ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Ryzneuta 20 mg solution for injection

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 (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 6.6.

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 listed in Appendix V.

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%).

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Ryzneuta in one or more subsets of the paediatric population in the treatment of chemotherapy-induced neutropenia (see section 4.2 for information on paediatric use).

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.

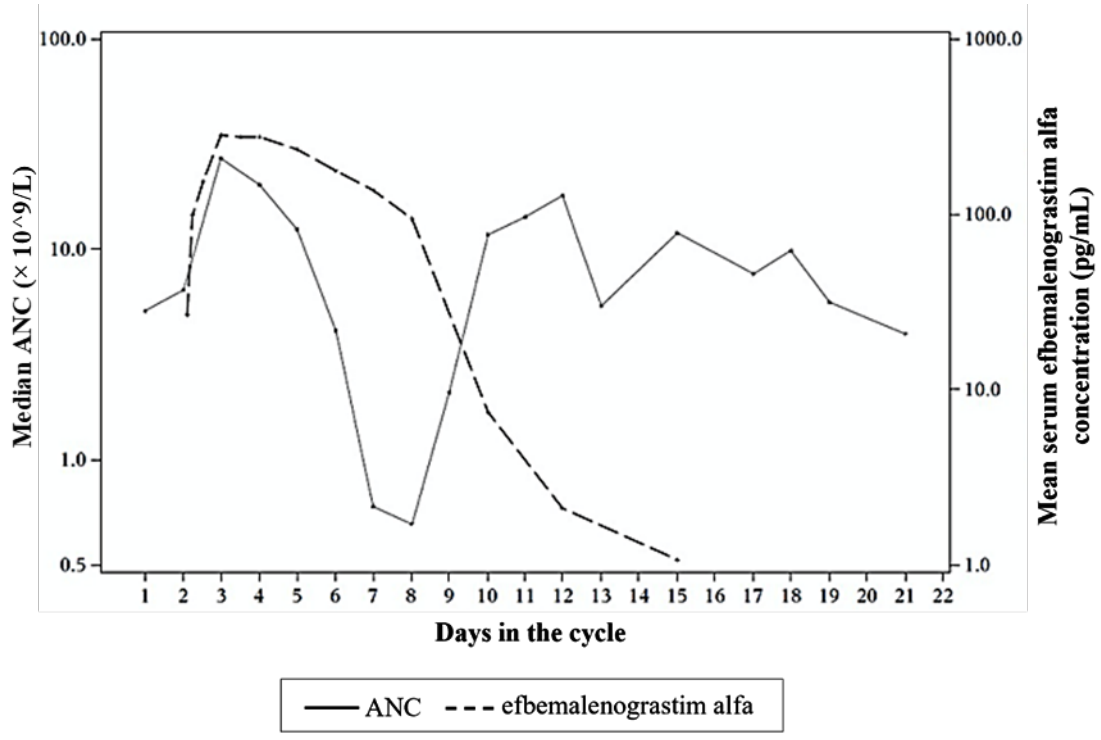
Elimination

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
Edetic acid
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

3 years.

6.4 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.

6.5 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.

6.6 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. MARKETING AUTHORISATION HOLDER

Evive Biotechnology Ireland LTD
20 Kildare Street
Dublin 2
D02 T3V7
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1793/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 March 2024

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)

Evive Biopharmaceutical Beijing, Ltd
Suite 202, Building 3,
No. 99 Kechuang 14th street, BDA Beijing, China

Name and address of the manufacturer(s) responsible for batch release

Catalent Germany Schorndorf GmbH.
Steinbeisstrasse 1-2,
D-73614 Schorndorf, Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON LABEL

1. NAME OF THE MEDICINAL PRODUCT

Ryzneuta 20 mg solution for injection
efbemalenograstim alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 20 mg of efbemalenograstim alfa in 1 mL solution for injection.

3. LIST OF EXCIPIENTS

Excipients: sodium acetate trihydrate, glacial acetic acid, sorbitol (E420), polysorbate 20, edetic acid, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 pre-filled syringe

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For Single-use only
For Subcutaneous Use only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Keep the pre-filled syringe in the outer carton in order to protect from light.
Do not freeze or shake.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Evive Biotechnology Ireland LTD
20 Kildare Street
Dublin 2
D02 T3V7
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1793/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER (TRAY) PACK FOR PREFILLED SYRINGE

1. NAME OF THE MEDICINAL PRODUCT

Ryzneuta 20 mg solution for injection
efbemalenograstim alfa

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Evive Biotechnology Ireland LTD

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SYRINGE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Ryzneuta 20 mg injection
efbemalenograstim alfa
SC

2. METHOD OF ADMINISTRATION

Subcutaneous use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Ryzneuta 20 mg solution for injection
efbemalenograstim alfa

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Ryzneuta is and what it is used for

What Ryzneuta is and what it is used for
Ryzneuta contains the active substance efbemalenograstim alfa. Efbemalenograstim alfa is a protein that is produced in cells in a laboratory. It belongs to a group of proteins called “cytokines” and is very similar to a natural protein made by your own body called granulocyte colony-stimulating factor, which is involved in the production of white blood cells in the bone marrow. White blood cells help your body fight infection, but chemotherapy can cause a decrease in the amount of white blood cells in your body. If the number of white blood cells is too low, your body is not able to fight off bacteria, and this may increase risk of infections.

Ryzneuta is used in adult patients who are receiving cancer medicines known as “chemotherapy”. Ryzneuta is given to:
- reduce the duration of “neutropenia” (low white blood cell count);
- reduce the chance of having “febrile neutropenia” (low white blood cell count with a fever).

Neutropenia, and febrile neutropenia can be caused by the use of medicines that destroy rapidly growing cells, such as chemotherapy.

How Ryzneuta works
Ryzneuta works by helping your bone marrow make more white blood cells that help your body fight infection.

2. What you need to know before you are given Ryzneuta

Do not use Ryzneuta
- if you are allergic to efbemalenograstim alfa or any of the other ingredients of this medicine (listed in section 6).

Do not use Ryzneuta if this applies to you. If you are not sure, talk to your doctor, pharmacist or nurse before you are given Ryzneuta.

Warnings and precautions
Before you are given Ryzneuta, talk to your doctor, pharmacist or nurse if:
- you have recently had a serious lung infection, fluid in the lungs, inflamed lungs (interstitial lung disease) or an abnormal chest x-ray (lung infiltration)
- you have any altered blood counts (such as an increased white blood cells or anaemia) or low blood platelet counts, which reduces the ability of your blood to clot - your doctor may want to monitor you more closely
- you have sickle cell anaemia - your doctor may monitor your condition more closely
- you have an allergy to latex - the needle cap on the syringe may cause severe allergic reactions

If any of the above apply to you (or if you are not sure), talk to your doctor, pharmacist or nurse before you are given Ryzneuta.

During treatment with Ryzneuta, look out for the following signs and symptoms:
- low blood pressure such as weakness and lightheadedness, difficulty breathing, swelling of the face, red and flushed skin, skin rash and itchy areas of skin – may be signs of an allergic reaction
- cough, fever and difficulty breathing – may be signs of acute respiratory distress syndrome (ARDS)
- swelling or puffiness, passing water less often, difficulty breathing, stomach swelling and feeling full, and generally feeling tired – may be signs of capillary leak syndrome (a condition where fluid leaks from the small blood vessels).
- upper left abdominal pain or pain at the tip of your shoulder - may be signs of problems with your spleen (splenomegaly, splenic rupture)
- fever, stomach pain, general feeling of discomfort, back pain – may be signs of an inflamed aorta.

Tell your doctor straight away if you notice any of the signs above. You may need urgent medical treatment.

Blood and urine checks
Your doctor will check your blood and urine regularly – because medicines like Ryzneuta can harm the tiny filters (glomeruli) inside your kidneys.

Risk of blood cancer
If you get a blood cancer such as CML, AML or MDS or are likely to develop a blood cancer, you should not receive Ryzneuta, unless your doctor tells you to.

If the medicine stops working properly
If this medicine stops working as well as it should, your doctor will look for the reasons why. This might mean you have developed antibodies which stop the medicine from working properly.

Children and adolescents
This medicine should not be given to children and adolescents under 18 years because it is not known yet whether it is safe and effective in this age group.

Other medicines and Ryzneuta
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before you are given this medicine.

Pregnancy

It is not recommended to use Ryzneuta during pregnancy. There might be a risk to your unborn baby. If you think you may be pregnant or are planning to have a baby, ask your doctor for advice before you are given this medicine.

Contraception in females
Women who could become pregnant should use an effective contraceptive (birth control) method whilst using Ryzneuta.

Breastfeeding
It is not known if Ryzneuta passes into breast milk. Tell your doctor if you are breast-feeding or plan to do so. Your doctor will then help you decide whether to stop breast-feeding, or whether to stop taking Ryzneuta, considering the benefit of breast-feeding the baby and the benefit of Ryzneuta to the mother.

Driving and using machines
Ryzneuta has no, or very little effect on the ability to drive or use tools or machines.

Ryzneuta contains sorbitol (E420), sodium and latex
This medicine contains 50 mg sorbitol in each 20 mg dose.
This medicine contains less than 1 mmol sodium (23 mg) per 20 mg dose, that is to say essentially 'sodium-free'.
The needle cap of the pre-filled syringe contains dry natural rubber (latex), which may cause allergic reactions.

3. How Ryzneuta is given

How you will be given Ryzneuta
Ryzneuta is given by a trained health professional. You should always be given Ryzneuta exactly as described by your doctor. You should check with your doctor or pharmacist if you are unsure.
This medicine is given as an injection under your skin (subcutaneous injection).

How much and how often Ryzneuta is given
The recommended dose is one 20 mg injection, which is given at the end of each chemotherapy cycle - at least 24 hours after your last dose of chemotherapy for that cycle.

If you are given more Ryzneuta than you should
You may observe similar adverse events as when you are given the recommended dose. You should talk to your doctor, pharmacist, or nurse if you are given more Ryzneuta than you should.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Tell your doctor if you experience these symptoms.

Most serious side effects
Tell your doctor or nurse right away and get medical help immediately if you develop any of the following symptoms.
- Reactions such as serious allergic reactions, including anaphylaxis and angioedema (rash, weakness, drop in blood pressure, difficulty breathing, swelling of the face).
- Pain in the upper left side of the abdomen or left shoulder pain could be symptoms of an increased spleen size and splenic rupture, the latter of which may be fatal.
- Cough, difficult or painful breathing, anxiety and restlessness can be signs of pulmonary conditions, such as pulmonary oedema, interstitial pneumonia, pulmonary infiltrates, pulmonary fibrosis, respiratory failure and acute respiratory distress syndrome.
- 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. These

symptoms generally develop in a rapid fashion. These could be symptoms of capillary leak syndrome, which causes blood to leak from the small blood vessels into your body and needs urgent medical attention.

Other side effects

Very common side effects (may affect more than 1 in 10 people)
- bone pain

Common side effects (may affect up to 1 in 10 people)
- pain in back, joints, limbs
- feeling sick (nausea)
- vomiting
- diarrhoea
- felling tired
- feeling weak or generally unwell
- fever
- vertigo
- headache
- changes in blood tests:
  high level of white blood cell
  high level of alanine aminotransferase (ALT)
  high level of aspartate aminotransferase (AST)

Uncommon side effects (may affect up to 1 in 100 people)
- herpes infection
- loss of appetite
- dizziness
- taste disorder
- muscle spasm
- sensation of numbness, tingling, burning (peripheral neuropathy)
- drowsiness
- watery eyes
- heart beating very fast
- hot flush
- vasculitis (inflammation of the blood vessels in the skin)
- dry nose, nose bleeding
- pain in mouth or throat
- cough
- difficulty breathing
- inflammation of the mucous membrane of the mouth (stomatitis)
- dry mouth
- problems with digestion (e.g. heartburn)
- abdominal (belly) pain
- swallowing problems
- hair loss (alopecia)
- skin reactions such as rash, itch, hives, red spot, blister, papules, eczema, dry skin
- cold sweat
- night sweats
- pain in nails
- muscle pain
- neck pain
- injection site reactions including injection site redness, pain, itching
- fluid retention causing swelling in the lower legs or hands (peripheral swelling)
- chills
- thirst
- weight increased

- changes in blood tests:
  high level of neutrophil (a type of white blood cells)
  low level of neutrophil
  low level of white blood cell
  low level of hemoglobin(anaemia)
  low level of blood platelet
  high level of blood sugar
  high level of creatinine (measure of kidney function)
  high level of gamma-glutamyltransferase (liver enzyme)

Side effects that have been seen with similar medicines, but not yet with Ryzneuta
- blood disorders (myelodysplastic syndrome [MDS] or acute myeloid leukaemia [AML])
- sickle cell crises in patients with sickle cell anaemia
- inflammation of aorta (the large blood vessel which transports blood from the heart to the body)
- Stevens-Johnson syndrome, which can appear as reddish target-like or circular patches often with central blisters on the trunk, skin peeling, ulcers of mouth, throat, nose, genitals and eyes and can be preceded by fever and flu-like symptoms.
- Sweet's syndrome (acute febrile neutrophilic dermatosis), manifested as plum-coloured, raised, painful lesions on the limbs and sometimes the face and neck with fever. But other factors may play a role.
- damage to the tiny filters inside your kidneys.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Ryzneuta

Your doctor, pharmacist or nurse is responsible for storing this medicine and disposing of any unused product correctly. The following information is intended for healthcare professionals.

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the syringe label after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C – 8 °C).
You may take Ryzneuta out of the refrigerator and keep it at room temperature (not above 30 °C) for no longer than 2 days. Once Ryzneuta has been removed from the refrigerator and has reached room temperature (not above 30 °C), it must either be used within 2 days or disposed of.
Do not freeze. Ryzneuta may be used if it is accidentally frozen for a single period of less than 24 hours.

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

Do not use this medicine if you notice it is cloudy or there are particles in it.

Do not throw away any medicines via wastewater or household waste.

6. Contents of the pack and other information

What Ryzneuta contains

- The active substance is efbemalenograstim alfa. Each pre-filled syringe contains 20 mg of efbemalenograstim alfa in 1 mL of solution.
- The other ingredients are sodium acetate trihydrate, glacial acetic acid, sorbitol (E420), polysorbate 20, edetic acid (EDTA) and water for injections. See section 2. “Ryzneuta contains sorbitol (E420), sodium and latex.”

What Ryzneuta looks like and contents of the pack

Ryzneuta is a clear, colourless solution for injection (injection) in a glass pre-filled syringe (20 mg/1 mL) with an attached stainless-steel needle and needle cap.

Each pack contains 1 pre-filled syringe.

Marketing Authorisation Holder

Evive Biotechnology Ireland LTD
20 Kildare Street
Dublin 2
D02 T3V7, Ireland

Manufacturer

Catalent Germany Schorndorf GmbH
Steinbeisstrasse 1-2,
D-73614 Schorndorf, Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

APOGEPHA Arzneimittel GmbH
Kyffhäuserstr. 27
01309 Dresden
Telefon: 0351 3363-3
Telefax: 0351 3363-440
E-Mail: info@apogepha.de

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

RYZNEUTA - Instructions for use

Instructions for Use
Ryzneuta 20 mg solution for injection
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

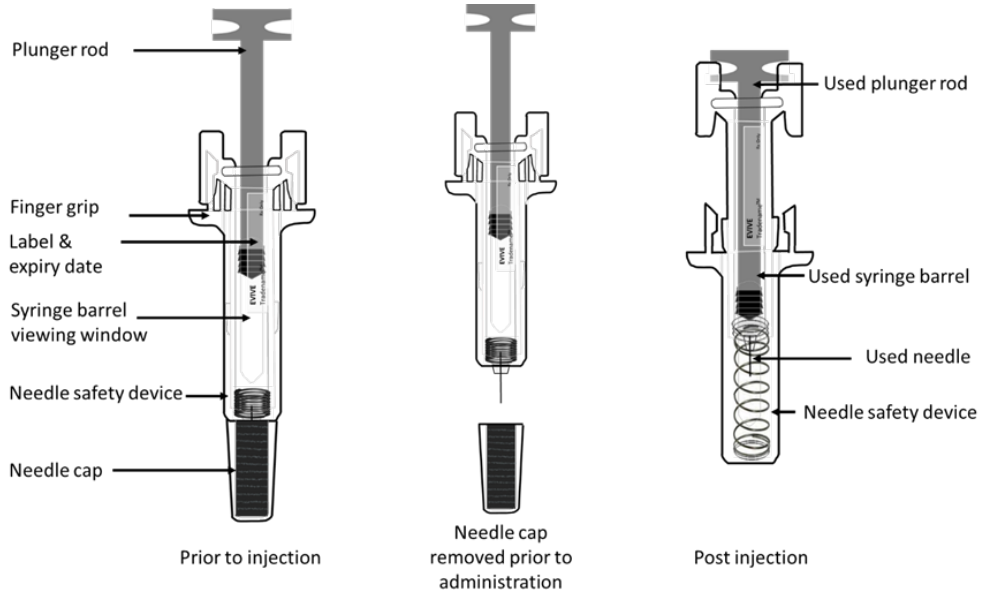


Figure A **Figure B** **Figure C**

Important: before you begin injection

- Ryzneuta is for subcutaneous injection only (inject directly into the fatty layer under the skin).
- 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). The patient should not be given Ryzneuta if 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:

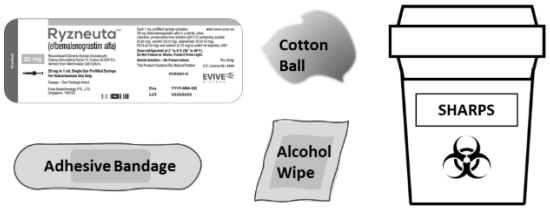
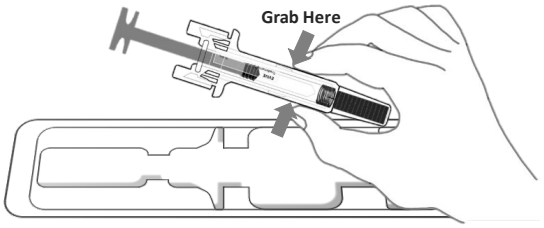
× Do not use after the expiry date shown on the prefilled syringe label.
× Do not shake the prefilled syringe.

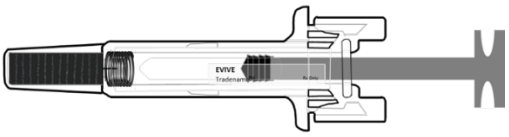
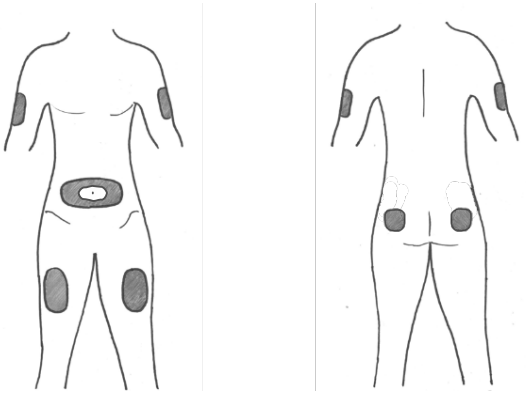
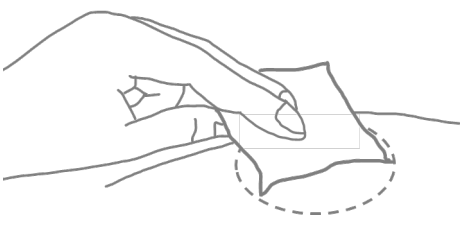
- × Do not reuse the prefilled syringe.
- × Do not remove the grey needle cap from the prefilled syringe until you are ready to inject.
- × Do not use the prefilled syringe if the carton is open or damaged.
- × Do not use the prefilled syringe if it has been dropped on a hard surface. The prefilled syringe 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.

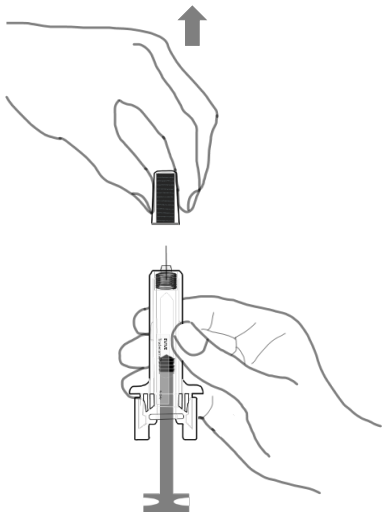
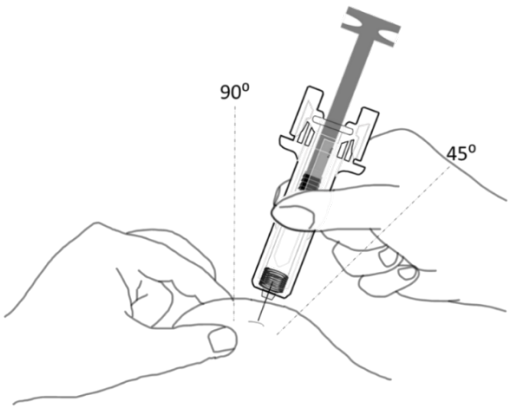
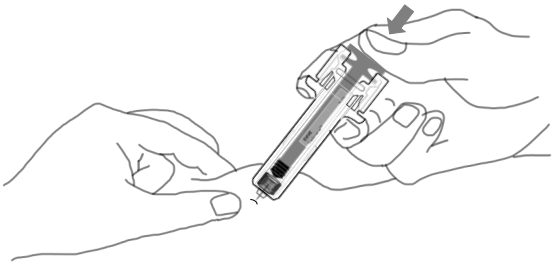
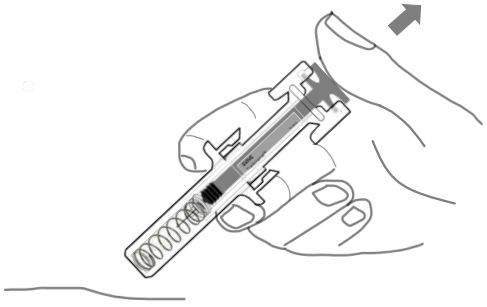
Supplies needed to give the injection:

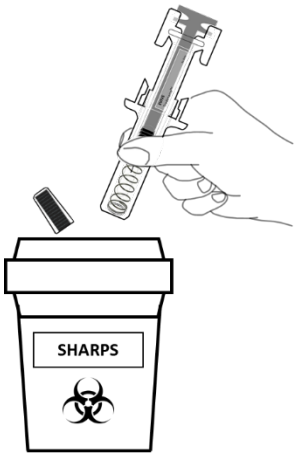
- One Ryzneuta prefilled syringe
- Alcohol wipe
- Cotton ball or gauze pad
- Adhesive bandage
- Sharps disposal container - see "Disposing of Ryzneuta" at the end of these instructions.

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	

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. • Outer area of the upper arm. 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 on patient 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.	
Disposing of Ryzneuta		
12	Put the used prefilled syringe in a sharps disposal container right away after use. × Do not throw away any medicines via wastewater or household waste.	
13	When your sharps disposal container is almost full, follow your community guidelines or local laws for the right way to dispose of your sharps disposal container.	