PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]**Pexegra™**

Pegfilgrastim injection

Sterile Solution, 6 mg in 0.6 mL solution (10 mg/mL)

Subcutaneous Use Only

Professed Standard

Hematopoietic Agent

Granulocyte Colony-Stimulating Factor (G-CSF)

ATC Code: L03AA02

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Date of Initial Approval:
DEC 13, 2024

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RECENT MAJOR LABEL CHANGES

Not applicable.

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Sections or subsections that are not applicable at the time of authorization are not listed.

Pexegra (pegfilgrastim injection) is a biosimilar drug (biosimilar) to Neulasta®.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Pexegra (pegfilgrastim injection) is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-neoplastic drugs.

1.1 Pediatrics (< 18 years of age)

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

2 CONTRAINDICATIONS

Pexegra (pegfilgrastim) is contraindicated in patients with known hypersensitivity to *E. coli*-derived products, pegfilgrastim, filgrastim, or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Splenic rupture, including fatal cases, has been reported following the administration of pegfilgrastim and its parent compound, filgrastim (see 7 WARNINGS AND PRECAUTIONS, General).
- Severe sickle cell crises have been associated with the use of pegfilgrastim in patients with sickle cell trait or sickle cell disease. Severe sickle cell crises, in some cases resulting in death, have also been associated with filgrastim, the parent compound of pegfilgrastim (see 7 WARNINGS AND PRECAUTIONS, Hematologic).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Pexegra (pegfilgrastim) should be administered no sooner than 24 hours after the administration of cytotoxic chemotherapy and no later than 14 days before subsequent administration of cytotoxic chemotherapy (see 7 WARNINGS AND PRECAUTIONS).

Renal impairment, including end-stage renal disease, appears to have no effect on the pharmacokinetics of pegfilgrastim and no dosage adjustment is required.

4.2 Recommended Dose and Dosage Adjustment

The recommended dosage of Pexegra is a single subcutaneous injection of 6 mg, administered once per cycle of chemotherapy. Pexegra should be administered no sooner than 24 hours after the

administration of cytotoxic therapy and no later than 14 days before subsequent administration of cytotoxic chemotherapy (see 7 WARNINGS AND PRECAUTIONS).

4.3 Reconstitution

Not applicable. Product does not need to be reconstituted.

4.4 Administration

Pexegra is intended for subcutaneous injection only and should not be given by any other route of administration. Pexegra should not be mixed with any diluents.

Pexegra should not be vigorously shaken.

Pexegra is supplied in prefilled syringes with an UltraSafe Plus™ Passive Needle Guard. Following administration of Pexegra from the prefilled syringe, the Needle Guard is automatically activated to cover the needle after the injection is given. The prefilled syringe should be disposed of by placing the entire prefilled syringe with activated Needle Guard into a sharps disposal container.

4.5 Missed Dose

If a scheduled dose is missed, Pexegra should not be administered less than 14 days before subsequent administration of cytotoxic chemotherapy.

5 OVERDOSAGE

The maximum tolerated dose of Pexegra (pegfilgrastim) has not been determined in humans. Pegfilgrastim administered at a dose of 300 mcg/kg (n = 12), approximately three times the recommended dose, exhibited an adverse event profile similar to that observed at the recommended dose.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To ensure the traceability of biologic products, health professionals should record the brand name, the non-proprietary (active ingredient) name and other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Subcutaneous	Sterile solution for Injection / 6 mg/0.6 mL (10 mg/mL)	Acetic acid, polysorbate 20, sodium hydroxide, sorbitol, water for injection

Pexegra is a sterile, clear, colourless to slightly yellow, preservative-free liquid for subcutaneous injection, formulated at pH 4.0. Each single-use syringe (0.6 mL) of Pexegra (10 mg/mL) contains pegfilgrastim (6 mg), acetic acid (0.36 mg), polysorbate 20 (0.02 mg), sodium hydroxide (0.03 mg), sorbitol (30 mg) and water for injection.

Availability of Dosage Forms

Pexegra is supplied as a preservative-free solution (0.6 mL) of pegfilgrastim (10 mg/mL) in a single-dose prefilled syringe with a 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.

To reduce the risk of accidental needle sticks to users, each single-use prefilled syringe is equipped with an UltraSafe Plus™ Passive Needle Guard that is automatically activated to cover the needle after injection.

Pexegra is provided as a blistered prefilled syringe packaged in a carton containing one sterile prefilled syringe.

Description

Pexegra (pegfilgrastim) is a polyethylene glycol modified (PEGylated) non-glycosylated form of recombinant human granulocyte colony-stimulating factor (filgrastim) with an additional N-terminal methionine. Pexegra is derived from filgrastim (rhG-CSF) by the covalent attachment of linear polyethylene glycol (PEG) molecule with approximate molecular weight of 20 kDa to the N-terminal methionine by a secondary amine linkage. Filgrastim is expressed in *Escherichia coli* (*E. coli*) as a 175 amino acid protein with a molecular weight of approximately 19 kDa. Pexegra (pegfilgrastim) has an approximate weight of 39 kDa.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

Pexegra (pegfilgrastim) has not been evaluated for PBPC (peripheral blood progenitor cell) mobilization. Therefore, it should not be used in that setting.

Splenic Rupture

Splenic rupture, including fatal cases, has been reported following the administration of pegfilgrastim and its parent compound, filgrastim. Patients received Pexegra who report left upper abdominal and/or shoulder tip pain should be evaluated for an enlarged spleen or splenic rupture.

Simultaneous Use with Chemotherapy and Radiation Therapy

The safety and efficacy of pegfilgrastim administered concurrently with cytotoxic chemotherapy have not been established. Because of the potential for an increased in sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy, Pexegra should not be administered in the period between 14 days before and 24 hours after administration of cytotoxic chemotherapy (see 4 DOSAGE AND ADMINISTRATION).

The safety and efficacy of pegfilgrastim have not been evaluated in patients receiving chemotherapy associated with delayed myelosuppression (e.g., nitrosoureas), mitomycin C, or myelosuppressive doses of anti-metabolites such as 5-fluorouracil (5-FU). Concomitant use of Pexegra with 5-FU or anti-metabolites has not been evaluated in humans, although it has been studied and shown to potentiate myelosuppression in animal models (see 16 NON-CLINICAL TOXICOLOGY).

The safety and efficacy of pegfilgrastim has not been evaluated in patients receiving radiation therapy, except for patients with breast or lung cancer.

Carcinogenesis and Mutagenesis

No carcinogenesis or mutagenesis studies were conducted with Pexegra.

Potential Effect on Malignant Cells

Pexegra (pegfilgrastim) and filgrastim are growth factors that primarily stimulate production of neutrophils and neutrophil precursors by binding to the G-CSF receptor. Overall, the possibility that Pexegra can act as a growth factor for any tumor type cannot be excluded. The use of Pexegra in chronic myeloid leukemia (CML) and myelodysplastic syndrome (MDS) has not been studied.

MDS and AML in Breast and Lung Cancer Patients

In the post-marketing observational study setting, findings showed that pegfilgrastim is associated with an increased risk of MDS and AML in breast and lung cancer patients when used in conjunction with chemotherapy and/or radiotherapy. Monitor patients for signs and symptoms of MDS/AML in these settings.

Cardiovascular

Aortitis

Aortitis has been reported in patients receiving pegfilgrastim and may present with generalized signs and symptoms such as fever and increased inflammatory markers. Consider aortitis in patients who develop these signs and symptoms without known etiology.

Capillary Leak Syndrome

Capillary leak syndrome (CLS) has been reported after the administration of pegfilgrastim or filgrastim. CLS can cause circulatory shock and may be fatal, 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 treatment, which may include a need for intensive care.

Hematologic

Sickle Cell Crises

Severe sickle cell crises have been associated with the use of pegfilgrastim in patients with sickle cell trait or sickle cell disease. Severe sickle cell crises, in some cases resulting in death, have also been associated with filgrastim, the parent compound of pegfilgrastim. Only physicians qualified by specialized training or experience in the treatment of patients with sickle cell trait and sickle cell disease should prescribe Pexegra for such patients, and only after careful consideration of the potential risks and benefits.

Leukocytosis

In clinical studies with pegfilgrastim, white blood cell counts of 100 x 10^9/L or greater have been reported in less than 1% of patients with cancer receiving myelosuppressive chemotherapy (n = 930) and were not associated with any reported adverse clinical effects (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests). In studies of pegfilgrastim administration after chemotherapy, most reported side effects were consistent with those usually seen as a result of cytotoxic chemotherapy (see 8 ADVERSE REACTIONS). Because of the potential for patients to receive

full doses of chemotherapy on the prescribed schedule, patients may be at greater risk of thrombocytopenia, anemia, and nonhematologic consequences of increased chemotherapy doses (please refer to the prescribing information for specific chemotherapy agents). Regular monitoring of hematocrit value and platelet count is recommended. Furthermore, care should be exercised in the administration of Pexegra in conjunction with drugs known to lower platelet count.

Thrombocytopenia

Thrombocytopenia, including serious events, has been reported in patients receiving pegfilgrastim. Platelet counts should be monitored regularly as clinically indicated.

Immune

Hypersensitivity/Allergic Reactions

Hypersensitivity, including serious allergic reactions and anaphylactic reactions, skin rash, urticaria and erythema/flushing occurring on initial or subsequent treatment have been reported both with pegfilgrastim and filgrastim. In some cases, symptoms have recurred with re-challenge, suggesting a causal relationship. In rare cases, allergic reactions, including anaphylactic reactions, recurred within days after initial anti-allergic treatment was discontinued. If a serious allergic reaction or an anaphylactic reaction occurs, appropriate therapy should be administered, and further use of Pexegra should be discontinued. Antibodies to filgrastim or pegfilgrastim have been reported, although no neutralizing antibodies have been reported (see 8 ADVERSE REACTIONS; Immunogenicity). Do not administer Pexegra to patients with a history of hypersensitivity to filgrastim or pegfilgrastim.

Cutaneous Vasculitis

Uncommon (≥ 1/1,000 to < 1/100) events of cutaneous vasculitis have been reported in patients treated with pegfilgrastim. The mechanism of vasculitis in patients receiving pegfilgrastim is unknown.

Monitoring and Laboratory Tests

To assess a patient's hematologic status and ability to tolerate myelosuppressive chemotherapy, a complete blood count (CBC) and platelet count should be obtained before chemotherapy is administered. Pegfilgrastim produced ANC (absolute neutrophil count) profiles similar to daily filgrastim, including earlier ANC nadir, shorter duration of severe neutropenia, and accelerated ANC recovery, compared with ANC profiles observed without growth factor support. Regular monitoring of hematocrit value, white blood cell count and platelet count, as clinically indicated, is recommended.

Renal

Glomerulonephritis

Glomerulonephritis has been reported in patients receiving filgrastim and pegfilgrastim. Generally, events of glomerulonephritis resolved after dose reduction or withdrawal of filgrastim and pegfilgrastim. Urinalysis monitoring is recommended.

Reproductive Health: Female and Male Potential

- **Fertility**

  No studies evaluating reproduction in humans were conducted with Pexegra.

- **Function**

  No studies evaluating sexual function in humans were conducted with Pexegra.

Respiratory

Acute Respiratory Distress Syndrome (ARDS)

Acute respiratory distress syndrome (ARDS) has been reported following administration of pegfilgrastim and is postulated to be secondary to an influx of neutrophils to sites of inflammation in the lungs. Neutropenic patients receiving Pexegra who develop fever, lung infiltrates, or respiratory distress should be evaluated for the possibility of ARDS. In the event that ARDS occurs, Pexegra should be discontinued and/or withheld until resolution of ARDS and patients should receive appropriate medical management for this condition.

7.1 Special Populations

7.1.1 Pregnant Women

There were no pregnant women exposed to pegfilgrastim in clinical trials. Pexegra should be used during pregnancy only if the potential benefit outweighs the risk to the fetus (see 16 NON-CLINICAL TOXICOLOGY).

7.1.2 Breast-feeding

It is not known whether pegfilgrastim is excreted in human milk. Because many drugs are excreted in human milk, Pexegra is not recommended for women who are breastfeeding. Pexegra should only be administered to a nursing woman if the potential benefit outweighs the risk.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): The safety and effectiveness of pegfilgrastim in pediatric patients have not been established.

7.1.4 Geriatrics

Geriatrics (> 65 years of age): Of the total number of subjects with cancer who received pegfilgrastim in clinical studies (n = 930), 139 subjects (15%) were 65 years or older and 18 subjects (2%) were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients; however, due to the small number of elderly subjects, small but clinically relevant differences cannot be excluded.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The most frequently reported study drug-related adverse event was bone pain, for which the incidence in patients treated with pegfilgrastim was similar to that in patients treated with filgrastim. Bone pain was generally reported as mild-to-moderate, could be controlled in most patients with non-narcotic analgesia.

See 7 WARNINGS AND PRECAUTIONS regarding Splenic Rupture, ARDS, Hypersensitivity/Allergic Reactions, and Sickle Cell Crises.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Safety data are based on 7 randomized clinical trials involving 932 patients with lymphoma and solid tumours (breast and thoracic) who received pegfilgrastim after nonmyeloablative cytotoxic chemotherapy. Common adverse events occurred at similar rates between the treatment arms in both the filgrastim-controlled trials (pegfilgrastim, n = 465; filgrastim, n = 331) and the placebo-controlled trial (pegfilgrastim, n = 467; placebo, n = 461). Most adverse experiences were attributed by the investigator as the sequelae of the underlying malignancy or cytotoxic chemotherapy. In the filgrastim-controlled trials, these adverse experiences occurred at rates between 15% and 72% and included: nausea, fatigue, alopecia, diarrhea, vomiting, constipation, fever, anorexia, skeletal pain, headache, taste perversion, dyspepsia, myalgia, insomnia, abdominal pain, arthralgia, generalized weakness, peripheral edema, dizziness, granulocytopenia, stomatitis, mucositis and neutropenic fever. A summary of the most frequently reported adverse reactions in these randomized clinical trials can be found in Table 2 and 3.

In clinical trials comparing pegfilgrastim to filgrastim, medullary bone pain was reported in 26% of pegfilgrastim-treated patients, which was comparable to the incidence in filgrastim-treated patients. In the study comparing pegfilgrastim to placebo, the incidence of bone pain was 23% vs. 16%, respectively. This bone pain was generally reported to be of mild-to-moderate severity. Approximately 17% (for all bone pain type AEs; 10% for specifically “bone pain”) of all subjects utilized non-narcotic analgesics and less than 6% utilized narcotic analgesics in association with bone pain. No patient withdrew from study due to bone pain.

Across all studies, no life-threatening or fatal adverse events were attributed to pegfilgrastim. There was only one serious adverse event (dyspnea) reported as possibly related to pegfilgrastim in a single patient. No events of pleuritis, pericarditis, or other major systemic reactions to pegfilgrastim were reported.

No clinically significant changes in vital signs were observed. No evidence of interaction of pegfilgrastim with other drugs was observed in the course of clinical trials (see 7 WARNINGS AND PRECAUTIONS).

Table 2 – Most Frequently* Reported Adverse Reactions in Randomized Clinical Trials with Filgrastim as Comparator

Body System and Preferred Term	Pegfilgrastim n = 465 (%)	Filgrastim n = 331 (%)
Application Site		
Injection Site Pain	16 (3%)	9 (3%)

Body System and Preferred Term	Pegfilgrastim n = 465 (%)	Filgrastim n = 331 (%)
Body as a Whole		
Pain	8 (2%)	4 (1%)
Chest Pain (Non-Cardiac)	4 (1%)	3 (1%)
Edema Periorbital	3 (1%)	0 (0%)
Fever	3 (1%)	4 (1%)
CNS/PNS		
Headache	20 (4%)	12 (4%)
Musculoskeletal		
Skeletal Pain	96 (21%)	89 (27%)
Myalgia	32 (7%)	25 (8%)
Arthralgia	27 (6%)	19 (6%)
Back Pain	19 (4%)	26 (8%)
Limb Pain	12 (3%)	7 (2%)
Musculoskeletal Pain	5 (1%)	4 (1%)
Neck Pain	4 (1%)	3 (1%)

* Most frequently reported events were considered to be those events reported in ≥ 1% of the patients in the pegfilgrastim group.

Table 3 – Most Frequently* Reported Adverse Reactions in Randomized Clinical Trials with Placebo Control

Body System and Preferred Term	Pegfilgrastim n = 467 (%)	Placebo n = 461 (%)
Blood and Lymphatic System Disorders		
Leukocytosis	5 (1%)	1 (0%)
Gastrointestinal Disorders		
Diarrhea	9 (2%)	10 (2%)
General Disorders and Administration Site Conditions		
Pyrexia	8 (2%)	9 (2%)
Fatigue	3 (1%)	5 (1%)
Infections and Infestations		
Influenza	6 (1%)	5 (1%)

Body System and Preferred Term	Pegfilgrastim n = 467 (%)	Placebo n = 461 (%)
Musculoskeletal and Connective Tissue Disorders		
Bone Pain	62 (13%)	41 (9%)
Myalgia	26 (6%)	23 (5%)
Arthralgia	32 (7%)	19 (4%)
Polymyalgia	8 (2%)	7 (2%)
Musculoskeletal Pain	14 (3%)	5 (1%)
Pain in Limb	11 (2%)	5 (1%)
Back Pain	8 (2%)	4 (1%)
Polyarthralgia	5 (1%)	0 (0%)
Nervous System Disorders		
Headache	6 (1%)	2 (0%)
Skin and Subcutaneous Tissue Disorders		
Alopecia	8 (2%)	9 (2%)

* Most frequently reported adverse events were those reported in ≥ 1% of the patients in the pegfilgrastim group.

8.3 Less Common Clinical Trial Adverse Reactions

The following adverse drug reactions were reported at an incidence of < 1% in controlled clinical studies (occurring in more than 1 patient, with higher frequency than filgrastim):

General Disorders and Administration Site Conditions: injection site bruising;

Infections and Infestations: rhinitis;

Nervous System Disorders: hypertonia;

Skin and Subcutaneous Tissue Disorders: periorbital edema.

The following adverse drug reactions were reported at an incidence of < 1% in controlled clinical studies (occurring in more than 1 patient, with higher frequency than placebo):

General Disorders and Administration Site Conditions: chest pain, pain.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Spontaneously reversible elevations in LDH, alkaline phosphatase, and uric acid of mild-to-moderate severity were observed. Most changes have been attributed to post-cytokine bone marrow expansion as well as to chemotherapy and metastatic disease. The incidences of these changes, presented for pegfilgrastim versus filgrastim and placebo, were: LDH (18% versus 29% and 18%), alkaline phosphatase (11% versus 16% and 12%), and uric acid [10% versus 9% and 13% (1% of uric acid reported cases for filgrastim and pegfilgrastim treatment groups were classified as severe)].

In clinical studies with pegfilgrastim, white blood cell counts of 100 x 10^9/L or greater have been reported in less than 1% of patients with cancer receiving myelosuppressive chemotherapy (n = 930) and were not associated with any reported adverse clinical effects.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The incidence of antibody development in patients receiving pegfilgrastim has not been adequately determined. While available data suggest that a small proportion of patients developed binding antibodies to filgrastim or pegfilgrastim, the nature and specificity of these antibodies has not been adequately studied. No neutralizing antibodies have been detected using a cell-based bioassay in 46 (9%, n = 534) patients who apparently developed binding antibodies. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay, and the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, concomitant medications, and underlying disease. Therefore, comparison of the incidence of antibodies to pegfilgrastim with the incidence of antibodies to other products may be misleading.

Cytopenias resulting from an antibody response to exogenous growth factors have been reported on rare occasions in patients treated with other recombinant growth factors. There is a theoretical possibility that an antibody directed against pegfilgrastim may cross-react with endogenous G-CSF, resulting in immune-mediated neutropenia, but this has not been observed in clinical studies.

8.5 Post-Market Adverse Reactions

In addition to the events listed above, reports of adverse reactions have been identified post-market in patients receiving pegfilgrastim, including:

- Splenomegaly (enlarged spleen) and Splenic rupture (see 7 WARNINGS AND PRECAUTIONS, General, Splenic Rupture)
- Aortitis (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular)
- Capillary Leak Syndrome (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular)
- Sickle cell crisis (see 7 WARNINGS AND PRECAUTIONS, Hematologic)
- Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukaemia (AML) in Breast and Lung Cancer Patients (see 7 WARNINGS AND PRECAUTIONS, Hematologic)
- Allergic reactions (see 7 WARNINGS AND PRECAUTIONS, Immune, Hypersensitivity/Allergic Reactions)
- Cutaneous Vasculitis (see 7 WARNINGS AND PRECAUTIONS, Immune)
- Glomerulonephritis (see 7 WARNINGS AND PRECAUTIONS, Renal)
- Acute respiratory distress syndrome (ARDS) (see 7 WARNINGS AND PRECAUTIONS, Respiratory)
- Injection site reactions (pain, induration, and local erythema)
- Generalized erythema and flushing
- Sweet's syndrome (acute febrile neutrophilic dermatosis)

9 DRUG INTERACTIONS

9.1 Drug Interactions Overview

No serious drug interactions have been identified.

9.2 Drug Interactions Overview

Drug interactions between pegfilgrastim and other drugs have not been studied. Drugs such as lithium that may potentiate the release of neutrophils should be used with caution; such patients should have more frequent monitoring of their neutrophil counts.

9.3 Drug-Behavioural Interactions

Drug-behavioural interactions have not been established.

9.4 Drug-Drug Interactions

Interactions with other drugs have not been established.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

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.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Both pegfilgrastim and filgrastim 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. Studies on cellular proliferation, receptor binding, and neutrophil function demonstrate that filgrastim and pegfilgrastim have the same mechanism of action. Pegfilgrastim has reduced renal clearance and prolonged persistence *in vivo* as compared to filgrastim.

10.2 Pharmacodynamics

See information in 10.3 below.

10.3 Pharmacokinetics

The pharmacokinetics and pharmacodynamics of pegfilgrastim were studied in patients with cancer. The pharmacokinetics of pegfilgrastim were nonlinear in cancer patients and clearance decreased with increases in dose. Neutrophil-mediated clearance is an important component of the clearance of pegfilgrastim, and serum clearance is related to the number of neutrophils (neutrophil-mediated, self-

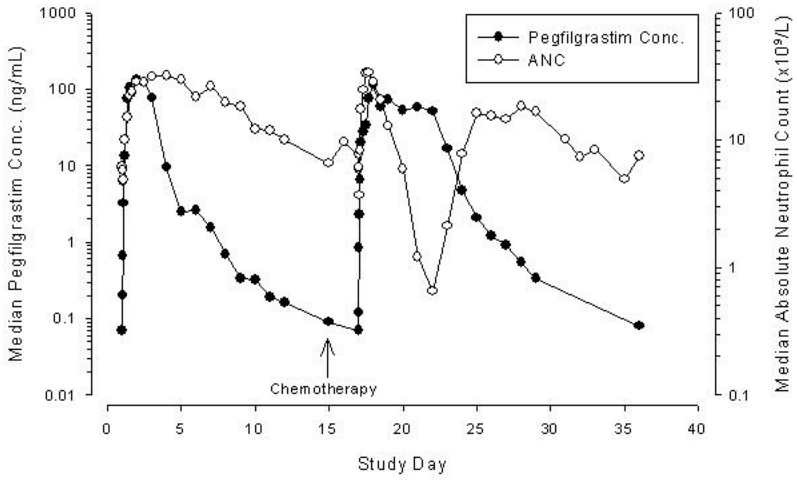
regulating clearance). Consistent with a self-regulating clearance mechanism, the serum concentration of pegfilgrastim declined rapidly at the onset of neutrophil recovery, following myelosuppressive chemotherapy (see Figure 1). In addition to numbers of neutrophils, body weight appeared to be a factor. 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 in cancer patients. The half-life of pegfilgrastim ranged from 25 to 49 hours after SC injection.

Table 4 – Summary of Pegfilgrastim Pharmacokinetic Parameters in Cancer Patients after SC administration

	C_{max}	$t_{½}$ (h)	$AUC_{0-\infty}$	Clearance
Single Dose* Median	78.3-175 ng/mL	25-49 hr	5640-15000 ng·hr/mL	6.68-17.7 mL/hr/kg

* Doses of 100 mcg/kg and 6 mg

Figure 1 – Median Pegfilgrastim Serum Concentration and Absolute Neutrophil Count Profiles in Patients with Non-Small Cell Lung Cancer (n = 3) After a Single Injection of Pegfilgrastim 100 mcg/kg Administered Before and After Chemotherapy



Special Populations and Conditions

- **Pediatrics:** The pharmacokinetic profile in pediatric populations has not been assessed.
- **Geriatrics:** No differences were observed in the pharmacokinetics of geriatrics patients with cancer (≥ 65 years of age) compared to younger patients (< 65 years of age) (see 7 WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics)
- **Sex:** No sex-related differences were observed in the pharmacokinetics of pegfilgrastim.
- **Ethnic Origin:** The effect of ethnic origin on pharmacokinetics has not been adequately assessed.
- **Hepatic Insufficiency:** The pharmacokinetic profile in patients with hepatic insufficiency has not been assessed.

- **Renal Insufficiency:** Renal impairment, including end-stage renal disease, appears to have no effects on the pharmacokinetics of pegfilgrastim.

11 STORAGE, STABILITY AND DISPOSAL

Pexegra (pegfilgrastim) should be stored refrigerated at 2° to 8°C (36° to 46°F) in the outer carton to protect from light. Do not shake. Before injection, PEXEGRA may be allowed to reach room temperature for a maximum of 72 hours. Discard syringes stored at room temperature for more than 72 hours.

Freezing should be avoided; however, if accidentally frozen Pexegra should be allowed to thaw in the refrigerator before administration. If frozen a second time, Pexegra should be discarded.

Pexegra should be visually inspected for discolouration and particulate matter before administration. Pexegra should not be administered if discolouration or particulates are observed.

12 SPECIAL HANDLING INSTRUCTIONS

Pexegra (pegfilgrastim) should not be vigorously shaken. Freezing should be avoided. Store in the carton provided to protect from light.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	pegfilgrastim
Chemical name:	pegylated non-glycosylated recombinant methionyl human granulocyte colony-stimulating factor
Molecular formula and molecular mass:	$CH_3O(C_2H_4O)_nC_3H_6C_{845}H_{1338}N_{223}O_{243}S_9$ Pegfilgrastim has a total molecular weight of 39,000 daltons
Structural formula:	Pegfilgrastim is composed of filgrastim (recombinant methionyl human G-CSF) with a 20,000 dalton polyethylene glycol (PEG) molecule covalently bound to the N-terminal methionine residue. Filgrastim is a 175 amino acid protein manufactured by recombinant DNA technology. Filgrastim is produced by *Escherichia coli* (*E. coli*) bacteria into which the human G-CSF gene has been inserted. Filgrastim has an amino acid sequence that is identical to the natural sequence predicted by human DNA sequence analysis, except for the addition of an N-terminal methionine necessary for expression in *E. coli*. Because filgrastim is produced in *E. coli*, the protein is non-glycosylated and thus differs from G-CSF isolated from a human cell.

Product Characteristics:

Pexegra is a sterile, clear, colourless to slightly yellow, preservative-free liquid.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Table 5 – Summary of Patient Demographics for Clinical Trials in Specific Indication

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n = number)	Mean age (Range) years	Gender
980226	Phase 3, double-blind, randomized, filgrastim controlled	Single SC dose of 100 mcg/kg/day pegfilgrastim or daily SC dose of 5 mcg/kg/day filgrastim, up to 4 cycles	310 (154 pegfilgrastim, 156 filgrastim)	50.9 (25-81) pegfilgrastim 51.8 (26-87) filgrastim	306 female, 4 male

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n = number)	Mean age (Range) years	Gender
990749	Phase 3, double-blind, randomized, filgrastim controlled	6 mg single dose of pegfilgrastim SC or 5 mcg/kg/day filgrastim up to 14 days, up to 4 cycles	157 (80 pegfilgrastim, 77 filgrastim)	51.9 (31-75) pegfilgrastim 52.6 (30-74) filgrastim	156 female, 1 male
20010144	Phase 3, double-blind, placebo controlled, randomized	Pegfilgrastim, 6 mg SC, single dose every 3 weeks, up to 12 weeks	928 (463 pegfilgrastim, 465 placebo)	51.9 (21-88) pegfilgrastim 52.1 (24-76) placebo	99% female

Study Results

Clinical Experience: Response to Pegfilgrastim

Pegfilgrastim administered as a single SC injection, after each cycle of chemotherapy, has been shown to be safe and effective in reducing neutropenia and associated clinical sequelae in a variety of chemotherapy settings.

Pegfilgrastim has been evaluated in three Phase 3, randomized, double-blind, controlled studies. Results from two active controlled studies (n = 467) conducted in patients with breast cancer undergoing up to 4 cycles of chemotherapy with doxorubicin and docetaxel demonstrated non-inferiority of pegfilgrastim to filgrastim. A clinically and statistically similar reduction in the duration of severe neutropenia (absolute neutrophil count [ANC] < 0.5 x 10^9/L; WHO grade 4) was seen in patients who received a single injection of pegfilgrastim, either 6 mg fixed dose or 100 mcg/kg, compared with patients who received a mean of 11 daily injections (cycle 1) of filgrastim 5 mcg/kg/day.

The mean (std dev) duration of severe neutropenia in cycle 1 in patients who received a single fixed-dose (6 mg) SC injection of pegfilgrastim (n = 68) was 1.8 (1.4) days compared with 1.6 (1.1) days in patients who received daily injections (range: 7-14 injections) of filgrastim (n = 62). The difference in means was 0.18 days (95% CI of -0.23 to 0.61). Durations of severe neutropenia were also comparable between treatment groups in all subsequent cycles. The rate of febrile neutropenia (temperature ≥ 38.2˚C with an ANC < 0.5 x 10^9/L) across all cycles was lower for patients receiving pegfilgrastim (13%) compared to patients receiving filgrastim (20%) (-7% difference; 95% CI of -19% to +5%). A single SC injection of pegfilgrastim per chemotherapy cycle was safe and well tolerated (see 8 ADVERSE REACTIONS).

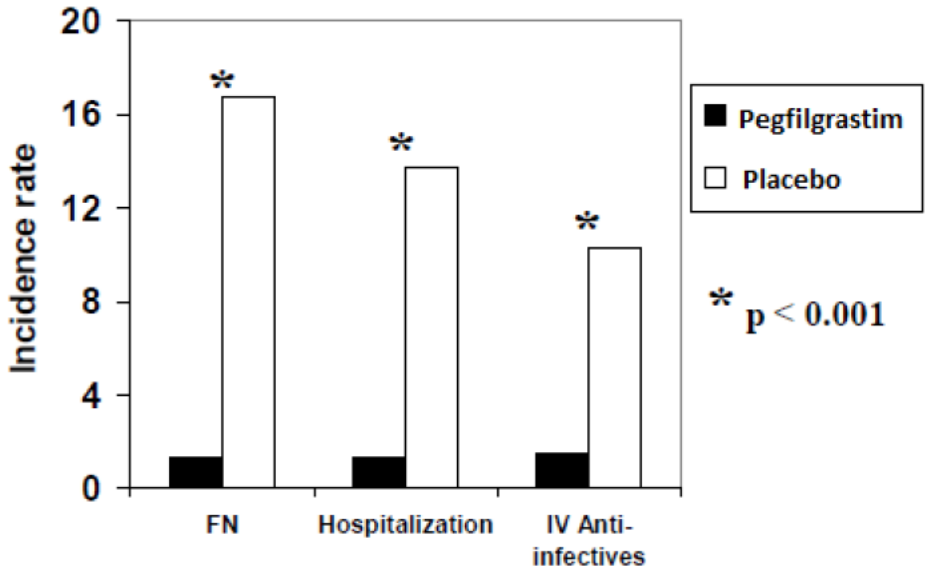
The third study employed a placebo control and evaluated the effect of pegfilgrastim on the incidence of febrile neutropenia when administered in first and all subsequent cycles of a moderately myelosuppressive chemotherapy regimen, docetaxel administered at 100 mg/m^2 Q3W for 4 cycles, which has been reported to be associated with a febrile neutropenia rate of 10% to 20%.

In this study, 928 patients with metastatic or non-metastatic breast cancer were treated with docetaxel. On day 2 of cycle 1, patients were randomized to receive either a single SC dose of 6 mg of pegfilgrastim or placebo. Patients who received pegfilgrastim in cycle 1 were scheduled to receive

pegfilgrastim in all subsequent cycles. Patients who received placebo in cycle 1 were scheduled to receive placebo in all subsequent cycles; however, patients who experienced febrile neutropenia would receive open-label pegfilgrastim.

The incidence of febrile neutropenia was statistically significantly lower for patients randomized to receive pegfilgrastim versus placebo (1% versus 17%, $p \leq 0.001$). The incidence of hospitalizations and IV anti-infective use associated with a clinical diagnosis of febrile neutropenia was significantly lower in the pegfilgrastim group compared with placebo [1% versus 14%, $p \leq 0.001$; and 2% versus 10%, $p \leq 0.001$, respectively (see Figure 2)].

Figure 2 – Percentage of Subjects with Febrile Neutropenia (FN), Who Were Hospitalized, and Who Received IV Anti-infectives for FN



Data from Phase 2 studies in patients with various malignancies undergoing a variety of chemotherapy regimens further support the safety and efficacy of pegfilgrastim. Dose-finding studies in patients with breast cancer (n = 152), thoracic tumours (n = 92), and non-Hodgkin's lymphoma (NHL) (n = 49) demonstrated that the efficacy of a single injection of pegfilgrastim 100 mcg/kg was similar to daily injections of filgrastim 5 mcg/kg/day, and superior to pegfilgrastim doses of 30 or 60 mcg/kg, at reducing the duration of severe neutropenia and the rate of febrile neutropenia. A randomized phase II study of patients with NHL or Hodgkin's lymphoma (n = 60) further supports the safety and efficacy of pegfilgrastim.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

Preclinical Studies

The preclinical toxicology of pegfilgrastim was studied in Sprague-Dawley® rats and cynomolgus monkeys. A single-dose IV study was conducted in rats. Pegfilgrastim caused no clinical signs or mortality at single IV doses up to 10,000 mcg/kg in rats.

Repeat-dose studies included 2-week SC (every-other-day dosing) and 6-month SC/IV (weekly dosing) studies in rats and a 1-month SC (weekly dosing) study in monkeys. Dosing was intermittent to mimic intended human use of pegfilgrastim. Pegfilgrastim was well tolerated for 6 months at once-weekly doses up to 1000 mcg/kg SC or 300 mcg/kg IV in rats, and for 1 month at once-weekly doses up to 750 mcg/kg SC in cynomolgus monkeys. No effects on body weight, food consumption, or survival were observed. Pegfilgrastim caused an increase in leukocyte counts, primarily segmented neutrophils, but also some increases in band neutrophils, monocytes, and lymphocytes. Pegfilgrastim also modestly decreased erythrocyte counts, hemoglobin and hematocrit levels, decreased serum cholesterol, slightly decreased serum potassium, and increased serum alkaline phosphatase. Splenomegaly was the principal gross pathological finding. Histopathological examination revealed increased neutrophilic granulopoiesis in bone marrow and extramedullary hematopoiesis in spleen, liver, and/or lymph nodes. Leukocytosis in spleen, liver, and lymph nodes, and mild inflammation and mononuclear cell infiltrate at the injection site were additionally observed in monkeys treated with pegfilgrastim. Observed changes tended to reverse upon cessation of treatment. Changes specific to every-other-day dosing in rats (≥ 500 mcg/kg only) included slightly increased serum ALT and/or AST, mild myelofibrosis in bone marrow, and increased osteoblastic/osteoclastic activity in bone. Little or no seroreactivity to pegfilgrastim was evident in rats, whereas a dose- and time-dependent increase in seroreactivity was observed in monkeys; however, pegfilgrastim-induced neutrophil increases were maintained.

Pegfilgrastim has been shown to have adverse effects in pregnant rabbits when given every-other-day at doses as low as 50 mcg/kg. Nonclinical data in pregnant rats indicate that very low levels of pegfilgrastim may cross the placenta.

Pegfilgrastim administered SC to pregnant rabbits at doses of 200 and 250 mcg/kg every-other-day during the period of organogenesis was associated with an increased incidence of abortions. Increased post-implantation loss due to early resorptions and decreased numbers of live fetuses were observed at pegfilgrastim doses of 200 to 1000 mcg/kg every other day.

Decreased maternal food consumption and/or weight gain and decreased fetal weight were observed at doses of 50 to 1000 mcg/kg every other day. Pegfilgrastim did not cause visceral or skeletal malformations in rabbit fetuses at doses as high as 200 mcg/kg every-other-day and did not cause external malformations in rabbit fetuses at doses as high as 1000 mcg/kg every other day.

Pegfilgrastim was not associated with an increase in external, visceral, or skeletal malformations in fetuses when administered by SC injection to pregnant rats during the period of organogenesis at dose levels up to 1000 mcg/kg every other day. However, an increased incidence of wavy ribs, generally regarded as a reversible pathological finding, was observed in rat fetuses at dose levels of 300 and 1000 mcg/kg every other day. No maternal or neonatal toxicities were observed in female rats administered once-weekly SC injections of pegfilgrastim up to 1000 mcg/kg in a pre- and postnatal developmental study.

Filgrastim is known to be negative in bacterial mutagenesis assays (Ames assay). Pegfilgrastim did not cause precancerous or cancerous lesions in Sprague-Dawley® rats after once-weekly SC injections of up

to 1000 mcg/kg for 6 months. Given the similar biochemical activity to filgrastim, the chemical nature of the PEG moiety, and extensive clinical experience with filgrastim, it is considered unlikely that pegfilgrastim would be carcinogenic when used as directed.

Pegfilgrastim is a growth factor that primarily stimulates production of neutrophils and neutrophil precursors; however, the G-CSF receptor through which pegfilgrastim and filgrastim act has been found on tumour cell lines, including some myeloid, T-lymphoid, lung, head and neck, and bladder tumour cell lines. *In vitro* proliferation has been observed in response to filgrastim in some of these cell lines, particularly acute myeloid leukemia (AML) cell lines.

Indices of mating or fertility in male and female Sprague-Dawley® rats were not adversely affected by once-weekly SC injections of pegfilgrastim of up to 1000 mcg/kg for 2 to 4 weeks before and during cohabitation.

17 SUPPORTING PRODUCT MONOGRAPHS

NEULASTA (Pegfilgrastim Injection, Sterile Solution, 6 mg (10 mg/mL)), submission control 242732, Product Monograph, Amgen Canada Inc. (JAN 08, 2021)

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]Pexegra™

Pegfilgrastim injection

Read this carefully before you start taking **Pexegra** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Pexegra**.

Pexegra is a biosimilar biologic drug (biosimilar) to the reference biologic drug Neulasta®. A biosimilar is authorized based on its similarity to a reference biologic drug that was already authorized for sale.

Serious Warnings and Precautions

- Your spleen may become enlarged and can rupture while taking Pexegra. A ruptured spleen can cause death. Call your doctor right away if you have pain in the left upper stomach area or left shoulder tip area.
- If you have a sickle cell trait or sickle cell disease, make sure that you tell your doctor before you start taking Pexegra so that the potential risks and benefits can be discussed. In patients with sickle cell trait or sickle cell disease, severe sickle cell crises have been associated with the use of pegfilgrastim. Severe sickle cell crises, in some cases resulting in death, have also been associated with filgrastim, the parent compound of pegfilgrastim.

What is Pexegra used for?

Pexegra is used to treat neutropenia (nu-tro-**peen**-ee-ah). Neutropenia is a condition where the body makes too few white blood cells and which may be caused by drugs used to treat cancer. Neutropenia is the most serious common side-effect of chemotherapy. Neutropenia predisposes your body to infections and prevents you from fighting them. Your doctor has decided to prescribe Pexegra for you to increase the number of neutrophils (**nu**-tro-fils), which will fight infections.

Pexegra is a man-made, long-acting form of granulocyte colony-stimulating factor (G-CSF), a substance naturally produced by the body.

How does Pexegra work?

Pexegra works by stimulating the bone marrow to make white blood cells. To make sure Pexegra is working, your doctor may ask that you have regular blood tests to count the number of white blood cells. It is important to follow the doctor's instructions about these tests.

What are the ingredients in Pexegra?

Medicinal ingredient: pegfilgrastim

Non-medicinal ingredients: acetic acid, polysorbate 20, sodium hydroxide, sorbitol, water for injection

Pexegra comes in the following dosage forms:

Pexegra is available in a single-use prefilled syringe with UltraSafe Plus™ Passive Needle Guard. Each single-use syringe (0.6 mL) of Pexegra (10 mg/mL) contains 6 mg of pegfilgrastim, the active substance.

Each blister packaged syringe is provided in a carton. The needle cap on the prefilled syringe is not made with natural rubber latex.

Do not use Pexegra if:

- You are allergic to pegfilgrastim (Pexegra), filgrastim, or any of the ingredients of Pexegra.
- You are allergic to other products made using the bacteria *Escherichia coli*. Talk to your doctor if you have any questions about this information.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Pexegra. Talk about any health conditions or problems you may have, including:

- If you have common signs of infection, such as fever, chills, rash, sore throat, diarrhea, or redness, swelling, or pain around a cut or sore. If you notice any of these symptoms during treatment with Pexegra, tell your doctor or nurse immediately. Pexegra can reduce the risk of infection, but it may not prevent all infections. An infection can still happen during the short time when your white blood cell levels are low.
- If there is a lump, swelling, or bruising at the injection site that does not go away, talk to your doctor. Occasionally a problem may develop at the injection site.
- If you have sickle cell trait or sickle cell disease, tell your doctor prior to treatment. If you develop left upper abdominal pain or pain at the tip of your shoulder, tell your doctor or nurse immediately.

Other warnings you should know about:

Your doctor will decide if you are able to give yourself a subcutaneous (i.e., under the skin) injection. Pexegra should only be injected on the day the doctor has determined for you and should not be injected until 24 hours after receiving your last dose of chemotherapy in each cycle. (If you are injecting someone else with Pexegra, it is important that you inform yourself about Pexegra to know how and when to give the Pexegra injection.)

Make sure your doctor knows about all medications you are taking before starting Pexegra injections. Patients taking lithium may need more frequent blood tests.

More information about Pexegra is available in the Product Monograph. Any questions should be discussed with your doctor.

Pregnancy and breastfeeding and Pexegra

Pexegra has not been studied in pregnant women, and its effects on developing babies are not known. It is possible that Pexegra can get into human breast milk. If you are pregnant, plan to become pregnant, think you may be pregnant, or are breast feeding, you should consult your doctor before using Pexegra.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Pexegra:

Drug interactions between Pexegra and other drugs have not been studied. Drugs such as lithium may affect the release of neutrophils into the blood stream. You should discuss your treatment with your doctor before using Pexegra.

How to take Pexegra:

Usual dose:
The recommended dosage of Pexegra is a single subcutaneous injection, just under the skin, of 6 mg (the contents of one prefilled syringe), administered once per cycle of chemotherapy. You must wait at least 24 hours after your course of cancer chemotherapy before injecting Pexegra. Pexegra should not be administered less than 14 days before your next chemotherapy cycle.

Overdose:

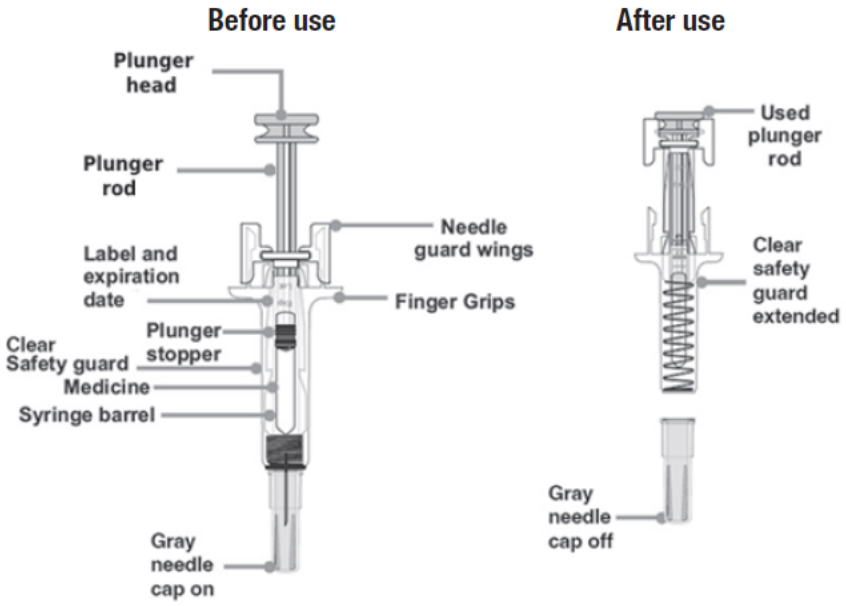
If you think you, or a person you are caring for, have taken too much Pexegra, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

As there should be a two-week period between Pexegra and your next course of cancer chemotherapy, if you miss a planned dose, consult your doctor before taking the missed dose.

How to take Pexegra:

Guide to parts



Important: The needle is covered by the gray needle cap before use. Read the complete Patient Medication Information for important information you need to know about Pexegra before using it.

Storing the prefilled syringe

- Store Pexegra in the refrigerator between 2˚C and 8˚C.
- **Do not** freeze.
- Keep the prefilled syringe in the original pack to protect from light or physical damage.
- Take the prefilled syringe out of the refrigerator 30 minutes before use and allow it to reach room temperature before preparing an injection.

- Throw away any Pexegra that has been left at room temperature (20˚C to 25˚C) for more than 72 hours.
- Keep the Pexegra prefilled syringe out of the reach of children.

Using the prefilled syringe

- **It is important that you do not try to give the injection unless you or your caregiver has received training from your healthcare professional.**
- Make sure the name Pexegra appears on the pack and the prefilled syringe label.
- Check the pack and prefilled syringe label to make sure the dose strength is 6 mg/0.6 mL.
- **Do not** use a prefilled syringe after the expiration date on the label.
- **Do not** shake the prefilled syringe.
- **Do not** use the prefilled syringe if the pack is opened or damaged.
- **Do not** remove the gray needle cap from the prefilled syringe until you are ready to inject.
- **Do not** use the prefilled syringe if it has been dropped on a hard surface. The prefilled syringe may be broken even if you cannot see the break. Use a new prefilled syringe.
- **Do not** attempt to activate the needle safety guard prior to injection.

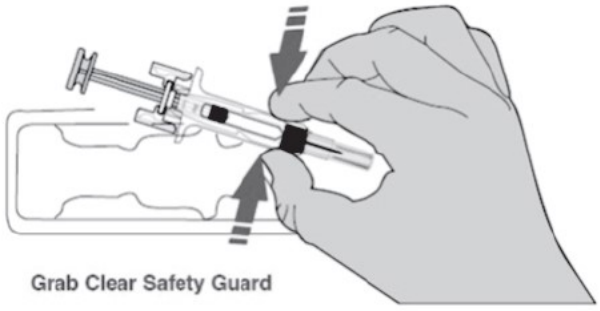
Call your healthcare professional if you or your caregiver have any questions.

Step 1: Prepare

A. Remove the prefilled syringe pack from the refrigerator. Remove the syringe tray from the pack. On a clean, well-lit surface, place the syringe tray at room temperature for **30** minutes before you give an injection.

- **Do not** use the prefilled syringe if the pack is damaged.
- **Do not** warm the prefilled syringe by using a heat source such as hot water or microwave.
- **Do not** leave the prefilled syringe in direct sunlight.
- **Do not** shake the prefilled syringe.

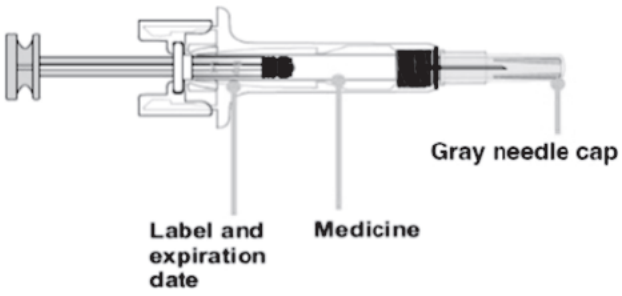
Open the tray by peeling away the cover. Grab the clear safety guard to remove the prefilled syringe from the tray.



For safety reasons:

- **Do not** grab the plunger rod.
- **Do not** grab the gray needle cap.

B. Inspect the medicine and prefilled syringe.



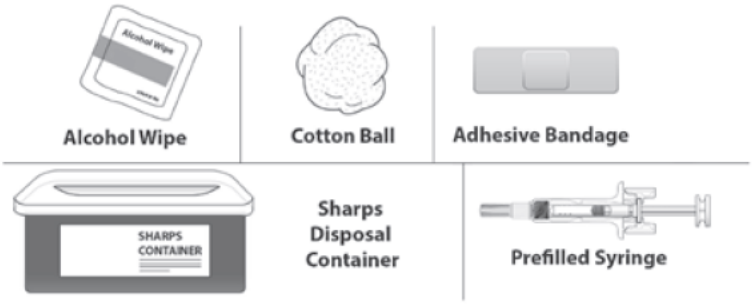
Make sure the medicine in the prefilled syringe is clear and colourless to slightly yellow.

- **Do not** use the prefilled syringe if:
  - The medicine is cloudy or discoloured or contains flakes or particles.
  - Any part appears cracked or broken.
  - The prefilled syringe has been dropped.
  - The gray needle cap is missing or not securely attached.
  - The expiration date printed on the label has passed.

  In all cases, use a new prefilled syringe and call your healthcare professional.

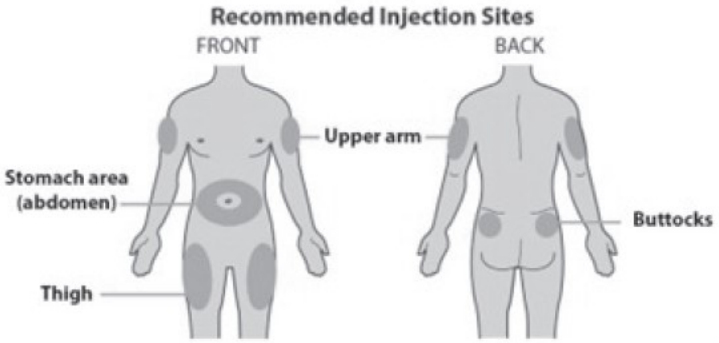
C. Gather all materials needed for the injection.
Wash your hands thoroughly with soap and water.
On a clean, well-lit work surface, place the:

- Prefilled syringe
- Alcohol wipe
- Cotton ball or gauze pad
- Adhesive bandage
- Sharps disposal container



Step 2: Get ready

D. Prepare and clean the injection site(s).



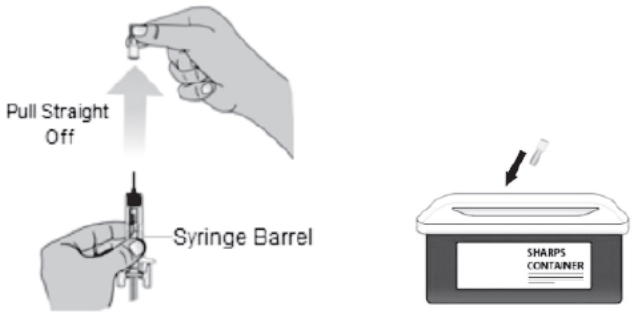
You can use:

- Thigh
- Stomach area (abdomen), except for a 5 cm area around the navel (belly button)
- Upper outer area of the buttocks (only if someone else is giving you the injection)
- Outer area of upper arm (only if someone else is giving you the injection)

Clean the injection site with an alcohol wipe. Let the skin dry.

- **Do not** touch this area again before injecting.
- If you want to use the same injection site, make sure it is not the same spot on the injection site you used for a previous injection.
- **Do not** inject into areas where the skin is tender, bruised, red or hard. Avoid injecting into areas with scars or stretch marks.

E. Hold the prefilled syringe by the barrel. Carefully pull the gray needle cap straight off and away from the body.

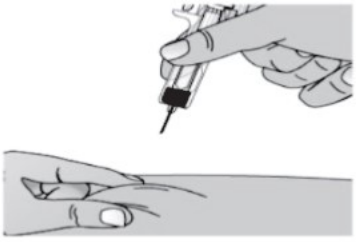


- **Do not** remove the gray needle cap from the prefilled syringe until you are ready to inject.
- **Do not** twist or bend the gray needle cap.
- **Do not** hold the prefilled syringe by the plunger rod.
- **Do not** put the gray needle cap back onto the prefilled syringe.

Important: Throw away the gray needle cap into the sharps disposal container.

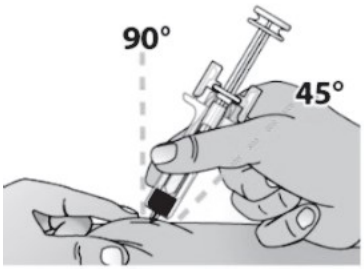
Step 3: Subcutaneous (under the skin) injection

F. Pinch the injection site to create a firm surface.

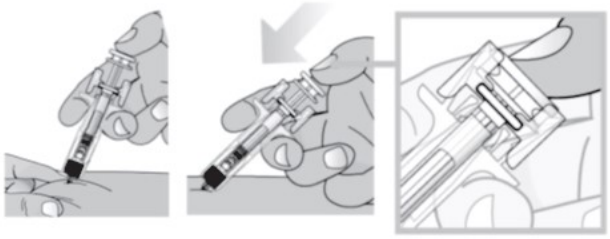


Important: Keep skin pinched while injecting.

G. Hold the pinch. Insert the needle into the skin at 45 to 90 degrees.



H. Using slow and constant pressure, push the plunger rod until it reaches the bottom and the plunger head is completely between the needle guard wings.

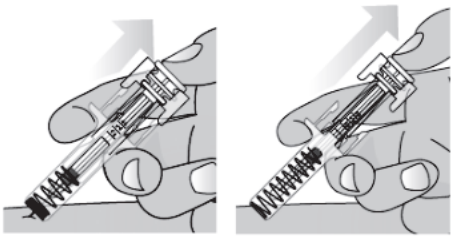


Important: When you remove the syringe, if it looks like the medicine is still in the syringe barrel, this means you have not received a full dose. Call your healthcare professional right away.

Step 4: Finish

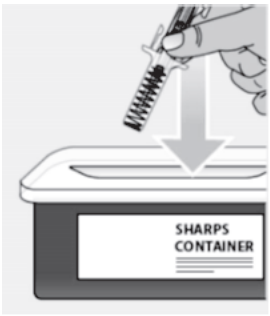
I. **Before you finish!**

- While you continue to hold the syringe, slowly let go of the plunger head.
- As you let go of the plunger head, the needle will automatically slide into the clear safety guard until the needle is completely covered.



Important: If the clear safety guard does not activate after Step I, remove the needle from the skin and throw away the used prefilled syringe as instructed in Step J right away. Keep your hands away from the needle at all times.

J. Discard (throw away) the used prefilled syringe.



- Put the used prefilled syringe in a sharps disposal container right away after use. **Do not** throw away the syringe in the household trash.
- If you do not have a sharps disposal container, you may use a household container that is:
  - Made of a heavy-duty plastic,
  - Can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
  - Upright and stable during use,
  - Leak-resistant, and
  - Properly labeled to warn of hazardous waste inside the container.
- Please check with your healthcare professional for instructions on how to properly dispose of the sharps disposal container.
- **Do not** reuse the prefilled syringe.
- **Do not** recycle the prefilled syringe or sharps disposal container or throw them into the household trash.

Important: Always keep the sharps disposal container out of the reach of children.

K. Examine the injection site.
If there is blood, press a cotton ball or gauze pad on the injection site. **Do not** rub the injection site. Apply an adhesive bandage if needed.

What are possible side effects from using Pexegra?

These are not all the possible side effects you may have when taking Pexegra. If you experience any side effects not listed here, tell your healthcare professional.

- **Spleen Rupture.** Your spleen may become enlarged and can rupture while taking Pexegra. A ruptured spleen can cause death. The spleen is located in the upper left section of your stomach area. Call your doctor right away if you have pain in the left upper stomach area or left shoulder tip area. This pain could mean your spleen is enlarged or ruptured.
- **Serious Allergic Reactions.** Serious allergic reactions can also happen. These reactions may cause a rash over the whole body, shortness of breath, wheezing, a drop in blood pressure (usually causing dizziness or lightheadedness), swelling around the mouth or eyes, fast pulse, or sweating. If you experience an allergic reaction during the injection of Pexegra, the injection should be stopped immediately. **If at any time a serious allergic reaction occurs, immediately call a doctor or emergency services (for example, call 911).**
- **A serious lung problem called acute respiratory distress syndrome (ARDS)**. Call your doctor or seek emergency care right away if you have shortness of breath, trouble breathing or a fast rate of breathing.
- **Kidney injury (glomerulonephritis)** has been seen in patients who received Pexegra. Call your doctor immediately if you experience puffiness in your face or ankles, blood in your urine or brown coloured urine, or if you notice that you urinate less often than usual.

What are the most common side effects of Pexegra?

The most common side effect that you may experience is aching in the bones and muscles. If this occurs, it can usually be relieved with a non-acetylsalicylic acid over-the-counter pain reliever. Ask your doctor which is the most suitable one for you.

Some patients experience redness, swelling, or itching at the site of injection. This may be an allergy to the ingredients in Pexegra, or it may be a local reaction. If you notice any of these signs or symptoms, call your doctor.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
UNCOMMON ≥ 0.1% and < 1%			
Bone Pain		√	
Low platelet counts (thrombocytopenia) (including the following symptoms: easy bruising and increased bleeding).		√	
Allergic reactions (including the following symptoms: rash over the whole body, shortness of breath, a drop in blood pressure (usually causing dizziness or lightheadedness), swelling around the mouth or eyes, fast pulse, weakness, sweating; severe		√	√

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
redness or swelling or itching at injection site).			
Acute respiratory distress syndrome (including the following symptoms: fever, shortness of breath, cough, or congestion in your lungs).		√	√
VERY RARE < 0.01%			
Splenomegaly (including the following symptoms: pain in the left upper stomach area or left shoulder tip area).		√	
*** FREQUENCY NOT KNOWN**			
Splenic rupture (including the following symptoms: left upper abdominal pain or pain at the tip of your shoulder).		√	
Cutaneous vasculitis (including the following symptoms: A rash in the skin surface that looks like purple or red spots or bumps, clusters of small dots, splotches or hives. Your skin may also be itchy.)		√	
Capillary Leak Syndrome (including the following symptoms: swelling or puffiness, which may be associated with passing water less frequently, difficulty breathing, abdominal swelling and feeling of fullness, and a general feeling of tiredness).		√	
Kidney Injury (glomerulonephritis) (including the following symptoms: puffiness in the face or ankles, blood in urine or brown coloured urine, or urinating less often than usual).		√	√
**Abnormal number of immature bone marrow cells (myelodysplastic syndrome) that could lead to a type of cancer (acute myeloid leukemia) (including the following symptoms:		√	√

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
fever, bone pain, bruising, difficulty breathing, bleeding and a general feeling of tiredness).			

* Reported in the post-marketing setting where the incidence is not known.

** Adverse events in breast and lung cancer patients receiving chemotherapy and/or radiotherapy.

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Pexegra should be stored in the refrigerator at 2˚C to 8˚C, but not in the freezer. Keep the blistered syringe in the carton to protect from light. Do not shake. If Pexegra is accidentally frozen, allow it to thaw in the refrigerator before giving the next dose. However, if frozen a second time, do not use it and contact your healthcare professional. Pexegra can be left at room temperature for up to 72 hours. For any questions about storage, contact your healthcare professional.

Keep out of reach and sight of children.

If you want more information about Pexegra:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; or by calling 1-866-399-9091.

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