patients with cancer, discontinue ZARXIO if the leukocyte count rises to >100,000/mm\textsuperscript{3}.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.

ZARXIO is a registered trademark of Novartis AG.
Neupogen is a registered trademark of Amgen Inc.
The PIONEER Study

Cardinal Adverse Events (Between-Group Comparison)4

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>ZARXIO (N=107) n (%)</th>
<th>Neupogen® (N=107) n (%)</th>
<th>Comparison ZARXIO - Neupogen® (%; 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alopecia</td>
<td>62 (57.9)</td>
<td>63 (58.9)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>39 (36.4)</td>
<td>43 (40.2)</td>
<td></td>
</tr>
<tr>
<td>Asthenia</td>
<td>30 (28.0)</td>
<td>42 (39.3)</td>
<td></td>
</tr>
<tr>
<td>Bone pain</td>
<td>19 (17.8)</td>
<td>23 (21.5)</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>17 (15.9)</td>
<td>12 (11.2)</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>8 (7.5)</td>
<td>11 (10.3)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6 (5.6)</td>
<td>12 (11.2)</td>
<td></td>
</tr>
<tr>
<td>Leukopenia</td>
<td>6 (5.6)</td>
<td>4 (3.7)</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>5 (4.7)</td>
<td>9 (8.4)</td>
<td></td>
</tr>
</tbody>
</table>

The overall safety profile of ZARXIO was similar across all 6 cycles with continuous treatment.4

Prescribing Information Adverse Reactions3,6

The following most common adverse reactions listed in the ZARXIO Prescribing Information are based on the reference biologic.

**ADVERSE REACTIONS**

Most common adverse reactions in patients:

- With nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs (≥ 5% difference in incidence compared to placebo) are thrombocytopenia, nausea, pyrexia, chest pain, pain, fatigue, back pain, arthralgia, bone pain, pain in extremity, dizziness, cough, dyspnea, rash, blood lactate dehydrogenase increased and blood alkaline phosphatase increased
- With AML (≥ 2% difference in incidence) are epistaxis, back pain, pain in extremity, erythema, and rash maculo-papular
- With nonmyeloid malignancies undergoing myeloablative chemotherapy followed by BMT (≥ 5% difference in incidence) are rash and hypersensitivity
- Undergoing peripheral blood progenitor cell mobilization and collection (≥ 5% incidence) are bone pain, pyrexia, blood alkaline phosphatase increased and headache
- With severe chronic neutropenia (SCN) (≥ 5% difference in incidence) are arthralgia, bone pain, back pain, muscle spasms, musculoskeletal pain, pain in extremity, splenomegaly, anemia, upper respiratory tract infection, urinary tract infection, epistaxis, chest pain, diarrhea, hypoesthesia, and alopecia

Important Safety Information

**WARNINGS AND PRECAUTIONS (cont’d)**

- Cutaneous vasculitis has been reported in patients treated with filgrastim products. In most cases, the severity of cutaneous vasculitis was moderate or severe. Most of the reports involved patients with SCN receiving long-term filgrastim therapy. Hold ZARXIO therapy in patients with cutaneous vasculitis. ZARXIO may be started at a reduced dose when the symptoms resolve and the ANC has decreased.
- The possibility that ZARXIO acts as a growth factor for any tumor type cannot be excluded. The safety of filgrastim products in chronic myeloid leukemia (CML) and myelodysplasia has not been established. When ZARXIO is used to mobilize PBPC, tumor cells may be released from the marrow and subsequently collected in the leukapheresis product. Available data is limited and inconclusive.

The safety profile of ZARXIO as compared to Neupogen® was not markedly different.2,4

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.

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Neupogen is a registered trademark of Amgen Inc.
ZARXIO Shares the Following 5 Indications
With Neupogen® (filgrastim)3,6

1. Patients with Cancer Receiving Myelosuppressive Chemotherapy
ZARXIO is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever.

2. Patients with Acute Myeloid Leukemia Receiving Induction or Consolidation Chemotherapy
ZARXIO is indicated to reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML).

3. Patients with Cancer Undergoing Bone Marrow Transplantation
ZARXIO is indicated to reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation.

4. Patients Undergoing Autologous Peripheral Blood Progenitor Cell Collection and Therapy
ZARXIO is indicated for the mobilization of autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis.

5. Patients with Severe Chronic Neutropenia
ZARXIO is indicated for chronic administration to reduce the incidence and duration of sequelae of neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia.

Important Safety Information

WARNINGS AND PRECAUTIONS (cont’d)
• The safety and efficacy of ZARXIO given simultaneously with cytotoxic chemotherapy have not been established. Do not use ZARXIO in the period 24 hours before through 24 hours after the administration of cytotoxic chemotherapy. The safety and efficacy of ZARXIO have not been evaluated in patients receiving concurrent radiation therapy. Avoid the simultaneous use of ZARXIO with chemotherapy and radiation therapy.
• Increased hematopoietic activity of the bone marrow in response to growth factor therapy has been associated with transient positive bone-imaging changes on nuclear imaging.

ZARXIO Prefilled Syringe3
ZARXIO is available in prefilled syringes, in the same 2 dosage strengths as Neupogen®3,6
• 300 mcg/0.5 mL
• 480 mcg/0.8 mL

Identical dosing schedule and route of administration to Neupogen®3,6

ZARXIO is administered by subcutaneous injection, short intravenous infusion (15 to 30 minutes), or continuous intravenous infusion.7

You should not inject a dose of ZARXIO less than 0.3 mL (180 mcg) from a ZARXIO prefilled syringe. A dose less than 0.3 mL cannot be accurately measured using the ZARXIO prefilled syringe.7

Important Safety Information

ADVERSE REACTIONS
Most common adverse reactions in patients:
• With nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs (≥ 5% difference in incidence compared to placebo) are thrombocytopenia, nausea, pyrexia, chest pain, pain, fatigue, back pain, arthralgia, bone pain, pain in extremity, dizziness, cough, dyspnea, rash, blood lactate dehydrogenase increased and blood alkaline phosphatase increased
• With AML (≥ 2% difference in incidence) are epistaxis, back pain, pain in extremity, erythema, and rash maculo-papular
• With nonmyeloid malignancies undergoing myeloablative chemotherapy followed by BMT (≥ 5% difference in incidence) are rash and hypersensitivity
• Undergoing peripheral blood progenitor cell mobilization and collection (≥ 5% incidence) are bone pain, pyrexia, blood alkaline phosphatase increased and headache

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ZARXIO is a registered trademark of Novartis AG.
Neupogen is a registered trademark of Amgen Inc.
UltraSafe Passive is a registered trademark of Safety Syringes, Inc.
Important Safety Information

ADVERSE REACTIONS (cont’d)

- With severe chronic neutropenia (SCN) (≥ 5% difference in incidence) are arthralgia, bone pain, back pain, muscle spasms, musculoskeletal pain, pain in extremity, splenomegaly, anemia, upper respiratory tract infection, urinary tract infection, epistaxis, chest pain, diarrhea, hypoaesthesia, and alopecia

To report SUSPECTED ADVERSE REACTIONS, contact Sandoz Inc. at 1-800-525-8747 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.

References:
6. Effective January 1, 2016, Corresponding Required Modifier when billing Q5101 for Zarxio is ZA-Novartis/Sandoz.

For the ZARXIO prefilled syringe, direct administration of less than 0.3 mL is not recommended.

<table>
<thead>
<tr>
<th>PRODUCT ATTRIBUTES</th>
<th>ZARXIO³</th>
<th>Neupogen® (filgrastim)⁶</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identical routes of administration</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Identical dosing schedules</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Identical dosage strengths</td>
<td>✔️</td>
<td>✔️</td>
</tr>
</tbody>
</table>

HCPCS code Q5101 Injection, Filgrastim (G-CSF), Biosimilar, 1 microgram

Effective January 1, 2016, Corresponding Required Modifier when billing Q5101 for Zarxio is ZA-Novartis/Sandoz.

TRUST the totality of evidence for ZARXIO® (filgrastim-sndz) and the expertise of Sandoz²,³

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Neupogen is a registered trademark of Amgen Inc.