

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ZIEXTENZO safely and effectively. See full prescribing information for ZIEXTENZO.

### ZIEXTENZO® (pegfilgrastim-bmez) injection, for subcutaneous use

Initial U.S. Approval: 2019

ZIEXTENZO (pegfilgrastim-bmez) is biosimilar\* to NEULASTA® (pegfilgrastim).

#### RECENT MAJOR CHANGES

Indications and Usage, Patients with Hematopoietic Subsyndrome of Acute Radiation Syndrome (1.2) 02/2024

Dosage and Administration, Patients with Hematopoietic Subsyndrome of Acute Radiation Syndrome (2.2) 02/2024

#### INDICATIONS AND USAGE

ZIEXTENZO 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. (1.1)
- Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome). (1.2)

#### Limitations of Use

ZIEXTENZO is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.

#### DOSAGE AND ADMINISTRATION

Patients with cancer receiving myelosuppressive chemotherapy

- 6 mg administered subcutaneously once per chemotherapy cycle. (2.1)
- Do not administer between 14 days before and 24 hours after administration of cytotoxic chemotherapy. (2.1)
- Use weight based dosing for pediatric patients weighing less than 45 kg; refer to Table 1. (2.3)

Patients acutely exposed to myelosuppressive doses of radiation

- Two doses, 6 mg each, administered subcutaneously one week apart. Administer the first dose as soon as possible after suspected or confirmed exposure to myelosuppressive doses of radiation, and a second dose one week after. (2.2)
- Use weight based dosing for pediatric patients weighing less than 45 kg; refer to Table 1. (2.3)

#### DOSAGE FORMS AND STRENGTHS

Injection: 6 mg/0.6 mL solution in a single-dose prefilled syringe for manual use only. (3)

## CONTRAINDICATIONS

Patients with a history of serious allergic reactions to human granulocyte colony-stimulating factors such as pegfilgrastim products or filgrastim products. (4)

## WARNINGS AND PRECAUTIONS

- Fatal splenic rupture: Evaluate patients who report left upper abdominal or shoulder pain for an enlarged spleen or splenic rupture. (5.1)
- Acute respiratory distress syndrome (ARDS): Evaluate patients who develop fever, lung infiltrates, or respiratory distress. Discontinue ZIEXTENZO in patients with ARDS. (5.2)
- Serious allergic reactions, including anaphylaxis: Permanently discontinue ZIEXTENZO in patients with serious allergic reactions. (5.3)
- Fatal sickle cell crises: Discontinue ZIEXTENZO if sickle cell crisis occurs. (5.4)
- Glomerulonephritis: Evaluate and consider dose-reduction or interruption of ZIEXTENZO if causality is likely. (5.5)
- Thrombocytopenia: Monitor platelet counts. (5.7)
- Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML): Monitor patients with breast and lung cancer using ZIEXTENZO in conjunction with chemotherapy and/or radiotherapy for signs and symptoms of MDS/AML. (5.10)

## ADVERSE REACTIONS

Most common adverse reactions (≥ 5% difference in incidence compared to placebo) are bone pain and pain in extremity. (6.1)

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).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

\*Biosimilar means that the biological product is approved based on data demonstrating that it is highly similar to an FDA-approved biological product, known as a reference product, and that there are no clinically meaningful differences between the biosimilar product and the reference product. Biosimilarity of ZIEXTENZO has been demonstrated for the condition(s) of use (e.g., indication(s), dosing regimen(s)), strength(s), dosage form(s), and route(s) of administration described in its Full Prescribing Information.

Revised: 02/2024

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## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

#### 1.1 Patients with Cancer Receiving Myelosuppressive Chemotherapy

ZIEXTENZO is 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 [see *Clinical Studies (14.1)*].

##### Limitations of Use

ZIEXTENZO is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.

#### 1.2 Patients with Hematopoietic Subsyndrome of Acute Radiation Syndrome

ZIEXTENZO is indicated to increase survival in patients acutely exposed to myelosuppressive doses of radiation [see *Dosage and Administration (2.2)* and *Clinical Studies (14.2)*].

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Patients with Cancer Receiving Myelosuppressive Chemotherapy

The recommended dosage of ZIEXTENZO is a single subcutaneous injection of 6 mg administered once per chemotherapy cycle. For dosing in pediatric patients weighing less than 45 kg, refer to Table 1. Do not administer ZIEXTENZO between 14 days before and 24 hours after administration of cytotoxic chemotherapy.

#### 2.2 Patients with Hematopoietic Subsyndrome of Acute Radiation Syndrome

The recommended dose of ZIEXTENZO is two doses, 6 mg each, administered subcutaneously one week apart. For dosing in pediatric patients weighing less than 45 kg, refer to Table 1. Administer the first dose as soon as possible after suspected or confirmed exposure to radiation levels greater than 2 gray (Gy). Administer the second dose one week after the first dose.

Obtain a baseline complete blood count (CBC). Do not delay administration of ZIEXTENZO if a CBC is not readily available. Estimate a patient's absorbed radiation dose (i.e., level of radiation exposure) based on information from public health authorities, biodosimetry if available, or clinical findings such as time to onset of vomiting or lymphocyte depletion kinetics.

#### 2.3 Administration

ZIEXTENZO is administered subcutaneously via a single-dose prefilled syringe for manual use.

Prior to use, remove the carton from the refrigerator and allow the ZIEXTENZO prefilled syringe to reach room temperature for a minimum of 15-30 minutes. Discard any prefilled syringe left at room temperature for greater than 120 hours.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. ZIEXTENZO is supplied as a clear and colorless to slightly yellowish solution. Do not administer ZIEXTENZO if discoloration or particulates are observed.

The ZIEXTENZO syringe plunger stopper and needle cap are not made with natural rubber latex.

##### *Pediatric Patients weighing less than 45 kg*

The ZIEXTENZO prefilled syringe is not designed to allow for direct administration of doses less than 0.6 mL (6 mg). The syringe does not bear graduation marks, which are necessary to accurately measure doses of ZIEXTENZO less than 0.6 mL (6 mg) for direct administration to patients. Thus, the direct administration to patients requiring dosing of less than 0.6 mL (6 mg) is not recommended due to the potential for dosing errors. Refer to Table 1.

**Table 1. Dosing of ZIEXTENZO for pediatric patients weighing less than 45 kg**

Body Weight	ZIEXTENZO Dose	Volume to Administer
Less than 10 kg*	See below*	See below*
10 - 20 kg	1.5 mg	0.15 mL
21 - 30 kg	2.5 mg	0.25 mL
31 - 44 kg	4 mg	0.4 mL

\*For pediatric patients weighing less than 10 kg, administer 0.1 mg/kg (0.01 mL/kg) of ZIEXTENZO.

### 3 DOSAGE FORMS AND STRENGTHS

ZIEXTENZO is a clear, colorless to slightly yellowish, preservative-free solution available as:

- Injection: 6 mg/0.6 mL in a single-dose prefilled syringe for manual use only.

### 4 CONTRAINDICATIONS

ZIEXTENZO is contraindicated in patients with a history of serious allergic reactions to pegfilgrastim products or filgrastim products. Reactions have included anaphylaxis [see *Warnings and Precautions (5.3)*].

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 Splenic Rupture

Splenic rupture, including fatal cases, can occur following the administration of pegfilgrastim products. Evaluate for an enlarged spleen or splenic rupture in patients who report left upper abdominal or shoulder pain after receiving ZIEXTENZO.

#### 5.2 Acute Respiratory Distress Syndrome

Acute respiratory distress syndrome (ARDS) can occur in patients receiving pegfilgrastim products. Evaluate patients who develop fever and lung infiltrates or respiratory distress after receiving ZIEXTENZO, for ARDS. Discontinue ZIEXTENZO in patients with ARDS.

#### 5.3 Serious Allergic Reactions

Serious allergic reactions, including anaphylaxis, can occur in patients receiving pegfilgrastim products. The majority of reported events occurred upon initial exposure. Allergic reactions, including anaphylaxis, can recur within days after the discontinuation of initial anti-allergic treatment. Permanently discontinue ZIEXTENZO in patients with serious allergic reactions. Do not administer ZIEXTENZO to patients with a history of serious allergic reactions to pegfilgrastim products or filgrastim products.

#### 5.4 Use in Patients with Sickle Cell Disorders

Severe and sometimes fatal sickle cell crises can occur in patients with sickle cell disorders receiving pegfilgrastim products. Discontinue ZIEXTENZO if sickle cell crisis occurs.

#### 5.5 Glomerulonephritis

Glomerulonephritis has occurred in patients receiving pegfilgrastim 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 pegfilgrastim products. If glomerulonephritis is suspected, evaluate for cause. If causality is likely, consider dose-reduction or interruption of ZIEXTENZO.

#### 5.6 Leukocytosis

White blood cell (WBC) counts of  $100 \times 10^9/L$  or greater have been observed in patients receiving pegfilgrastim products. Monitoring of complete blood count (CBC) during ZIEXTENZO therapy is recommended.

#### 5.7 Thrombocytopenia

Thrombocytopenia has been reported in patients receiving pegfilgrastim products. Monitor platelet counts.

## 5.8 Capillary Leak Syndrome

Capillary leak syndrome has been reported after G-CSF administration, including pegfilgrastim products, and is characterized by hypotension, hypoalbuminemia, edema and hemoconcentration. 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 standard symptomatic treatment, which may include a need for intensive care.

## 5.9 Potential for Tumor Growth Stimulatory Effects on Malignant Cells

The granulocyte colony-stimulating factor (G-CSF) receptor through which pegfilgrastim products and filgrastim products act has been found on tumor cell lines. The possibility that pegfilgrastim products act as a growth factor for any tumor type, including myeloid malignancies and myelodysplasia, diseases for which pegfilgrastim products are not approved, cannot be excluded.

## 5.10 Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML) in Patients with Breast and Lung Cancer

MDS and AML have been associated with the use of pegfilgrastim products in conjunction with chemotherapy and/or radiotherapy in patients with breast and lung cancer. Monitor patients for signs and symptoms of MDS/AML in these settings.

## 5.11 Aortitis

Aortitis has been reported in patients receiving pegfilgrastim products. It may occur as early as the first week after start of therapy. Manifestations may include generalized signs and symptoms such as fever, abdominal pain, malaise, back pain, and increased inflammatory markers (e.g., c-reactive protein and white blood cell count). Consider aortitis in patients who develop these signs and symptoms without known etiology. Discontinue ZIEXTENZO if aortitis is suspected.

## 5.12 Nuclear Imaging

Increased hematopoietic activity of the bone marrow in response to growth factor therapy has been associated with transient positive bone imaging changes. This should be considered when interpreting bone imaging results.

# 6 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in greater detail in other sections of the labeling:

- Splenic Rupture [see Warnings and Precautions (5.1)]
- Acute Respiratory Distress Syndrome [see Warnings and Precautions (5.2)]
- Serious Allergic Reactions [see Warnings and Precautions (5.3)]
- Use in Patients with Sickle Cell Disorders [see Warnings and Precautions (5.4)]
- Glomerulonephritis [see Warnings and Precautions (5.5)]
- Leukocytosis [see Warnings and Precautions (5.6)]
- Thrombocytopenia [see Warnings and Precautions (5.7)]
- Capillary Leak Syndrome [see Warnings and Precautions (5.8)]
- Potential for Tumor Growth Stimulatory Effects on Malignant Cells [see Warnings and Precautions (5.9)]
- Myelodysplastic syndrome [see Warnings and Precautions (5.10)]
- Acute myeloid leukemia [see Warnings and Precautions (5.10)]
- Aortitis [see Warnings and Precautions (5.11)]

## 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Pegfilgrastim clinical trials safety data are based upon 932 patients receiving pegfilgrastim in seven randomized clinical trials. The population was 21 to 88 years of age and 92% female. The ethnicity was 75% Caucasian, 18% Hispanic, 5% Black, and 1% Asian. Patients with breast (n = 823), lung and thoracic tumors (n = 53) and

lymphoma (n = 56) received pegfilgrastim after nonmyeloablative cytotoxic chemotherapy. Most patients received a single 100 mcg/kg (n = 259) or a single 6 mg (n = 546) dose per chemotherapy cycle over 4 cycles.

The following adverse reaction data in Table 2 are from a randomized, double-blind, placebo-controlled study in patients with metastatic or non-metastatic breast cancer receiving docetaxel 100 mg/m<sup>2</sup> every 21 days (Study 3). A total of 928 patients were randomized to receive either 6 mg pegfilgrastim (n = 467) or placebo (n = 461). The patients were 21 to 88 years of age and 99% female. The ethnicity was 66% Caucasian, 31% Hispanic, 2% Black, and < 1% Asian, Native American, or other.

The most common adverse reactions occurring in ≥ 5% of patients and with a between-group difference of ≥ 5% higher in the pegfilgrastim arm in placebo-controlled clinical trials are bone pain and pain in extremity.

**Table 2. Adverse Reactions with ≥ 5% Higher Incidence in Pegfilgrastim Patients Compared to Placebo in Study 3**

Body System Adverse Reaction	Placebo (N = 461)	Pegfilgrastim 6 mg SC on Day 2 (N = 467)
Musculoskeletal and connective tissue disorders		
Bone pain	26%	31%
Pain in extremity	4%	9%

### *Leukocytosis*

In clinical studies, leukocytosis (WBC counts > 100 x 10<sup>9</sup>/L) was observed in less than 1% of 932 patients with non-myeloid malignancies receiving pegfilgrastim. No complications attributable to leukocytosis were reported in clinical studies.

## 6.2 Immunogenicity

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies, including those of pegfilgrastim or of other pegfilgrastim products.

Binding antibodies to pegfilgrastim were detected using a BIAcore assay. The approximate limit of detection for this assay is 500 ng/mL. Pre-existing binding antibodies were detected in approximately 6% (51/849) of patients with metastatic breast cancer. Four of 521 pegfilgrastim-treated subjects who were negative at baseline developed binding antibodies to pegfilgrastim following treatment. None of these 4 patients had evidence of neutralizing antibodies detected using a cell-based bioassay.

## 6.3 Postmarketing Experience

The following adverse reactions have been identified during post approval use of pegfilgrastim products. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Splenic rupture and splenomegaly (enlarged spleen) [see Warnings and Precautions (5.1)]
- Acute respiratory distress syndrome (ARDS) [see Warnings and Precautions (5.2)]
- Allergic reactions/hypersensitivity, including anaphylaxis, skin rash, urticaria, generalized erythema, and flushing [see Warnings and Precautions (5.3)]
- Sick cell crisis [see Warnings and Precautions (5.4)]
- Glomerulonephritis [see Warnings and Precautions (5.5)]
- Leukocytosis [see Warnings and Precautions (5.6)]
- Thrombocytopenia [see Warnings and Precautions (5.7)]
- Capillary Leak Syndrome [see Warnings and Precautions (5.8)]
- Injection site reactions
- Sweet's syndrome (acute febrile neutrophilic dermatosis), cutaneous vasculitis
- Myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) in patients with breast and lung cancer receiving chemotherapy and/or radiotherapy [see Warnings and Precautions (5.10)]
- Aortitis [see Warnings and Precautions (5.11)]
- Alveolar hemorrhage

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

Although available data with ZIEXTENZO or pegfilgrastim product use in pregnant women are insufficient to establish whether there is a drug associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes, there are available data from published studies in pregnant women exposed to filgrastim products. These studies have not established an association of filgrastim product use during pregnancy with major birth defects, miscarriage, or adverse maternal or fetal outcomes.

In animal studies, no evidence of reproductive/developmental toxicity occurred in the offspring of pregnant rats that received cumulative doses of pegfilgrastim approximately 10 times the recommended human dose (based on body surface area). In pregnant rabbits, increased embryoletality and spontaneous abortions occurred at 4 times the maximum recommended human dose simultaneously with signs of maternal toxicity (*see Data*).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

#### Data

##### Animal Data

Pregnant rabbits were dosed with pegfilgrastim subcutaneously every other day during the period of organogenesis. At cumulative doses ranging from the approximate human dose to approximately 4 times the recommended human dose (based on body surface area), the treated rabbits exhibited decreased maternal food consumption, maternal weight loss, as well as reduced fetal body weights and delayed ossification of the fetal skull; however, no structural anomalies were observed in the offspring from either study. Increased incidences of post-implantation losses and spontaneous abortions (more than half the pregnancies) were observed at cumulative doses approximately 4 times the recommended human dose, which were not seen when pregnant rabbits were exposed to the recommended human dose.

Three studies were conducted in pregnant rats dosed with pegfilgrastim at cumulative doses up to approximately 10 times the recommended human dose at the following stages of gestation: during the period of organogenesis, from mating through the first half of pregnancy, and from the first trimester through delivery and lactation. No evidence of fetal loss or structural malformations was observed in any study. Cumulative doses equivalent to approximately 3 and 10 times the recommended human dose resulted in transient evidence of wavy ribs in fetuses of treated mothers (detected at the end of gestation but no longer present in pups evaluated at the end of lactation).

### 8.2 Lactation

#### Risk Summary

There are no data on the presence of pegfilgrastim products in human milk, the effects on the breastfed child, or the effects on milk production. Other filgrastim products are secreted poorly into breast milk, and filgrastim products are not absorbed orally by neonates. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ZIEXTENZO and any potential adverse effects on the breastfed child from ZIEXTENZO or from the underlying maternal condition.

### 8.4 Pediatric Use

The safety and effectiveness of ZIEXTENZO have been established in pediatric patients. No overall differences in safety were identified between adult and pediatric patients based on postmarketing surveillance and review of the scientific literature.

Use of ZIEXTENZO in pediatric patients for chemotherapy-induced neutropenia is based on ZIEXTENZO's approval as a biosimilar to pegfilgrastim and evidence from adequate and well-controlled studies of pegfilgrastim in adults with additional pharmacokinetic and safety data of pegfilgrastim in pediatric patients with sarcoma [*see Clinical Pharmacology (12.3) and Clinical Studies (14.1)*].

The use of ZIEXTENZO to increase survival in pediatric patients acutely exposed to myelosuppressive doses of radiation is based on ZIEXTENZO's approval as a biosimilar to pegfilgrastim and evidence from efficacy studies of pegfilgrastim conducted in animals and clinical data supporting the use of pegfilgrastim in patients

with cancer receiving myelosuppressive chemotherapy. Efficacy studies of pegfilgrastim products could not be conducted in humans with acute radiation syndrome for ethical and feasibility reasons. Results from population modeling and simulation indicate that two doses of pegfilgrastim (Table 1), administered one week apart provide pediatric patients with exposures comparable to that in adults receiving two 6 mg doses one week apart [see *Dosage and Administration (2.3)*, *Clinical Pharmacology (12.3)* and *Clinical Studies (14.2)*].

## 8.5 Geriatric Use

Of the 932 patients with cancer who received pegfilgrastim in clinical studies, 139 (15%) were aged 65 and over, and 18 (2%) were aged 75 and over. No overall differences in safety or effectiveness were observed between patients aged 65 and older and younger patients.

## 10 OVERDOSAGE

Overdosage of pegfilgrastim products may result in leukocytosis and bone pain. Events of edema, dyspnea, and pleural effusion have been reported in a single patient who administered pegfilgrastim on 8 consecutive days in error. In the event of overdose, the patient should be monitored for adverse reactions [see *Adverse Reactions (6)*].

## 11 DESCRIPTION

Pegfilgrastim-bmez is a covalent conjugate of recombinant methionyl human G-CSF and monomethoxypolyethylene glycol. Recombinant methionyl human G-CSF is a water-soluble 175 amino acid protein with a molecular weight of approximately 19 kilodaltons (kD). Recombinant methionyl human G-CSF is obtained from the bacterial fermentation of a strain of *E coli* transformed with a genetically engineered plasmid containing the human G-CSF gene. To produce pegfilgrastim-bmez, a 20 kD monomethoxypolyethylene glycol molecule is covalently bound to the N-terminal methionyl residue of recombinant methionyl human G-CSF. The average molecular weight of pegfilgrastim-bmez is approximately 39 kD.

ZIEXTENZO for manual subcutaneous injection is supplied in 0.6 mL prefilled syringes. The prefilled syringe does not bear graduation marks and is designed to deliver the entire contents of the syringe (6 mg/0.6 mL).

The delivered 0.6 mL dose from the prefilled syringe for manual subcutaneous injection contains 6 mg pegfilgrastim-bmez (based on protein weight) in a sterile, clear, colorless to slightly yellowish, preservative-free solution (pH 4.0, sodium hydroxide may be added as necessary to adjust pH) containing acetic acid (0.36 mg), polysorbate 20 (0.02 mg), sorbitol (30 mg), and Water for Injection, USP.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Pegfilgrastim products are colony-stimulating factors that act on hematopoietic cells by binding to specific cell surface receptors, thereby stimulating proliferation, differentiation, commitment, and end cell functional activation.

### 12.2 Pharmacodynamics

Animal data and clinical data in humans suggest a correlation between pegfilgrastim products' exposure and the duration of severe neutropenia as a predictor of efficacy. Selection of the dosing regimen of ZIEXTENZO is based on reducing the duration of severe neutropenia.

### 12.3 Pharmacokinetics

The pharmacokinetics of pegfilgrastim was studied in 379 patients with cancer. The pharmacokinetics of pegfilgrastim was nonlinear, and clearance decreased with increases in dose. Neutrophil receptor binding is an important component of the clearance of pegfilgrastim, and serum clearance is directly related to the number of neutrophils. In addition to numbers of neutrophils, body weight appeared to be a factor. Patients with higher body weights experienced higher systemic exposure to pegfilgrastim after receiving a dose normalized for body weight. A large variability in the pharmacokinetics of pegfilgrastim was observed. The half-life of pegfilgrastim ranged from 15 to 80 hours after subcutaneous injection.

#### *Specific Populations*



No gender-related differences were observed in the pharmacokinetics of pegfilgrastim, and no differences were observed in the pharmacokinetics of geriatric patients ( $\geq 65$  years of age) compared with younger patients ( $< 65$  years of age) [see *Use in Specific Populations (8.5)*].

### Renal Impairment

In a study of 30 subjects with varying degrees of renal dysfunction, including end stage renal disease, renal dysfunction had no effect on the pharmacokinetics of pegfilgrastim.

### Pediatric Patients with Cancer Receiving Myelosuppressive Chemotherapy

The pharmacokinetics and safety of pegfilgrastim were studied in 37 pediatric patients with sarcoma in Study 4 [see *Clinical Studies 14.1*]. The mean ( $\pm$  standard deviation [SD]) systemic exposure ( $AUC_{0-inf}$ ) of pegfilgrastim after subcutaneous administration at 100 mcg/kg was 47.9 ( $\pm 22.5$ ) mcg·hr/mL in the youngest age group (0 to 5 years, n = 11), 22.0 ( $\pm 13.1$ ) mcg·hr/mL in the 6 to 11 years age group (n = 10), and 29.3 ( $\pm 23.2$ ) mcg·hr/mL in the 12 to 21 years age group (n = 13). The terminal elimination half-lives of the corresponding age groups were 30.1 ( $\pm 38.2$ ) hours, 20.2 ( $\pm 11.3$ ) hours, and 21.2 ( $\pm 16.0$ ) hours, respectively.

### Patients Acutely Exposed to Myelosuppressive Doses of Radiation

The pharmacokinetics of pegfilgrastim products is not available in patients acutely exposed to myelosuppressive doses of radiation. Based on limited pharmacokinetic data in irradiated non-human primates, the area under the concentration-time curve (AUC), reflecting the exposure to pegfilgrastim in non-human primates following a 300 mcg/kg dose of pegfilgrastim, appears to be greater than in humans receiving a 6 mg dose. Results from population modeling and simulation indicate that two 6 mg doses of pegfilgrastim administered one week apart in adults result in clinically relevant effects on duration of grade 3 and 4 neutropenia. In addition, weight based dosing in pediatric patients weighing less than 45 kg [see *Dosage and Administration, Section 2.3, Table 1*] provides exposures comparable to those in adults receiving two 6 mg doses one week apart.

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

No carcinogenicity or mutagenesis studies have been performed with pegfilgrastim products.

Pegfilgrastim did not affect reproductive performance or fertility in male or female rats at cumulative weekly doses approximately 6 to 9 times higher than the recommended human dose (based on body surface area).

## **14 CLINICAL STUDIES**

### **14.1 Patients with Cancer Receiving Myelosuppressive Chemotherapy**

Pegfilgrastim was evaluated in three randomized, double-blind, controlled studies. Studies 1 and 2 were active-controlled studies that employed doxorubicin 60 mg/m<sup>2</sup> and docetaxel 75 mg/m<sup>2</sup> administered every 21 days for up to 4 cycles for the treatment of metastatic breast cancer. Study 1 investigated the utility of a fixed dose of pegfilgrastim. Study 2 employed a weight-adjusted dose. In the absence of growth factor support, similar chemotherapy regimens have been reported to result in a 100% incidence of severe neutropenia ( $ANC < 0.5 \times 10^9/L$ ) with a mean duration of 5 to 7 days and a 30% to 40% incidence of febrile neutropenia. Based on the correlation between the duration of severe neutropenia and the incidence of febrile neutropenia found in studies with filgrastim, duration of severe neutropenia was chosen as the primary endpoint in both studies, and the efficacy of pegfilgrastim was demonstrated by establishing comparability to filgrastim-treated patients in the mean days of severe neutropenia.

In Study 1, 157 patients were randomized to receive a single subcutaneous injection of pegfilgrastim (6 mg) on day 2 of each chemotherapy cycle or daily subcutaneous filgrastim (5 mcg/kg/day) beginning on day 2 of each chemotherapy cycle. In Study 2, 310 patients were randomized to receive a single subcutaneous injection of pegfilgrastim (100 mcg/kg) on day 2 or daily subcutaneous filgrastim (5 mcg/kg/day) beginning on day 2 of each chemotherapy cycle.

Both studies met the major efficacy outcome measure of demonstrating that the mean days of severe neutropenia of pegfilgrastim-treated patients did not exceed that of filgrastim-treated patients by more than 1 day in cycle 1 of chemotherapy. The mean days of cycle 1 severe neutropenia in Study 1 were 1.8 days in the pegfilgrastim arm compared to 1.6 days in the filgrastim arm [difference in means 0.2 (95% CI -0.2, 0.6)] and in Study 2 were 1.7 days in the pegfilgrastim arm compared to 1.6 days in the filgrastim arm [difference in means 0.1 (95% CI - 0.2, 0.4)].

A secondary endpoint in both studies was days of severe neutropenia in cycles 2 through 4 with results similar to those for cycle 1.

Study 3 was a randomized, double-blind, placebo-controlled study that employed docetaxel 100 mg/m<sup>2</sup> administered every 21 days for up to 4 cycles for the treatment of metastatic or non-metastatic breast cancer. In this study, 928 patients were randomized to receive a single subcutaneous injection of pegfilgrastim (6 mg) or placebo on day 2 of each chemotherapy cycle. Study 3 met the major trial outcome measure of demonstrating that the incidence of febrile neutropenia (defined as temperature  $\geq 38.2^{\circ}\text{C}$  and ANC  $\leq 0.5 \times 10^9/\text{L}$ ) was lower for pegfilgrastim-treated patients as compared to placebo-treated patients (1% versus 17%, respectively,  $p < 0.001$ ). The incidence of hospitalizations (1% versus 14%) and IV anti-infective use (2% versus 10%) for the treatment of febrile neutropenia was also lower in the pegfilgrastim-treated patients compared to the placebo-treated patients.

Study 4 was a multicenter, randomized, open-label study to evaluate the efficacy, safety, and pharmacokinetics [see *Clinical Pharmacology (12.3)*] of pegfilgrastim in pediatric and young adult patients with sarcoma. Patients with sarcoma receiving chemotherapy age 0 to 21 years were eligible. Patients were randomized to receive subcutaneous pegfilgrastim as a single-dose of 100 mcg/kg ( $n = 37$ ) or subcutaneous filgrastim at a dose 5 mcg/kg/day ( $n = 6$ ) following myelosuppressive chemotherapy. Recovery of neutrophil counts was similar in the pegfilgrastim and filgrastim groups. The most common adverse reaction reported was bone pain.

## 14.2 Patients with Hematopoietic Subsyndrome of Acute Radiation Syndrome

Efficacy studies of pegfilgrastim products could not be conducted in humans with acute radiation syndrome for ethical and feasibility reasons. Approval of this indication was based on efficacy studies conducted in animals and data supporting pegfilgrastim's effect on severe neutropenia in patients with cancer receiving myelosuppressive chemotherapy [see *Dosage and Administration (2.1)*].

The recommended dose of ZIEXTENZO is two doses, 6 mg each, administered one week apart for humans exposed to myelosuppressive doses of radiation. For pediatric patients weighing less than 45 kg, dosing of ZIEXTENZO is weight based and is provided in Table 1 [see *Dosage and Administration (2.3)*]. This dosing regimen is based on population modeling and simulation analyses. The exposure associated with this dosing regimen is expected to provide sufficient pharmacodynamic activity to treat humans exposed to myelosuppressive doses of radiation [see *Clinical Pharmacology (12.3)*]. The safety of pegfilgrastim at a dose of 6 mg has been assessed on the basis of clinical experience in patients with cancer receiving myelosuppressive chemotherapy.

The efficacy of pegfilgrastim for the acute radiation syndrome setting was studied in a randomized, placebo-controlled non-human primate model of radiation injury. Rhesus macaques were randomized to either a control ( $n = 23$ ) or treated ( $n = 23$ ) cohort. On study day 0, animals ( $n = 6$  to 8 per irradiation day) were exposed to total body irradiation (TBI) of  $7.50 \pm 0.15$  Gy delivered at  $0.8 \pm 0.03$  Gy/min, representing a dose that would be lethal in 50% of animals by 60 days of follow-up (LD50/60). Animals were administered subcutaneous injections of a blinded treatment (control article [5% dextrose in water] or pegfilgrastim [300-319 mcg/kg/day]) on study day 1 and on study day 8. The primary endpoint was survival. Animals received medical management consisting of intravenous fluids, antibiotics, blood transfusions, and other support as required.

Pegfilgrastim significantly (at 0.0014 level of significance) increased 60-day survival in irradiated non-human primates: 91% survival (21/23) in the pegfilgrastim group compared to 48% survival (11/23) in the control group.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

### ZIEXTENZO single-dose prefilled syringe for manual use

ZIEXTENZO injection is a clear, colorless to slightly yellowish solution supplied in a prefilled single-dose syringe for manual use containing 6 mg pegfilgrastim-bmez, supplied with a 29-gauge, 1/2-inch needle with an UltraSafe Passive<sup>TM</sup> Needle Guard.

The ZIEXTENZO syringe plunger stopper and needle cap are not made with natural rubber latex.

ZIEXTENZO is provided in a dispensing pack containing one sterile 6 mg/0.6 mL prefilled syringe (NDC 61314-866-02).

ZIEXTENZO 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 refrigerated between 36°F to 46°F (2°C to 8°C) in the carton to protect from light. Do not shake. Discard syringes stored at room temperature for more than 120 hours. Avoid freezing; if frozen, thaw in the refrigerator before administration. Discard syringe if frozen more than once.

## **17 PATIENT COUNSELING INFORMATION**

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Advise patients of the following risks and potential risks with ZIEXTENZO:

- Splenic rupture and splenomegaly
- Acute Respiratory Distress Syndrome
- Serious allergic reactions
- Sickle cell crisis
- Glomerulonephritis
- Increased risk of Myelodysplastic Syndrome and/or Acute Myeloid Leukemia in patients with breast and lung cancer who receive ZIEXTENZO in conjunction with chemotherapy and/or radiation therapy
- Capillary Leak Syndrome
- Aortitis

Advise patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome) that efficacy studies of pegfilgrastim products for this indication could not be conducted in humans for ethical and feasibility reasons and that, therefore, approval of this use was based on efficacy studies conducted in animals [*see Clinical Studies (14.2)*].

Instruct patients who self-administer ZIEXTENZO using the single-dose prefilled syringe of the:

- Importance of following the Instructions for Use (see Instructions for Use).
- Dangers of reusing syringes.
- Importance of following local requirements for proper disposal of used syringes.

Manufactured by:  
Sandoz Inc.  
Princeton, NJ 08540  
US License No. 2003

**Patient Information**

ZIEXTENZO (zee-eks -TEN-zoh)  
(pegfilgrastim-bmez)  
injection  
Single-dose prefilled syringe

**What is ZIEXTENZO?**

ZIEXTENZO is a man-made form of granulocyte colony-stimulating factor (G-CSF). G-CSF is a substance produced by the body. It stimulates the growth of neutrophils, a type of white blood cell important in the body's fight against infection. Acute Radiation Syndrome: The effectiveness of pegfilgrastim for this use was only studied in animals, because it could not be studied in people.

**Do not take ZIEXTENZO** if you have had a serious allergic reaction to pegfilgrastim products or filgrastim products.

**Before you receive ZIEXTENZO, tell your healthcare provider about all of your medical conditions, including if you:**

- have a sickle cell disorder.
- have kidney problems.
- are pregnant or plan to become pregnant. It is not known if ZIEXTENZO will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if ZIEXTENZO passes into your breast milk.

**Tell your healthcare provider about all of the medicines you take**, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

**How will I receive ZIEXTENZO?**

- **ZIEXTENZO is given as an injection under your skin (subcutaneous injection) by a healthcare provider. If your healthcare provider decides that the subcutaneous injections can be given at home by you or your caregiver, follow the detailed "Instructions for Use" that comes with your ZIEXTENZO for information on how to prepare and inject a dose of ZIEXTENZO.**
- You and your caregiver will be shown how to prepare and inject ZIEXTENZO before you use it.
- You should not inject a dose of ZIEXTENZO to children weighing less than 45 kg from a ZIEXTENZO prefilled syringe. A dose less than 0.6 mL (6 mg) cannot be accurately measured using the ZIEXTENZO prefilled syringe.
- If you are receiving ZIEXTENZO because you are also receiving chemotherapy, the last dose of ZIEXTENZO should be injected at least 14 days before and 24 hours after your dose of chemotherapy.
- If you miss a dose of ZIEXTENZO, talk to your healthcare provider about when you should give your next dose.

**What are possible side effects of ZIEXTENZO?**

**ZIEXTENZO may cause serious side effects, including:**

- **Spleen Rupture.** Your spleen may become enlarged and can rupture. A ruptured spleen can cause death. Call your healthcare provider right away if you have pain in the left upper stomach area or your left shoulder.
- **A serious lung problem called Acute Respiratory Distress Syndrome (ARDS).** Call your healthcare provider or get emergency help right away if you have shortness of breath with or without a fever, trouble breathing, or a fast rate of breathing.
- **Serious allergic reactions.** ZIEXTENZO can cause serious allergic reactions. These reactions can cause a rash over your whole body, shortness of breath, wheezing, dizziness, swelling around your mouth or eyes, fast heart rate, and sweating. If you have any of these symptoms, stop using ZIEXTENZO and call your healthcare provider or get emergency medical help right away.
- **Sickle cell crises.** You may have a serious sickle cell crisis, which could lead to death, if you have a sickle cell disorder and receive ZIEXTENZO. Call your healthcare provider right away if you have symptoms of sickle cell crisis such as pain or difficulty breathing.
- **Kidney injury (glomerulonephritis).** ZIEXTENZO can cause kidney injury. Call your healthcare provider right away if you develop any of the following symptoms:
  - swelling of your face or ankles
  - blood in your urine or dark colored urine
  - you urinate less than usual
- **Increased white blood cell count (leukocytosis).** Your healthcare provider will check your blood during treatment with ZIEXTENZO.
- **Decreased platelet count (thrombocytopenia).** Your healthcare provider will check your blood during treatment with ZIEXTENZO. Tell your healthcare provider if you have unusual bleeding or bruising during treatment with ZIEXTENZO. This could be a sign of decreased platelet counts, which may reduce the ability of your blood to clot.

- **Capillary Leak Syndrome.** ZIEXTENZO can cause fluid to leak from blood vessels into your body's tissues. This condition is called "Capillary Leak Syndrome" (CLS). CLS can quickly cause you to have symptoms that may become life-threatening. Get emergency medical help right away if you develop any of the following symptoms:
  - swelling or puffiness and are urinating less than usual
  - trouble breathing
  - swelling of your stomach area (abdomen) and feeling of fullness
  - dizziness or feeling faint
  - a general feeling of tiredness

• **Myelodysplastic syndrome and acute myeloid leukemia.** If you have breast cancer or lung cancer, when ZIEXTENZO is used with chemotherapy and radiation therapy, or with radiation therapy alone, you may have an increased risk of developing a precancerous blood condition called myelodysplastic syndrome (MDS) or a blood cancer called acute myeloid leukemia (AML). Symptoms of MDS and AML may include tiredness, fever, and easy bruising or bleeding. Call your healthcare provider if you develop these symptoms during treatment with ZIEXTENZO.

• **Inflammation of the aorta (aortitis).** Inflammation of the aorta (the large blood vessel which transports blood from the heart to the body) has been reported in patients who received pegfilgrastim products. Symptoms may include fever, abdominal pain, feeling tired, and back pain. Call your healthcare provider if you experience these symptoms.

The most common side effects of ZIEXTENZO are pain in the bones, arms, and legs.

These are not all the possible side effects of ZIEXTENZO.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

#### **How should I store ZIEXTENZO?**

- Store ZIEXTENZO in the refrigerator between 36°F to 46°F (2°C to 8°C).
- Take ZIEXTENZO out of the refrigerator for at least 15 to 30 minutes before use and allow it to reach room temperature before preparing an injection.
- Avoid freezing. If ZIEXTENZO is accidentally frozen, allow the prefilled syringe to thaw in the refrigerator before injecting.
- Do not use a ZIEXTENZO prefilled syringe that has been frozen more than 1 time. Use a new ZIEXTENZO prefilled syringe.
- Keep the prefilled syringe in the original carton to protect from light or physical damage.
- Do not shake the prefilled syringe.
- Throw away (dispose of) any ZIEXTENZO that has been left at room temperature, 68°F to 95°F (20°C to 35°C), for more than 120 hours.

**Keep the ZIEXTENZO prefilled syringe out of the reach of children.**

#### **General information about the safe and effective use of ZIEXTENZO.**

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use ZIEXTENZO for a condition for which it was not prescribed. Do not give ZIEXTENZO to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about ZIEXTENZO that is written for health professionals.

#### **What are the ingredients in ZIEXTENZO?**

Active ingredient: pegfilgrastim-bmez

Inactive ingredients: acetic acid, polysorbate 20, sorbitol, and Water for Injection. Sodium hydroxide may be added as necessary to adjust pH.

Manufactured by: Sandoz Inc. Princeton, NJ 08540 US License No. 2003

For more information, visit [www.ziextenzo.com](http://www.ziextenzo.com) or call 1-800-525-8747

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
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