1. NAME OF THE MEDICINAL PRODUCT

RYZNEUTA 20mg (efbemalenograstim alfa) Solution for Injection in Prefilled Syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 20 mg of efbemalenograstim alfa* in 1 mL solution for injection. The concentration is 20 mg/mL.

*Recombinant human granulocyte colony-stimulating factor Fc fusion protein derived from mammalian cell culture.

The potency of this medicinal product should not be compared to the potency of another protein (pegylated or non-pegylated) of the same therapeutic class. For more information, see section 5.1.

Excipient with known effect

Each prefilled syringe contains 50 mg sorbitol (E420).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless solution for injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

RYZNEUTA is indicated for the reduction in the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes).

4.2 Posology and method of administration

RYZNEUTA therapy should be initiated and supervised by physicians experienced in oncology and/or haematology.

Posology

One 20 mg dose (a single pre-filled syringe) of RYZNEUTA is recommended for each chemotherapy cycle, given at least 24 hours after cytotoxic chemotherapy.

Special populations

Renal impairment
No dose change is recommended in patients with renal impairment, including those with end-stage renal disease.

Paediatric population

The safety and efficacy of RYZNEUTA in children have not yet been established and no data are available.

Method of administration

RYZNEUTA is for subcutaneous use. It is provided in a pre-filled syringe for manual

administration. The injections should be given into the thigh, abdomen, buttock or upper arm.

For instructions on handling of the medicinal product before administration, see section 6.5.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered medicinal product should be clearly recorded.

Malignant cell growth

Granulocyte colony-stimulating factor (G-CSF) can promote growth of myeloid cells *in vitro* and similar effects may be seen on some non-myeloid cells *in vitro*.

The safety and efficacy of efbemalenograstim alfa have not been investigated in patients with myelodysplastic syndrome, chronic myelogenous leukaemia, or acute myeloid leukaemia. Therefore, it should not be used in such patients.

The safety and efficacy of efbemalenograstim alfa have not been investigated in patients receiving high dose chemotherapy. This medicinal product should not be used to increase the dose of cytotoxic chemotherapy beyond established dosage regimens.

Pulmonary adverse events

Pulmonary adverse reactions, in particular interstitial pneumonia, have been reported after G-CSF administration. Patients with a recent history of pulmonary infiltrates or pneumonia may be at higher risk (see section 4.8).

The onset of pulmonary signs such as cough, fever, and dyspnoea in association with radiological signs of pulmonary infiltrates, and deterioration in pulmonary function along with increased neutrophil count may be preliminary signs of acute respiratory distress syndrome (ARDS). In such circumstances, efbemalenograstim alfa should be discontinued at the discretion of the physician and the appropriate treatment should be administered (see section 4.8).

Glomerulonephritis

Glomerulonephritis has been reported in patients receiving G-CSF (e.g. filgrastim and pegfilgrastim). Generally, events of glomerulonephritis resolved after dose reduction or withdrawal of G-CSF. Urinalysis monitoring is recommended.

Capillary leak syndrome

Capillary leak syndrome has been reported after G-CSF administration and is characterised by hypotension, hypoalbuminaemia, oedema and haemoconcentration. 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 (see section 4.8).

Splenomegaly and splenic rupture

Generally asymptomatic cases of splenomegaly have been reported after administration of efbemalenograstim alfa. Cases of splenic rupture, including some fatal cases, have been reported following administration of G-CSF (see section 4.8). Therefore, spleen size should be carefully monitored (e.g. clinical examination, ultrasound). A diagnosis of splenic rupture should be considered in patients reporting left upper abdominal pain or shoulder tip pain.

Thrombocytopenia and anaemia

Treatment with efbemalenograstim alfa alone does not preclude thrombocytopenia and anaemia because full dose myelosuppressive chemotherapy is maintained on the prescribed schedule. Regular monitoring of platelet count and haematocrit is recommended. Special care should be taken when administering single or combination chemotherapeutic agents which are known to cause severe thrombocytopenia.

Sickle cell anaemia

Sickle cell crises have been associated with the use of G-CSF in patients with sickle cell trait or sickle cell disease (see section 4.8). Therefore, physicians should use caution when prescribing efbemalenograstim alfa in patients with sickle cell trait or sickle cell disease, clinical parameters and laboratory status should be monitored appropriately and attentively by the physician for the possible association of this medicinal product with splenic enlargement and vaso-occlusive crisis.

Leukocytosis

White blood cell (WBC) counts of 100×10^9/L or greater have been observed in patients receiving G-CSF. No adverse events directly attributable to this degree of leukocytosis have been reported. Such elevation in white blood cells is transient, being typically seen 24 to 48 hours after administration and is consistent with the pharmacodynamic effects of this medicinal product. Consistent with the clinical effects and the potential for leukocytosis, a WBC count should be performed at regular intervals during therapy. If leukocyte counts exceed 50×10^9/L after the expected nadir, this medicinal product should be discontinued immediately.

Hypersensitivity

Hypersensitivity, including serious allergic reactions, occurring on initial or subsequent treatment have been reported in patients treated with G-CSF. Efbemalenograstim alfa should be permanently discontinued in patients with clinically significant hypersensitivity. Efbemalenograstim alfa should not be administered to patients with a history of hypersensitivity to efbemalenograstim alfa. Caution should be exercised if using efbemalenograstim alfa in patients with a history of serious allergic reactions to other G-CSF products as the risk of cross-reactivity cannot be excluded. In such circumstances, efbemalenograstim alfa should be administered at the discretion of the physician with

the appropriate assessment of risks and benefits. If a serious allergic reaction occurs, appropriate therapy should be administered, with close patient follow-up over several days.

Stevens-Johnson syndrome

Stevens-Johnson syndrome (SJS), which can be life-threatening or fatal, has been reported rarely in association with G-CSF treatment. If the patient has developed SJS with the use of efbemalenograstim alfa, treatment with efbemalenograstim alfa must not be restarted in this patient at any time.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Rates of generation of antibodies against efbemalenograstim alfa is generally low. Binding antibodies do occur as expected with all biologics; however, they have not been associated with neutralising activity at present.

Aortitis

Aortitis has been reported after G-CSF administration in healthy subjects and in cancer patients. The symptoms experienced included fever, abdominal pain, malaise, back pain and increased inflammatory markers (e.g. c-reactive protein and white blood cell count). In most cases aortitis was diagnosed by computed tomography (CT) scan and generally resolved after withdrawal of G-CSF (see also section 4.8).

Myelodysplastic syndrome and acute myeloid leukemia in breast and lung cancer patients

Myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) have been observed following the use of some G-CSF (e.g. pegfilgrastim) in conjunction with chemotherapy and/or radiotherapy in patients with breast and lung cancer (see section 4.8). Patients with breast and lung cancer should be monitored for signs and symptoms of MDS/AML.

Other warnings

The safety and efficacy of RYZNEUTA for the mobilisation of blood progenitor cells in patients or healthy donors has not been adequately evaluated.

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

Sorbitol

This medicinal product contains 50 mg sorbitol in each pre-filled syringe. The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per 20 mg dose, that is to say essentially ‘sodium-free’.

Rubber - latex

The needle cap of the pre-filled syringe contains dry natural rubber (latex), which may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Due to the potential sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy, efbemalenograstim alfa should be administered at least 24 hours after administration of cytotoxic chemotherapy, and at least 14 days before the next dose of chemotherapy. Concomitant use of RYZNEUTA with chemotherapy (i.e. administration on the same day) has been shown to potentiate myelosuppression.

Possible interactions with other haematopoietic growth factors and cytokines have not been specifically investigated in clinical trials.

The potential for interaction with lithium, which also promotes the release of neutrophils, has not been specifically investigated. There is no evidence that such an interaction would be harmful.

The safety and efficacy of RYZNEUTA have not been evaluated in patients receiving chemotherapy associated with delayed myelosuppression, e.g. nitrosoureas.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of efbemalenograstim alfa in pregnant women. Although studies in animals have not shown reproductive toxicity (see section 5.3), RYZNEUTA is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

There is insufficient information on the excretion of efbemalenograstim alfa in human milk; a risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from RYZNEUTA therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

Efbemalenograstim alfa did not affect reproductive performance or fertility in male or female rats at cumulative weekly doses approximately 2.2 times higher than the recommended human dose (based on body surface area) (see section 5.3).

4.7 Effects on ability to drive and use machines

RYZNEUTA has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions were bone pain (very common [≥ 1/10]). Back pain, arthralgia and pain in extremity were reported commonly (≥ 1/100 to < 1/10). Musculoskeletal pain was generally of mild to moderate severity, transient and could be controlled in most patients with standard analgesics.

Serious angioedema occurred on subsequent treatment with efbemalenograstim alfa (uncommon [≥ 1/1 000 to < 1/100]).

Splenomegaly, generally asymptomatic, is uncommon. Splenic rupture, including some fatal cases, has been reported following administration of G-CSF (see section 4.4)

Uncommon pulmonary adverse reactions such as pulmonary oedema occurred on treatment with efbemalenograstim alfa. Other pulmonary adverse reactions including interstitial pneumonia, pulmonary infiltrates and pulmonary fibrosis have been reported following administration of G-CSF. Cases of respiratory failure or ARDS have been reported following administration of G-CSF, which may be fatal (see section 4.4).

Isolated cases of sickle cell crises have been associated with the use of G-CSF in patients with sickle cell trait or sickle cell disease (see section 4.4).

Capillary leak syndrome, which can be life-threatening if treatment is delayed, has been reported in cancer patients undergoing chemotherapy following administration of G-CSFs; see section 4.4 and section "Description of selected adverse reactions" below.

Tabulated list of adverse reactions

The safety of efbemalenograstim alfa has been evaluated based on the results from clinical trials.. Adverse reactions are divided into groups according to the MedDRA system organ class (SOC) and into frequency groups using the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriouness.

Table 1. List of adverse reactions

MedDRA system organ class	**Adverse reactions**		
	Very common (≥ 1/10)	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1 000 to < 1/100)**
Infections and infestations			Herpes infection[2]
Blood and lymphatic system disorders			Leukopenia, Neutropenia, Thrombocytopenia, Anaemia, Splenomegaly
Metabolism and nutrition disorders			Hyperglycaemia, Decreased appetite
Nervous system disorders		Headache[1]	Dizziness, Taste disorder[2], Muscle spasticity, Peripheral neuropathy[2], Somnolence
Eye disorders			Lacrimation increased
Ear and labyrinth disorders		Vertigo[1]	
Cardiac disorders			Tachycardia, Palpitations
Vascular disorders			Vasculitis, Hot flush
Respiratory, thoracic and mediastinal disorders			Pulmonary oedema, Epistaxis, Oropharyngeal pain, Cough, Dyspnoea, Nasal dryness
Gastrointestinal disorders		Nausea[1], Diarrhoea[1], Vomiting[1]	Stomatitis, Dry mouth, Dyspepsia, Abdominal pain, Dysphagia
Skin and subcutaneous tissue disorders			Alopecia, Urticaria[1], Dermatitis allergic, Rash, Dermatitis, Erythema, Toxic skin eruption, Rash maculo-papular, Pruritus, Eczema, Dry skin, Skin disorder, Angioedema, Cold sweat, Night sweats, Onychalgia
Musculoskeletal and connective tissue disorders	Bone pain	Back pain, Arthralgia, Pain in extremity	Myalgia, Osteoarthropathy, Musculoskeletal discomfort, Neck pain
General disorders and administration site conditions		Asthenia[1], Fatigue[1], Pyrexia[1]	Injection site reactions[2], Peripheral swelling, Chills, Thirst
Investigations		White blood cell count increased[1], Alanine aminotransferase increased[1], Aspartate aminotransferase increased[1]	Neutrophil count increased, Blood creatinine increased, Gamma-glutamyltransferase increased, Weight increased

The frequency category was estimated from a statistical calculation based upon 488 patients receiving RYZNEUTA in four clinical trials.
[1] See section "Description of selected adverse reactions" below.
[2] Includes multiple adverse reaction terms.

Description of selected adverse reactions

Nausea, vomiting, diarrhoea, asthenia, fatigue, pyrexia, vertigo and headaches were commonly observed in patients receiving chemotherapy.

One case of serious urticaria was reported after efbemalenograstim alfa treatment.

White blood cell count increased was commonly reported after efbemalenograstim alfa treatment. Leukocytosis (white blood cell counts > 100×10^9/L) have been reported following the administration of G-CSF; (see section 4.4).

Increases in alanine aminotransferase (ALT), aspartate aminotransferase (AST) have been commonly observed in patients after receiving efbemalenograstim alfa following cytotoxic chemotherapy. These elevations are transient and return to baseline.

Certain adverse reactions have not yet been observed in efbemalenograstim alfa clinical studies, but are generally accepted as being attributable to G-CSF and derivatives:

An increased risk of MDS/AML has been observed in an epidemiological study following the use of some G-CSF in conjunction with chemotherapy and/or radiotherapy in patients with breast and lung cancer (see section 4.4).

Hypersensitivity reactions have been reported after G-CSF administration (see section 4.4).

Cases of capillary leak syndrome have been reported after G-CSF administration and is characterised by hypotension, hypoalbuminaemia, oedema and haemoconcentration. Capillary leak syndrome generally occurred in patients with advanced malignant disease, sepsis, taking multiple chemotherapy medicinal products or undergoing apheresis (see section 4.4).

Aortitis may occur following the administration of G-CSF (see section 4.4).

Stevens-Johnson syndrome, Sweet's syndrome (acute febrile neutrophilic dermatosis) may occur following the administration of G-CSF (see section 4.4).

Glomerulonephritis may occur following administration of G-CSF (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose

A single subject administered 40 mg efbemalenograstim alfa during a chemotherapy cycle (20 mg injections on consecutive days) reported adverse events that were similar to those in subjects receiving lower doses of efbemalenograsim alfa.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immunostimulants, colony stimulating factors; ATC Code: L03AA18

Mechanism of action

Human granulocyte-colony stimulating factor (G-CSF) is a glycoprotein, which regulates the production and release of neutrophils from the bone marrow.

Pharmacodynamic effects

Efbemalenograstim alfa is a recombinant fusion protein containing G-CSF, a 16 amino-acid linker, and the Fc portion of human IgG2. In solution, efbemalenograstim alfa forms covalentlylinked dimers (disulfide bonds between Fc moieties) and has an immunoglobulin-like structure. Efbemalenograstim alfa is a sustained duration form of G-CSF due to decreased renal clearance. Efbemalenograstim alfa and other G-CSFs have identical modes of action, causing a marked increase in peripheral blood neutrophil counts within 24 hours, with minor increases in monocytes and/or lymphocytes.

Neutrophils produced in response to G-CSF show normal or enhanced function as demonstrated by tests of chemotactic and phagocytic function. As with other haematopoietic growth factors, G-CSF has shown *in vitro* stimulating properties on human endothelial cells. G-CSF can promote growth of myeloid cells, including malignant cells, *in vitro* and similar effects may be seen on some non-myeloid cells *in vitro*.

Clinical efficacy and safety

In a randomised, placebo-controlled, double-blind study in patients with breast cancer, the effect of efbemalenograstim alfa on the duration of neutropenia and the incidence of febrile neutropenia was evaluated following administration of a chemotherapy regimen associated with a febrile neutropenia rate of 30-40% (docetaxel 75 mg/m^2 and doxorubicin 60 mg/m^2 every 3 weeks for 4 cycles). One hundred twenty-two patients were randomised 2:1 to receive either a single 20 mg dose of efbemalenograstim alfa or placebo approximately 24 hours (day 2) after chemotherapy in cycle 1; all subjects received efbemalenograstim alfa in cycles 2 – 4. The primary endpoint of mean duration of grade 4 neutropenia in cycle 1 was lower for patients randomised to receive efbemalenograstim alfa compared with placebo (1.3 days versus 3.9 days, $p < 0.001$), as was the incidence of febrile neutropenia (5% versus 26%, $p < 0.001$). Consistent with the reduction in febrile neutropenia, the incidence of IV anti-infective use in cycle 1 was also lower in the efbemalenograstim alfa group compared with placebo (4% versus 18%).

Two additional randomised, active-controlled studies compared efbemalenograstim alfa, given as a once-per-cycle 20 mg dose, to either once-per-cycle pegfilgrastim (n=393) or daily filgrastim (n=239) for reducing the duration of neutropenia and the incidence of febrile neutropenia in patients with breast cancer receiving myelosuppressive chemotherapy. In the pegfilgrastim comparison, patients with metastatic or non-metastatic breast cancer received a docetaxel and cyclophosphamide regimen. In this study, the mean duration of grade 4 neutropenia in cycle 1 for both the efbemalenograstim alfa and pegfilgrastim groups was 0.2 days (difference 0.0 days, 95% CI -0.1, 0.1). Over the entire study, the rate of febrile neutropenia was 3.0% of efbemalenograstim alfa-treated patients compared with 0.5% of pegfilgrastim-treated patients (difference 2.5%, 95% CI -7.3%, 12.4%). In the comparison to filgrastim (median of 8 daily doses), patients with non-metastatic breast cancer received an epirubicin and cyclophosphamide regimen. In this study, the mean duration of grade 4 neutropenia in cycle 1 for the efbemalenograstim alfa group was 0.3 days and in the filgrastim group was 0.2 days (median difference 0.0 days, 95% CI -0.0, 0.0). Over the entire study, the rate of febrile neutropenia was 0.8% of efbemalenograstim alfa-treated patients compared with 1.7% of filgrastim-treated patients (difference -0.8%, 95% CI -4%, 2%).

5.2 Pharmacokinetic properties

Absorption

After subcutaneous injection of efbemalenograstim alfa, the peak serum concentration of efbemalenograstim alfa occurs at 36 hours [min-max: 6-96 hours] after dosing and serum concentrations of efbemalenograstim alfa are maintained during the period of neutropenia after myelosuppressive chemotherapy.

Distribution

The apparent volume of distribution ranges from 395 to 5679 mL/kg.

Biotransformation

Efbemalenograstim alfa is expected to be metabolized into small peptides by catabolic pathways.

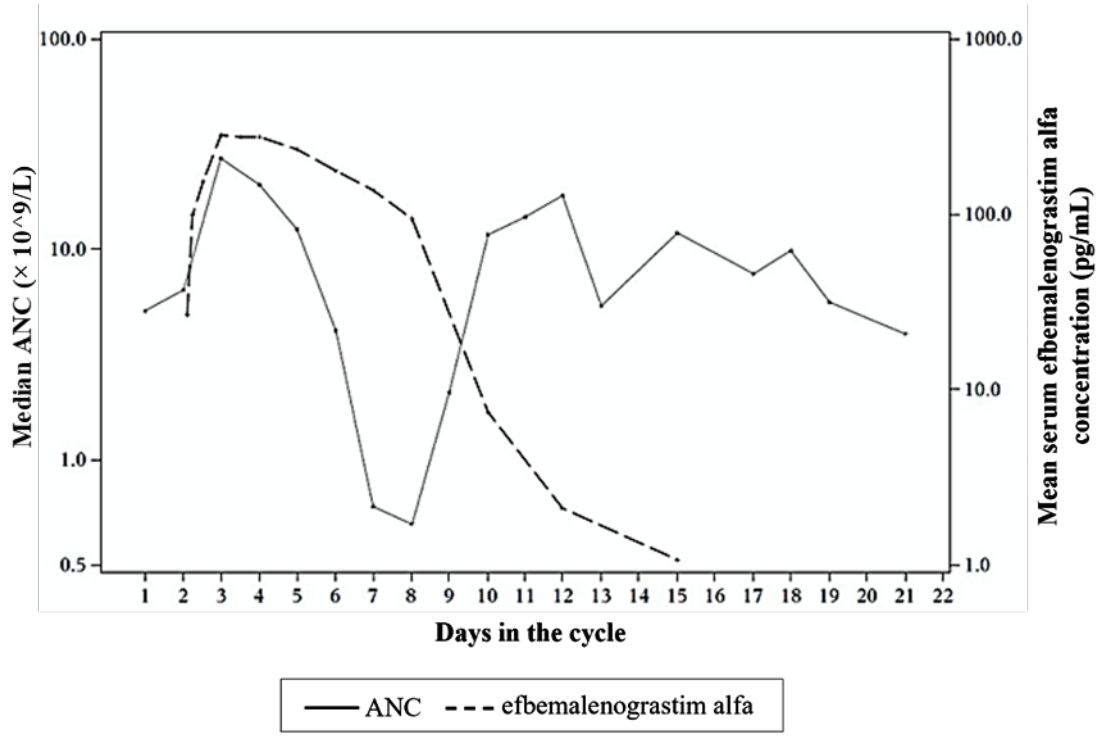
Elimination

Efbemalenograstim alfa appears to be mainly eliminated by neutrophil-mediated clearance, which becomes saturated at higher doses. Consistent with a self-regulating clearance mechanism, the serum concentration of efbemalenograstim alfa declines rapidly at the onset of neutrophil recovery (see Figure 1). The half-life ranged from 19 to 84 hours after subcutaneous injection.

Linearity/non-linearity

Efbemalenograstim alfa exhibited non-linearity and time-dependent pharmacokinetics over the dose range of 30 to 360 mcg/kg.

Figure 1. Profile of median efbemalenograstim alfa serum concentration and Absolute Neutrophil Count (ANC) in chemotherapy treated patients after a single 320 mcg/kg injection



Due to the neutrophil-mediated clearance mechanism, the pharmacokinetics of efbemalenograstim alfa is not expected to be affected by renal or hepatic impairment (see section 4.2).

Elderly

Limited data indicate that the pharmacokinetics of efbemalenograstim alfa in elderly subjects (> 65 years) is similar to that in adults.

Paediatric population

There are no data available on the pharmacokinetics of efbemalenograstim alfa in children.

5.3 Preclinical safety data

Preclinical data from conventional studies of repeated dose toxicity revealed the expected pharmacological effects including increases in leukocyte count, myeloid hyperplasia in bone marrow, extramedullary haematopoiesis and splenic enlargement.

There were no adverse events observed in offspring from pregnant rats or rabbits given efbemalenograstim alfa subcutaneously at cumulative doses approximately 2.6 and 0.7 times, respectively, the recommended human dose. Similar studies of other G-CSF products in rabbits have shown embryo/foetal toxicity (embryo loss) at cumulative doses approximately 4 times the recommended human dose, which were not seen when pregnant rabbits were exposed to the recommended human dose. Studies in rats indicated that reproductive performance, fertility, oestrous cycling, days between pairing and coitus, and intrauterine survival were unaffected by efbemalenograstim alfa given subcutaneously. The relevance of these findings for humans is not known.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium acetate trihydrate
Glacial acetic acid
Sorbitol (E420)
Polysorbate 20
Ethylene diamine tetraacetic acid (EDTA)
Water for injection

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).

RYZNEUTA may be exposed to room temperature (not above 30 °C) for a maximum single period of up to 48 hours. RYZNEUTA left at room temperature for more than 48 hours should be discarded.

Do not freeze. Accidental exposure to freezing temperatures for a single period of less than 24 hours does not adversely affect the stability of RYZNEUTA.

Keep the pre-filled syringe in the outer carton in order to protect from light.

6.4 Nature and contents of container

Pre-filled syringe (Type I glass), with a rubber stopper, stainless steel needle and needle cap.

The needle cap on the prefilled syringe contains dry natural rubber (latex) (see section 4.4).

Each pre-filled syringe contains 1 mL of solution for injection.

Pack size of one pre-filled syringe.

6.5 Special precautions for disposal and other handling

Before use, RYZNEUTA solution should be inspected visually for particulate matter. Only a solution that is clear and colourless should be injected

Do not shake. Excessive shaking may aggregate efbemalenograstim alfa, rendering it biologically inactive.

Allow the pre-filled syringe to reach room temperature for approximately 30 minutes before injecting.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7.

MANUFACTURER:
PCI San Diego, Inc.
11040 Roselle Street, San Diego, CA 92121 United States of America.

BATCH RELEASER:
Evive Biopharmaceutical Beijing, Ltd
Building 3 Floor 1 2 3, No. 99 Kechuang 14th street, Tongzhou Beijing, 101111, China.

PRODUCT REGISTRATION HOLDER:
DKSH Malaysia Sdn Bhd
B-11-01, The Ascent, Paradigm, No. 1, Jalan SS 7/26A, Kelana Jaya, 47301 Petaling Jaya, Selangor Darul Ehsan, Malaysia.

8. DATE OF REVISION OF THE TEXT

11 SEPTEMBER 2025

The following information is intended for healthcare professionals only:
RYZNEUTA - Instructions for use

Instructions for Use
Ryzneuta 20 mg solution for injection in pre-filled syringe
efbemalenograstim alfa
Injection for subcutaneous use

This leaflet contains information on how to inject Ryzneuta – please read the entire instructions before you start using Ryzneuta.

What the Ryzneuta Prefilled Syringe looks like

Figure A: New syringe with needle cap on
Figure B: New syringe with needle cap off
Figure C: Used syringe demonstrating activated safety device

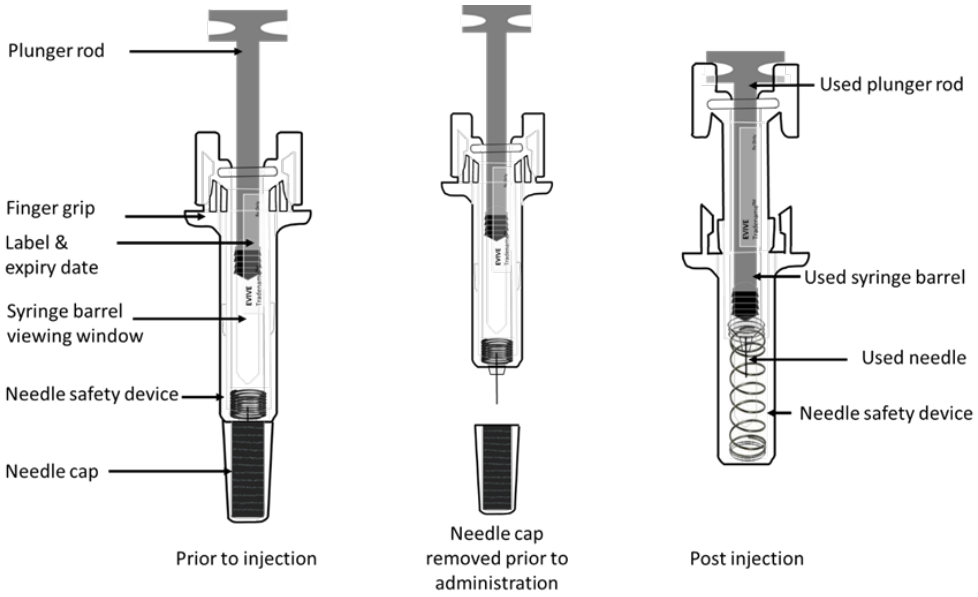


Figure A **Figure B** **Figure C**

Important: before you begin injection

- Ryzneuta is for subcutaneous injection only (inject directly into the fatty layer under the skin).
- Keep Ryzneuta out of the sight and the reach of children.
- Allow the syringe to come to room temperature for approximately 30 minutes before you give an injection.
- The needle is covered by a grey needle cap which must be removed before injection (see **Figure B**).
- The needle cap contains dry natural rubber (latex). You should not use Ryzneuta if you are allergic to latex.
- The prefilled syringe has a needle safety device that will be activated to cover the needle after the injection is given. The needle safety device will help prevent needle stick injuries (See **Figure C**).
- Throw away used syringes in a puncture-resistant, disposable sharps container as soon as you finish giving the injection. See "Disposing of Ryzneuta" at the end of the instructions.

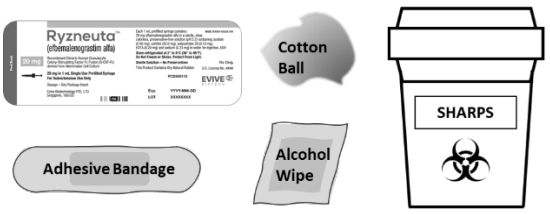
Cautions:

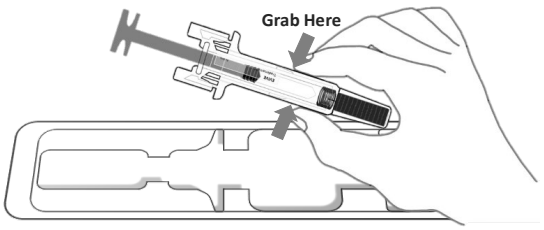
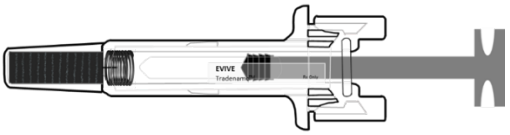
- × Do not use after the expiry date shown on the prefilled syringe label.
- × Do not shake the prefilled syringe.
- × Do not reuse the prefilled syringe.
- × Do not remove the grey needle cap from the prefilled syringe until you are ready to inject.
- × Do not use the prefilled syringe if the carton is open or damaged.
- × Do not grab the plunger rod.
- × 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 slide the clear safety device over the needle before you give the injection. This will "activate" or lock the clear safety device. If your device is already locked, use another prefilled syringe that has not been activated and is ready to use.

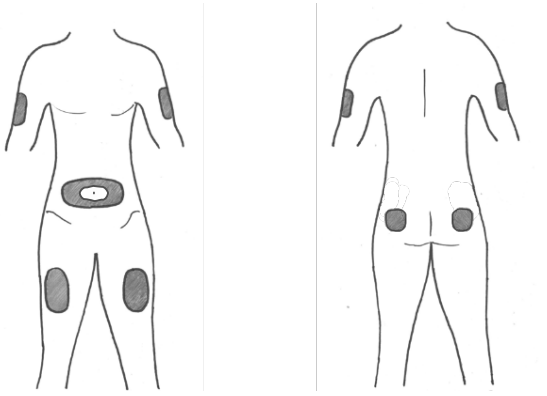
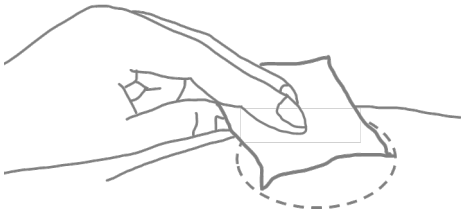
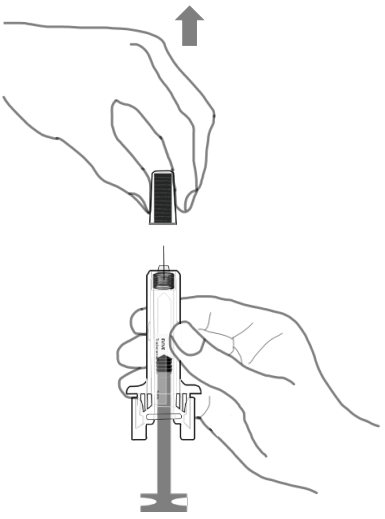
Supplies needed to give the injection:

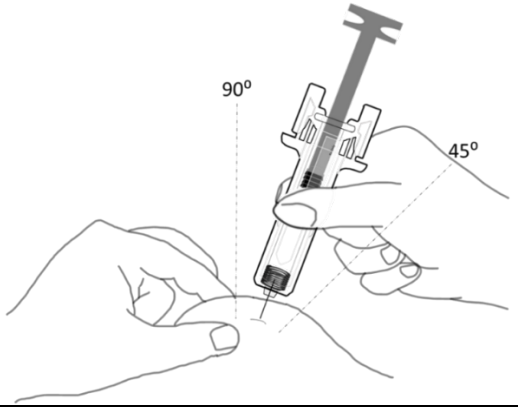
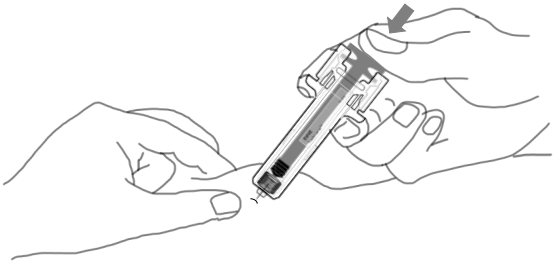
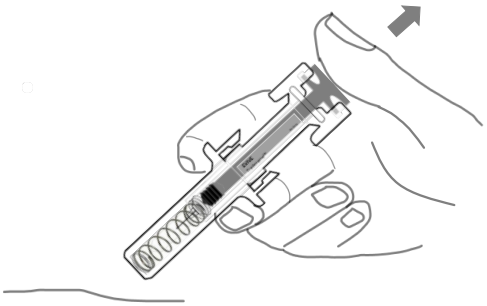
- One Ryzneuta prefilled syringe
- Alcohol wipe
- Cotton ball or gauze pad
- Adhesive bandage
- Sharps disposal container - see "Disposing of Ryzneuta" at the end of these instructions.

Preparing Ryzneuta for injection

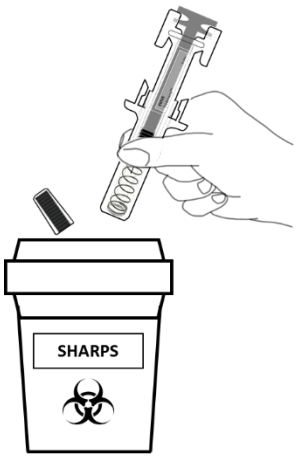
1	Remove Ryzneuta carton from the fridge. Remove the syringe tray from the carton and place it on a clean, flat work surface. Allow the syringe to come to room temperature for approximately 30 minutes before you give your injection. × Do not warm the syringe using a heat source or leave the syringe in direct sunlight.	
2	Gather all supplies and place on a clean, well-lit work surface: • Ryzneuta • Alcohol wipe • Cotton ball or gauze pad • Adhesive bandage • Sharps disposal container or equivalent containers that meet the local requirements	

3	Open syringe tray by peeling back the tray cover. Grab the clear needle safety device to remove the prefilled syringe from the tray as shown. For safety reasons: × Do not grab the plunger rod × Do not grab the grey needle cap. × Do not shake × Do not remove the cap from the syringe until you are ready to inject.	
4	Inspect the medicine and prefilled syringe. Make sure the medicine in the prefilled syringe is clear, colourless, and free of particles. × Do not use the prefilled syringe: • if the medicine is cloudy, discoloured, or contains particles. if any part appears cracked or broken. • if it has been dropped. • if the grey needle cap is missing or not securely attached. • if the expiry date printed on the label has passed. In all the above cases, use a new prefilled syringe.	
Preparing the injection site		

5	Choose an injection site as depicted in the diagram on the right (the grey area). You can use the: • Thigh. • Stomach area, except for a 5 cm area around the navel. • Upper outer area of the buttocks (only if someone else is giving you the injection). • Outer area of the upper arm (only if someone else is giving you the injection). If you want to use the same injection area (such as thigh or arm), make sure it is not at the same injection site you used for a previous injection. × Do not inject into areas where the skin is tender, bruised, red, or hard. × Do not inject into areas with scars or stretch marks.	
6	Wash your hands thoroughly with soap and water. Clean the injection site with an alcohol wipe. Let the skin dry. × Do not fan or blow on clean skin. × Do not touch this area again before injecting.	
Injecting Ryzneuta		
7	Hold the prefilled syringe by the syringe safety device. Carefully pull the grey needle cap straight off and away from the body. Keep your hands away from the needle at all times. × Do not twist or bend the grey needle cap. × Do not hold the prefilled syringe by the plunger rod. × Do not put the grey needle cap back onto the prefilled syringe. Dispose of (throw away) the grey needle cap in the regular trash or in a sharps	

	disposal container.	
8	Pinch the injection site to create a firm surface. • Hold the pinch. Insert the needle into the skin at 45 to 90 degrees. Important: Keep skin pinched while injecting, to avoid intramuscular injection, and do not touch the injection site.	
9	Using slow and constant pressure, push the blue plunger rod until it reaches the bottom. • The plunger rod must be pushed fully to inject the full dose.	
10	Once the entire dose has been injected, continue to push to activate the safety device. Slowly release the thumb from the plunger rod until the safety device is fully activated. • The needle will automatically pullback from the skin and into the barrel. • The device will lock into position and shield the needle. × Do not attempt to push the plunger rod to expose the needle.	
11	Once the needle has been removed, inspect the syringe barrel. • If it looks like the medicine is still in the syringe barrel, this means a full dose has not be administered. Examine the injection site. • If there is blood, press a cotton ball or gauze pad on the injection site. • Apply an adhesive bandage if needed. × Do not rub the site. Only use each syringe for one injection. If you have any problems, please ask your doctor or nurse for help and advice.	

Disposing of Ryzneuta

12	Put the used prefilled syringe in a sharps disposal container right away after use. Keep used syringes out of the sight and reach of children. × Do not throw away any medicines via wastewater or household waste.	
13	The used syringe should be disposed of in accordance with local requirements. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment	