AUSTRALIAN PI - ZIEXTENZO® (PEGFILGRASTIM)

1 NAME OF THE MEDICINE

ZIEXTENZO® (pegfilgrastim) is a long-acting form of recombinant human granulocyte colony-stimulating factor (G-CSF).

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 0.6 mL single use pre-filled syringe with an automatic needle guard contains 6 mg of pegfilgrastim.

ZIEXTENZO® (pegfilgrastim) is composed of filgrastim (recombinant methionyl human G-CSF) with an approximately 20,000 dalton polyethylene glycol (PEG) molecule covalently bound to the N-terminal methionine residue.

Filgrastim is a 175 amino acid protein manufactured by recombinant DNA technology. Filgrastim is produced by *Escherichia coli* (*E. coli*) bacteria into which has been inserted the human G-CSF gene. Filgrastim is unglycosylated and contains an N-terminal methionine necessary for expression in *E coli*. Pegfilgrastim has a total molecular weight of approximately 39,000 daltons.

ZIEXTENZO® (pegfilgrastim) is a biosimilar medicine to Neulasta®.
The comparability of ZIEXTENZO® with Neulasta has been demonstrated with regard to physicochemical characteristics and efficacy and safety outcomes [see PHARMACOLOGY, CLINICAL TRIALS and ADVERSE EFFECTS]. The evidence for comparability supports the use of ZIEXTENZO® for the listed indication.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

ZIEXTENZO® is a sterile, clear, colourless to slightly yellowish, preservative-free liquid for subcutaneous (SC) administration.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ZIEXTENZO® is indicated for the treatment of cancer patients following chemotherapy, to decrease the duration of severe neutropenia and so reduce the incidence of infection, as

manifested by febrile neutropenia.

4.2 Dose and method of administration

Dosage (dose and interval)

The recommended dosage of ZIEXTENZO® is a single SC injection of 6 mg administered once per chemotherapy cycle. ZIEXTENZO® should be administered approximately 24 hours after the administration of cytotoxic chemotherapy. In clinical studies, pegfilgrastim has been safely administered 14 days before chemotherapy (see Section 4.4 Special warnings and precautions for use).

Method of administration

ZIEXTENZO® contains no antimicrobial agent. ZIEXTENZO® is for single use in 1 patient only. Discard any residue.

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration. Do not use any products exhibiting particulate matter or discolouration.

Avoid shaking. Allow the ready to use pre-filled syringe with automatic needle guard to reach room temperature before injecting.

4.3 Contraindications

ZIEXTENZO® is contraindicated in patients with known hypersensitivity to *E. coli*-derived proteins, pegfilgrastim, filgrastim, or any other component of the product.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicines, the trade name and the batch number of the administered product should be clearly recorded in the patient's medical record and/or dispensing record.

Splenomegaly and splenic rupture

Cases of splenic rupture, including some fatal cases, have been reported following the administration of pegfilgrastim. Patients who report left upper abdominal pain and/or shoulder tip pain should be evaluated for an enlarged spleen or splenic rupture.

Sickle cell crisis

Sickle cell crises have been associated with the use of pegfilgrastim in patients with sickle cell disease. Clinicians should exercise caution, monitor patients accordingly when administering ZIEXTENZO®to patients with sickle cell trait or sickle cell disease and only consider use after careful evaluation of the potential benefits and risks.

Pulmonary Haemorrhage and Haemoptysis

Pulmonary haemorrhage and haemoptysis requiring hospitalisation have been reported in G-CSF-treated healthy donors undergoing peripheral blood progenitor cell (PBPC) collection mobilisation. Haemoptysis resolved with discontinuation of G-CSF.

Acute respiratory distress syndrome

In patients with sepsis receiving ZIEXTENZO®, the physician should be alert to the possibility of acute respiratory distress syndrome, due to the possible influx of neutrophils at the site of inflammation.

Glomerulonephritis

Glomerulonephritis has been reported in patients receiving pegfilgrastim. Generally, after withdrawal of pegfilgrastim, events of glomerulonephritis resolved. Monitoring of urinalysis is recommended.

Concurrent use with chemotherapy and radiotherapy

The safety and efficacy of pegfilgrastim given concurrently with cytotoxic chemotherapy have not been established. Because of the potential sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy, the use of pegfilgrastim is not recommended in the period 24 hours after the administration of chemotherapy (see Section 4.2 Dose and method of administration). In clinical studies, pegfilgrastim has been safely administered 14 days before chemotherapy. Clinical trials with pegfilgrastim have not involved patients treated with fluorouracil or other antimetabolites. In studies in mice, administration of pegfilgrastim at 0, 1 and 3 days before fluorouracil resulted in increased mortality; administration of pegfilgrastim 24 hours after fluorouracil did not adversely affect survival.

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

The safety and efficacy of pegfilgrastim have not been evaluated in patients receiving radiotherapy.

Use in myelodysplasia and leukaemia

The safety and efficacy of pegfilgrastim administration in patients with myelodysplasia or chronic myeloid leukaemia have not been established.

Randomised studies of filgrastim in patients undergoing chemotherapy for acute myeloid leukaemia demonstrate no stimulation of disease as measured by remission rate, relapse and survival.

Leukocytosis

In pegfilgrastim clinical studies self-limiting leukocytosis (WBC counts > 100 x 10^9/L) have been reported in < 0.5% of 930 subjects with non-myeloid malignancies receiving pegfilgrastim. Leukocytosis was not associated with any reported adverse clinical effects.

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. Rates of antibody generation against pegfilgrastim are generally low. Binding antibodies do develop but have not been associated with neutralising activity or adverse clinical consequences.

The detection of antibody formation is dependent on the sensitivity and specificity of the assay. The observed incidence of antibody positivity (including neutralising antibody) in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications and underlying disease, therefore comparison of the incidence of antibodies to other products may be misleading.

Thrombocytopenia and anaemia

In studies of pegfilgrastim administration following chemotherapy, most reported side effects were consistent with those usually seen as a result of cytotoxic chemotherapy (see Section 4.8 Adverse effects (undesirable effects)). Because of the potential for patients to receive higher doses of chemotherapy (ie, full doses on the prescribed schedule for a longer period), patients may be at greater risk of thrombocytopenia which should be monitored carefully. Anaemia and non-haematologic consequences of increased chemotherapy doses (please refer to the prescribing information for specific chemotherapy agents used) may also

occur. If there is a risk of these conditions regular monitoring of the complete blood count is recommended. Furthermore, care should be exercised in the administration of ZIEXTENZO® in conjunction with drugs known to lower the platelet count and in the presence of moderate or severe organ impairment.

Aortitis

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

Laboratory monitoring

To assess a patient's haematologic status and ability to tolerate myelosuppressive chemotherapy, a complete blood count and platelet count should be obtained before chemotherapy is administered. Pegfilgrastim produced absolute neutrophil count (ANC) profiles similar to daily filgrastim, including earlier ANC nadir, shorter duration of severe neutropenia and accelerated ANC recovery, compared with ANC profiles observed without growth factor support. Due to neutrophil mediated clearance, pegfilgrastim is likely to produce post-recovery ANC levels in the normal range, and the above-normal peak ANC levels commonly seen with daily filgrastim do not occur.

Use in hepatic impairment

See Section 5.2 Pharmacokinetic properties.

Use in renal impairment

See Section 5.2 Pharmacokinetic properties.

Use in the elderly patients

See Section 5.2 Pharmacokinetic properties.

Paediatric use

See Section 5.2 Pharmacokinetic properties.

Effects on laboratory tests

None known.

4.5 Interactions with other medicines and other forms of interactions

Drug interactions between pegfilgrastim and other drugs have not been fully evaluated.

Bone imaging

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

Lithium

The potential for pharmacodynamic 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.

4.6 Fertility, pregnancy and lactation

Effects on fertility

Pegfilgrastim did not affect the fertility of male or female rats when administered once weekly at SC doses of up to 1 mg/kg (about 2 to 13x the recommended human dose of 6 mg based on plasma AUC data for a single dose).

Use in pregnancy

Pregnancy Category B3

Pegfilgrastim crosses the placenta in pregnant rats. Administration of pegfilgrastim every second day over the period of organogenesis to rats and rabbits at SC doses up to 1 mg/kg and 200 µg/kg, respectively, produced no evidence of teratogenicity. The rat dose was 2 fold of the anticipated exposure at the maximal recommended human dose (based on AUC), while the rabbit dose was 0.6 fold the human dose (based on body surface area). An increased incidence of wavy ribs, considered a reversible change, was observed in rats at doses greater than 100 µg/kg.

Decreased maternal body weight gain, accompanied by decreased maternal food consumption and decreased fetal body weights were observed in rabbits at doses of 50 µg/kg SC and above. Increased post-implantation loss due to early resorptions and an

increased incidence of abortions were observed at pegfilgrastim doses above 50 µg/kg SC. Once weekly SC injections of pegfilgrastim to female rats from day 6 of gestation through day 18 of lactation at doses up to 1000 µg/kg/dose did not result in any adverse maternal effects. There were no deleterious effects on the growth and development of the offspring and no adverse effects were found upon fertility indices.

There are no adequate and well-controlled studies in pregnant women. ZIEXTENZO® should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Use in lactation

Whether pegfilgrastim is excreted in human milk is not known. Because many drugs are excreted in human milk, caution should be exercised if ZIEXTENZO® is administered to breastfeeding women.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Adverse effects (undesirable effects)

Safety data are based on seven randomised clinical trials involving over 930 patients with lymphoma and solid tumours (breast, lung and thoracic tumours) receiving pegfilgrastim after non-myeloablative cytotoxic chemotherapy. Most adverse experiences were the sequelae of the underlying malignancy or cytotoxic chemotherapy. They occurred at similar rates in subjects who received pegfilgrastim (n = 930), filgrastim (n = 331) or placebo (n = 463). These adverse experiences occurred at rates between 15% and 72%. They included: nausea, fatigue, alopecia, diarrhoea, vomiting, constipation, fever, anorexia, skeletal pain, headache, taste perversion, dyspepsia, myalgia, insomnia, abdominal pain, arthralgia, generalised weakness, peripheral oedema, dizziness, granulocytopenia, stomatitis, mucositis, and neutropenic fever. The most common observed adverse reaction related to pegfilgrastim therapy was medullary bone pain, which was reported in 26% of patients. This was comparable to the incidence of medullary bone pain related to filgrastim therapy. This bone pain was generally reported to be of mild-to-moderate severity, could be controlled in most patients with non-narcotic analgesics, and had a comparable duration for both pegfilgrastim and filgrastim-treated patients. Infrequently, bone pain was severe enough to require narcotic analgesics. No patient withdrew from the study due to bone

pain. In these randomised clinical trials, the following adverse events related to pegfilgrastim were reported.

Table 1. Adverse Events in Active Comparator Studies Related to pegfilgrastim at an

Musculoskeletal Pain	5 (1%)	14 (3%)
Pain in Limb	5 (1%)	11 (2%)
Back Pain	4 (1%)	8 (2%)
Polymyalgia	7 (2%)	8 (2%)
Polyarthralgia	0 (0%)	5 (1%)
Nervous system disorders		
Headache	2 (0%)	6 (1%)
Skin and subcutaneous tissue disorders		
Alopecia	9 (2%)	8 (2%)

Across all studies, no life-threatening or fatal adverse events were attributed to pegfilgrastim. In these studies, there was only 1 serious adverse event (dyspnoea) reported in a single patient as possibly related to pegfilgrastim.

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

Post marketing experience

Extremely rare cases of capillary leak syndrome have been reported in subjects receiving filgrastim, the parent compound of pegfilgrastim. Allergic Reactions: Allergic-type reactions, including anaphylactic reactions, skin rash, urticaria and erythema/flushing occurring on initial or subsequent treatment have been reported in patients receiving pegfilgrastim. In some cases, symptoms have recurred with rechallenge, suggesting a causal relationship. Allergic-type reactions to pegfilgrastim have rarely been reported in post-marketing experience.

If a serious reaction occurs, appropriate therapy should be administered, with close patient follow-up over several days. ZIEXTENZO® should be permanently discontinued in patients who experience a serious allergic reaction.

Injection site pain and erythema have been reported in patients receiving pegfilgrastim.

Cases of glomerulonephritis have been reported uncommonly 1/1000 and < 1/100) in patients receiving pegfilgrastim.

Cases of pulmonary haemorrhage and haemoptysis have been reported in patients receiving pegfilgrastim.

Cases of aortitis have been reported in patients receiving pegfilgrastim.

Rare cases 1/10,000 and < 1/1,000) of Sweet's syndrome (acute febrile dermatosis), splenomegaly, splenic rupture and sickle cell crisis have been reported in patients receiving pegfilgrastim.

Very rare (< 1/10,000) reactions of cutaneous vasculitis have been reported in patients receiving pegfilgrastim.

There has been no evidence for the development of neutralising antibodies, or of a blunted or diminished response to pegfilgrastim in treated patients, including those receiving up to 6 cycles of pegfilgrastim.

Comparability of ZIEXTENZO® with the reference medicine in terms of safety

Similar safety profiles between ZIEXTENZO® and the reference medicine were observed in the clinical studies in healthy volunteers, as well as in patients with breast cancer.

Common adverse events in healthy subjects

In the Phase 1 PK/PD study in healthy volunteers, the pattern and nature of adverse events (AEs) reported after administration of ZIEXTENZO® were consistent with the safety profile of the reference medicine. Most commonly observed adverse events were bone pain, myalgia, arthralgia and back pain.

Common adverse events in patients

Studies LA-EP06-301 and LA-EP06-302 were double-blind, randomised, parallel-group, multi-center studies of similar design and were conducted in female patients with breast cancer receiving established myelosuppressive chemotherapy. Patients were randomised to either ZIEXTENZO® or the reference product administered on Day 2 of each chemotherapy (docetaxel (75 mg/m^2) in combination with doxorubicin (50 mg/m^2) and

cyclophosphamide (500 mg/m^2) cycle for up to 6 cycles. Treatment duration was up to 18 weeks in both studies. In both studies, study drug administration was 6 mg dose SC in every cycle.

Studies LA-EP06-301 and LA-EP06-302 independently showed similar safety results: the overall incidences and pattern of AEs were similar in the ZIEXTENZO® treatment groups compared with the reference product treatment groups of both studies and are consistent with reported data for the reference product. In addition, the findings are consistent with the nature of the underlying disease and the safety profiles of the chemotherapeutic agents.

AEs that were reported in these studies are shown by preferred term in Table 3.

Table 3. Summary of adverse events in patients with breast cancer (at least 2% of patients in any treatment group in Pool 1), by preferred term – studies LA-EP06-301, LA-EP06-302, and Pool 1 (SAF set)

	LA-EP06-301		LA-EP06-302		Pool 1	
Preferred term	**ZIEXTENZO® (N=159) n (%)**	**reference medicine (N=157) n (%)**	**ZIEXTENZO® (N=155) n (%)**	**reference medicine (N=153) n (%)**	**ZIEXTENZO® (N=314) n (%)**	**reference medicine (N=310) n (%)**
Total number of patients with AEs	**140 (88.1)**	**130 (82.8)**	**149 (96.1)**	**146 (95.4)**	**289 (92.0)**	**276 (89.0)**
Alopecia	82 (51.6)	79 (50.3)	77 (49.7)	66 (43.1)	159 (50.6)	145 (46.8)
Nausea	65 (40.9)	59 (37.6)	73 (47.1)	58 (37.9)	138 (43.9)	117 (37.7)
Asthenia	63 (39.6)	56 (35.7)	58 (37.4)	56 (36.6)	121 (38.5)	112 (36.1)
Neutropenia	27 (17.0)	34 (21.7)	73 (47.1)	66 (43.1)	100 (31.8)	100 (32.2)
Vomiting	34 (21.4)	34 (21.7)	44 (28.4)	40 (26.1)	78 (24.8)	74 (23.9)
Diarrhea	23 (14.5)	31 (19.7)	33 (21.3)	39 (25.5)	56 (17.8)	70 (22.6)
Leukopenia	11 (6.9)	13 (8.3)	34 (21.9)	29 (19.0)	45 (14.3)	42 (13.5)
Fatigue	18 (11.3)	21 (13.4)	19 (12.3)	21 (13.7)	37 (11.8)	42 (13.5)
Pyrexia	10 (6.3)	12 (7.6)	22 (14.2)	23 (15.0)	32 (10.2)	35 (11.3)
Anemia	16 (10.1)	18 (11.5)	15 (9.7)	17 (11.1)	31 (9.9)	35 (11.3)
Thrombocytopenia	11 (6.9)	11 (7.0)	15 (9.7)	11 (7.2)	26 (8.3)	22 (7.1)
Headache	5 (3.1)	9 (5.7)	21 (13.5)	13 (8.5)	26 (8.3)	22 (7.1)
Febrile neutropenia	9 (5.7)	12 (7.6)	16 (10.3)	19 (12.4)	25 (8.0)	31 (10.0)
Abdominal pain	8 (5.0)	7 (4.5)	17 (11.0)	16 (10.5)	25 (8.0)	23 (7.4)
Myalgia	9 (5.7)	13 (8.3)	11 (7.1)	16 (10.5)	20 (6.4)	29 (9.4)
Stomatitis	8 (5.0)	13 (8.3)	12 (7.7)	15 (9.8)	20 (6.4)	28 (9.0)
Arthralgia	10 (6.3)	13 (8.3)	10 (6.5)	6 (3.9)	20 (6.4)	19 (6.1)
Pain	7 (4.4)	10 (6.4)	12 (7.7)	12 (7.8)	19 (6.1)	22 (7.1)
Pain in extremity	6 (3.8)	6 (3.8)	12 (7.7)	7 (4.6)	18 (5.7)	13 (4.2)
Bone pain	7 (4.4)	8 (5.1)	10 (6.5)	17 (11.1)	17 (5.4)	25 (8.1)

	LA-EP06-301		LA-EP06-302		Pool 1	
Preferred term	**ZIEXTENZO® (N=159) n (%)**	**reference medicine (N=157) n (%)**	**ZIEXTENZO® (N=155) n (%)**	**reference medicine (N=153) n (%)**	**ZIEXTENZO® (N=314) n (%)**	**reference medicine (N=310) n (%)**
Decreased appetite	7 (4.4)	16 (10.2)	9 (5.8)	13 (8.5)	16 (5.1)	29 (9.4)
Constipation	10 (6.3)	9 (5.7)	6 (3.9)	8 (5.2)	16 (5.1)	17 (5.5)
Cough	4 (2.5)	6 (3.8)	12 (7.7)	8 (5.2)	16 (5.1)	14 (4.5)
Edema peripheral	10 (6.3)	5 (3.2)	6 (3.9)	3 (2.0)	16 (5.1)	8 (2.6)
Erythema	14 (8.8)	16 (10.2)	1 (0.6)	1 (0.7)	15 (4.8)	17 (5.5)
Alanine aminotransferase increased	6 (3.8)	3 (1.9)	8 (5.2)	4 (2.6)	14 (4.5)	7 (2.3)
Aspartate aminotransferase increased	6 (3.8)	2 (1.3)	5 (3.2)	3 (2.0)	11 (3.5)	5 (1.6)
Neuropathy peripheral	4 (2.5)	1 (0.6)	6 (3.9)	7 (4.6)	10 (3.2)	8 (2.6)
Abdominal pain upper	2 (1.3)	2 (1.3)	8 (5.2)	5 (3.3)	10 (3.2)	7 (2.3)
Back pain	1 (0.6)	5 (3.2)	8 (5.2)	5 (3.3)	9 (2.9)	10 (3.2)
Leukocytosis	2 (1.3)	0	7 (4.5)	6 (3.9)	9 (2.9)	6 (1.9)
Dyspnea	2 (1.3)	1 (0.6)	6 (3.9)	4 (2.6)	8 (2.5)	5 (1.6)
Urinary tract infection	4 (2.5)	0	4 (2.6)	4 (2.6)	8 (2.5)	4 (1.3)
Dyspepsia	2 (1.3)	4 (2.5)	5 (3.2)	6 (3.9)	7 (2.2)	10 (3.2)
Respiratory tract infection viral	3 (1.9)	9 (5.7)	0	2 (1.3)	3 (1.0)	11 (3.5)

AE=treatment-emergent adverse event; n=number of patients with an event; N=number of patients in a treatment group; SAF set=safety analysis set.

Pool 1: pooled data from studies LA-EP06-301 and LA-EP06-302 were used for a combined analysis of safety. Only treatment-emergent AEs are reported, i.e. AEs occurring at the time or after the first administration of the study drug (ZIEXTENZO® or reference medicine) and not later than 30 days after the last dose of chemotherapy. Patients could have events in more than one category. Sorted by descending frequency in the ZIEXTENZO® treatment group of Pool 1.

The safety profile of ZIEXTENZO® was similar to the safety profile of the reference medicine with no clinically meaningful differences observed in healthy volunteers or patients.

Comparability of ZIEXTENZO® with the reference medicine in terms of immunogenicity

Immunogenicity of ZIEXTENZO® and the reference medicine was compared in healthy

subjects and breast cancer patients. Overall there was low immunogenicity which is consistent with data reported for the reference medicine.

The incidence of ADAs (anti-drug antibodies) post treatment was similarly low in all treatment groups, the detected ADAs were non-neutralizing and clinically not relevant. There was no unusual behaviour noted in individual PK and absolute neutrophil count (ANC) profiles indicative of potential effects of ADAs on pegfilgrastim systemic clearance or on the production and release of neutrophils.

The low detection rate of ADAs post treatment in both healthy volunteers and breast cancer patients and the absence of NAbs (neutralizing antibodies) in all three studies is consistent with data reported with the reference medicine.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after registration 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 at http://www.tga.gov.au/reporting-problems.

4.9 Overdose

There is no experience with overdose of pegfilgrastim in humans. In subjects administered doses of up to 5 times the recommended dose, adverse events were similar to those observed in subjects administered lower doses of pegfilgrastim. For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Human G-CSF is a glycoprotein which regulates the production and release of neutrophils from the bone marrow. Pegfilgrastim has reduced renal clearance and prolonged persistence *in vivo* compared to filgrastim. Pegfilgrastim and filgrastim have been shown to have identical modes of action. They cause a marked increase in peripheral blood neutrophil counts within 24 hours in subjects with healthy bone marrow, with minor increases in monocytes and/or lymphocytes. Similarly to filgrastim, neutrophils produced in response to pegfilgrastim show normal or enhanced function as demonstrated by tests

of chemotactic and phagocytic function.

Pharmacodynamic comparability of ZIEXTENZO® with the reference medicine

Pharmacodynamic (PD) similarity of ZIEXTENZO® was demonstrated in a single-dose, two-period crossover study in healthy subjects with a single SC administration of ZIEXTENZO® and the reference medicine.

PD similarity was shown in healthy subjects using absolute neutrophil count over time.

PD similarity between ZIEXTENZO® and the reference medicine was demonstrated with the lower and upper bounds of the 95% CIs (confidence intervals) of the geometric mean ratios of the primary PD endpoints $AUEC_{0\text{-last}}$ and E_{max} being entirely contained within the pre-defined margins of 0.80 to 1.25.

Table 4. Summary of the PD similarity analysis of the primary ANC PD parameters (ANC baseline corrected) - study LA-EP06-103 (PD analysis set)

			Geometric LSmeans		Ratio ZIEXTENZO®/reference medicine	
Treatment comparison	**PD parameter**	**N**	**ZIEXTENZO®**	**reference medicine**	**Point estimate**	**95% CI**
ZIEXTENZO® / reference medicine	$AUEC_{0\text{-last}}$ ($h\times10^9/L$)	169	3987	3927	1.0155	[0.9948; 1.0366]
	E_{max} ($10^9/L$)	169	32.6	32.7	0.9951	[0.9737; 1.0169]

ANC=absolute neutrophil count; CI=confidence interval; LSmeans=least square means; N=total number of subjects included in the analysis; PD=pharmacodynamics, $AUEC_{0\text{-last}}$ = Area under the effect curve measured from the time of dosing to the last measurable concentration ($h\times10^9/L$); E_{max} = Maximum effect attributable to the study drug ($10^9/L$)

Clinical trials

Three pivotal, randomised, double-blind clinical studies have been conducted in patients with solid tumours receiving a variety of chemotherapy regimens. Pegfilgrastim administered 24 hours after chemotherapy in the first cycle and all subsequent cycles of chemotherapy has been shown to be safe and effective in reducing neutropenia and associated clinical sequelae.

Studies 1 and 2 met the primary objective of demonstrating that the mean days of severe neutropenia of pegfilgrastim-treated patients ([ANC] < 0.5 x 10^9/L) did not exceed that of filgrastim-treated patients by more than one day in cycle 1 of chemotherapy.

Results from Study 1, a randomised, double-blind study conducted in patients with breast cancer (n = 155) undergoing 4 cycles of the highly myelosuppressive chemotherapy

regimen doxorubicin and docetaxel (AT), demonstrated a clinically and statistically similar reduction in the duration of severe neutropenia (ANC < 0.5 x 10^9/L) in cycle 1 in patients who received pegfilgrastim as a fixed dose of 6 mg compared with patients who received a mean of 11 daily injections of filgrastim 5 µg/kg/day (see Table 5). Durations of severe neutropenia were also comparable between treatment groups in all subsequent cycles. There was no significant difference in the incidence of febrile neutropenia between the groups in Study 1.

Table 5. Cycle 1 Duration of Severe Neutropenia and Study Incidence of Febrile Neutropenia and Infection in Pegfilgrastim Pivotal Trials

Endpoint	Study 1: 6mg		Study 2: 100 µg/kg	
	Pegfilgrastim n = 68 PP n = 77 mod ITT	**Filgrastim n = 62 PP n = 75 mod ITT**	**Pegfilgrastim n = 131 PP n = 149 mod ITT**	**Filgrastim n = 129 PP n = 147 mod ITT**
Mean days of severe neutropenia cycle 1	1.8	1.6	1.7	1.6
Difference in means (95% CI) per protocol	0.18 (-0.23, 0.61)		0.09 (-0.23, 0.40)	
Incidence of febrile neutropenia (all cycles)	13%	20%	9%	18%
Difference in incidence (95% CI) modified ITT	-7% (-19%, 5%)		-9% (-17%, -1%)	
Incidence of infection – culture-confirmed (all cycle)	9%	9%	10%	9%
Difference in incidence (95% CI) modified ITT	0% (-9.4%, 9.0%)		1% (-5.4%, 7.9%)	

PP = per protocol
Mod ITT = modified intention to treat

In study 2, patients with breast cancer (n = 301) were randomised to receive a single injection of pegfilgrastim 100 µg/kg or daily injections of filgrastim 5 µg/kg/day after each of 4 cycles of the highly myelosuppressive chemotherapy regimen doxorubicin and docetaxel (AT). In cycle 1, a single SC injection of pegfilgrastim resulted in a duration of severe

neutropenia that was clinically and statistically similar to that observed after a mean of 11 daily injections of filgrastim (see Table 5). Durations of severe neutropenia were also comparable between treatment groups in all subsequent cycles. There is a significant difference in the incidence of febrile neutropenia between the groups in Study 2.

Study 3 was a placebo-controlled study evaluating the effect of pegfilgrastim on the incidence of febrile neutropenia following administration of a moderately myelosuppressive chemotherapy regimen (docetaxel 100 mg/m^2 q 3 weeks for 4 cycles). This regimen is associated with a febrile neutropenia rate of up to 20%. In this study, 928 patients were randomised to receive either pegfilgrastim or placebo on Day 2 of each cycle. The incidence of patients with febrile neutropenia, was significantly lower in the patients randomised to receive pegfilgrastim vs placebo (1% vs 17%, $p < 0.001$, respectively). The incidence of hospitalisation and IV anti- infective use associated with a clinical diagnosis of febrile neutropenia was significantly lower in patients randomised to pegfilgrastim compared to placebo (1% vs 14%, $p < 0.001$; and 2% vs 10%, $p < 0.001$, respectively).

Data from phase 2 studies in patients with various malignancies undergoing a variety of chemotherapy regimens further support the safety and efficacy of pegfilgrastim. Dose-finding studies in patients with breast cancer (n = 152), thoracic tumours (n = 92) and non-Hodgkin's lymphoma (NHL) (n = 50) demonstrated that the efficacy of a single injection of pegfilgrastim 100 µg/kg was similar to daily injections of filgrastim 5 µg/kg/day and was superior to the lower dose of 30 µg/kg. A randomised phase 2 study of patients with NHL or Hodgkin's lymphoma (n = 60) further supports the safety and efficacy of pegfilgrastim.

A phase 2, randomised, double-blind study (n = 83) in patients receiving chemotherapy for *de novo* acute myeloid leukaemia compared pegfilgrastim (single dose of 6 mg) with filgrastim, administered during induction chemotherapy. Median time to recovery from severe neutropenia was estimated as 22 days in both treatment groups. Long term outcome was not studied.

Comparability of ZIEXTENZO® with the reference medicine in terms of efficacy

The efficacy of ZIEXTENZO® has been demonstrated in double-blind, randomised, parallel-group, multi-center studies of similar design (LA-EP06-301 and LA-EP06-302). Each study was conducted in female patients with breast cancer receiving established myelosuppressive chemotherapy. Patients were randomised to either ZIEXTENZO® or the

reference product administered on Day 2 of each chemotherapy (docetaxel 75 mg/m^2) in combination with doxorubicin (50 mg/m^2) and cyclophosphamide (500 mg/m^2) cycle for up to 6 cycles. In both studies, study drug administration was 6 mg dose SC in every cycle and treatment duration was up 18 weeks.

In studies LA-EP06-301 and LA-EP06-302, the primary objective (powered at 90% for each study) was to compare ZIEXTENZO® and the reference medicine in terms of the DSN (duration of severe neutropenia) in Cycle 1. The primary efficacy variable was defined as the mean DSN in Cycle 1. The DSN was defined as the number of consecutive days with grade 4 neutropenia (i.e. an ANC count <0.5×10^9/L) in Cycle 1.

The results of the ANCOVA model (adjusted for the stratification factors chemotherapy and region, and the covariate baseline ANC) demonstrated that ZIEXTENZO® is equivalent to the reference medicine because the 95% CI was contained within the defined margin of ±1 day for both studies (Table 6 and Table 7).

Table 6. Primary efficacy variable: Difference in the duration of severe neutropenia (DSN) in days in Cycle 1 – inferential test results of ANCOVA – studies LA-EP06-301 and LA-EP06-302 (FAS set)

Difference in DSN reference medicine minus ZIEXTENZO®	**LA-EP06-301 N=316**	**LA-EP06-302 N=308**
n	310	300
Difference (days)	0.07	-0.16
95% CI [LL, UL]	[-0.12, 0.26]	[-0.40, 0.08]

ANCOVA=analysis of covariance; CI=confidence interval; DSN=duration of severe neutropenia; FAS set=full analysis set; LL, UL=lower limit, upper limit; N=number of patients per treatment group; n=number of evaluable patients

The ANCOVA model assessing the treatment point estimate and corresponding CIs were adjusted for chemotherapy, and region as fixed effects, and study as a random effect. Baseline absolute neutrophil count (ANC), defined as the ANC value at Day 1 of Cycle 1, was a covariate.

Equivalence margins: ±1 day; non-inferiority margin: -0.6 days

Table 7. Primary efficacy variable: Duration of severe neutropenia (DSN) in days in Cycle 1 – studies LA-EP06-301 and LA-EP06-302 (FAS set)

	LA-EP06-301		**LA-EP06-302**	
DSN (days)	**ZIEXTENZO® N=159**	**reference medicine N=157**	**ZIEXTENZO® N=155**	**reference medicine N=153**
n[a]	155	155	151	149
Mean (SD)	0.75 (0.878)	0.83 (0.898)	1.36 (1.133)	1.19 (0.984)
Median (range)	1.00 (0.0-3.0)	1.00 (0.0-4.0)	1.00 (0.0-6.0)	1.00 (0.0-4.0)

ANC=absolute neutrophil count; DSN=duration of severe neutropenia; FAS set=full analysis set; n=number of evaluable patients; N=number of patients in a treatment group; SD=standard deviation

[a] Overall, 14 patients had missing ANC profiles and were excluded from the analysis.

5.2 Pharmacokinetic properties

Absorption

After a single 6 mg SC dose of pegfilgrastim in healthy subjects, the time to peak serum concentration of pegfilgrastim was variable, ranging from 4 to 60 hours with a medium value of 12 hours. After a 6 mg SC dose of pegfilgrastim in breast cancer patients receiving myelosuppressive chemotherapy, the range was from 22 to 120 hours with a median value of 24 hours. Serum concentrations of pegfilgrastim were maintained during the period of neutropenia after myelosuppressive chemotherapy.

Distribution

The distribution of pegfilgrastim was limited to the plasma compartment.

Metabolism

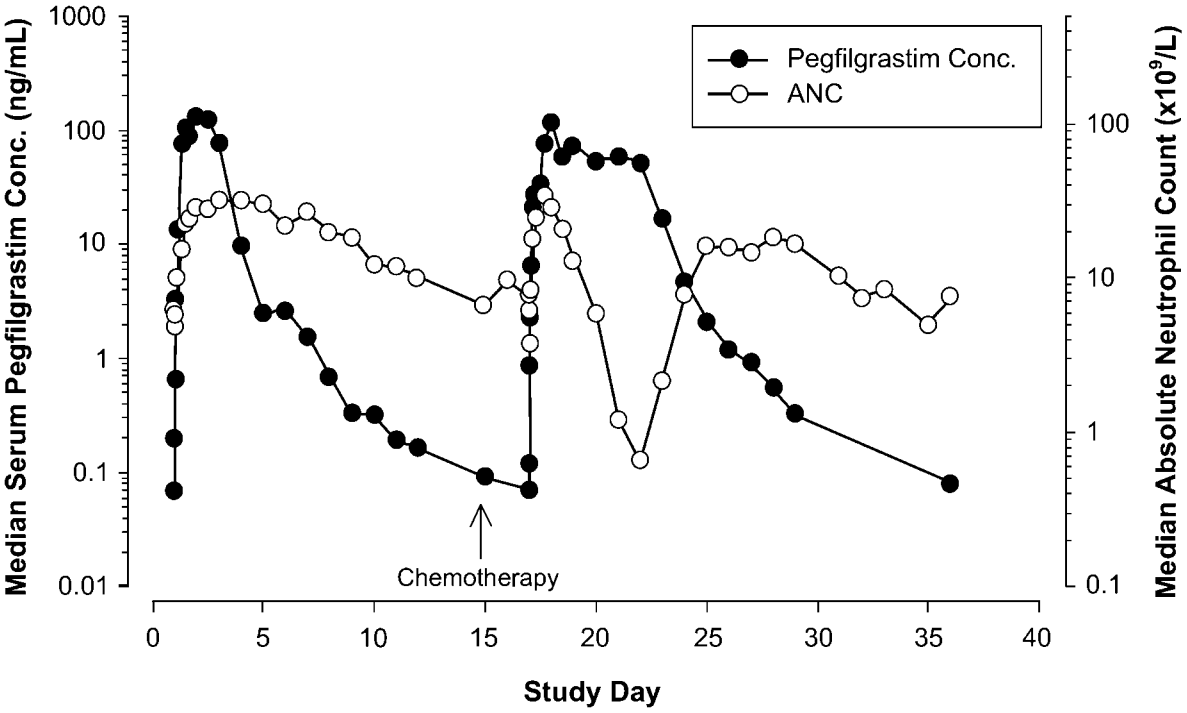
The metabolic pathway of pegfilgrastim has not been characterised.

Elimination

The elimination of pegfilgrastim was non-linear with respect to dose; serum clearance of pegfilgrastim decreased with increasing dose. The saturable clearance pathway was attributed to neutrophils and neutrophil precursors (neutrophil-mediated, self-regulating clearance).

Results from pharmacokinetic/ pharmacodynamic modelling support neutrophil-mediated clearance as the main route of elimination (> 99%). Consistent with a self-regulating clearance mechanism, the serum concentration of pegfilgrastim declined rapidly at the onset of neutrophil recovery following myelosuppressive chemotherapy (see Figure 1).

Figure 1. Median Pegfilgrastim Serum Concentration and ANC Profiles in Patients With Non-small Cell Lung Cancer (n = 3) After a Single Injection of Pegfilgrastim 100 µg/kg Administered Before and After Chemotherapy



Pharmacokinetic comparability of ZIEXTENZO® with the reference medicine

PK similarity of ZIEXTENZO® was demonstrated in a single-dose, two-period crossover study in healthy subjects with a single SC administration of ZIEXTENZO® and the reference medicine.

The assessment of PK similarity was based on the 90% CIs for the ratio of the geometric means between ZIEXTENZO® and the reference medicine for the three primary PK parameters $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, and C_{max}, which were all contained within the pre-defined PK similarity margins of 0.80 to 1.25 (Table 8).

Table 8. Summary of the PK similarity analysis of the primary PK parameters - study LA-EP06-103 (PK analysis set)

			Geometric LSmeans		Ratio ZIEXTENZO®/reference medicine	
Treatment comparison	PK parameter	N	ZIEXTENZO®	reference medicine	Point estimate	90% CI
ZIEXTENZO®/ reference medicine	$AUC_{0\text{-inf}}$ (h×ng/mL)	168	7652	6730	1.1370	[1.0559; 1.2244]
	$AUC_{0\text{-last}}$ (h×ng/mL)	169	7487	6547	1.1435	[1.0607; 1.2328]
	C_{max} (ng/mL)	169	209	189	1.1082	[1.0312; 1.1909]

CI=confidence interval; LSmeans=least square means; N=total number of subjects included in the analysis;

PK=pharmacokinetics, $AUC_{0\text{-}inf}$ = area under the serum concentration-time curve measured from the time of dosing and extrapolated to infinity (h×ng/mL); $AUC_{0\text{-}last}$ = area under the serum concentration-time curve measured from the time of dosing to the last measurable concentration (h×ng/mL); C_{max} = maximum observed serum concentration (ng/mL).

Special populations

Hepatic impairment

No studies have been conducted in patients with hepatic failure; however, the pharmacokinetics of ZIEXTENZO® are not expected to be affected by impaired hepatic function.

Renal impairment

Renal impairment, including end-stage renal disease, appears to have no effects on the pharmacokinetics of ZIEXTENZO®.

Elderly patients

The pharmacokinetics of pegfilgrastim in elderly cancer patients 65 years of age) were similar to those in younger subjects.

Paediatric patients

The safety and pharmacokinetics of pegfilgrastim were studied in 37 paediatric patients with sarcoma. The mean (± Standard Deviation) systemic exposure ($AUC_{0\text{-}inf}$) of pegfilgrastim after subcutaneous administration at 100 µg/kg was 22.0 (± 13.1) µg›hr/mL in the 6 - 11 years age group (n = 10), 29.3 (± 23.2) µg hr/mL in the 12 - 21 years age group (n = 13) and 47.9 (± 22.5) µg›hr/mL in the youngest age group (0 - 5 years, n = 11). The terminal elimination half-lives of the corresponding age groups were 20.2 (± 11.3) hours, 21.2 (± 16.0) hours and 30.1 (± 38.2) hours respectively. The most common adverse reaction was bone pain.

5.3 Preclinical safety data

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*.

Genotoxicity

No mutagenicity studies have been conducted with pegfilgrastim, although the parent

protein (filgrastim) was negative in bacterial mutagenicity assays, a test for chromosome aberrations in Chinese hamster lung cells *in vitro* and in an *in vivo* mouse micronucleus test.

Carcinogenicity

No carcinogenicity testing has been conducted for pegfilgrastim.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The product is formulated at pH 4.0 with 0.36 mg acetic acid, 30 mg sorbitol, 0.02 mg polysorbate 20, sodium hydroxide (if necessary for pH adjustment) in Water for Injection to 0.6 mL.

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store at 2°C to 8°C (Refrigerate. Do not freeze). Avoid shaking. Protect from light. ZIEXTENZO® may be exposed to room temperature (up to 25°C) for a maximum single period of up to 72 hours. ZIEXTENZO® left at room temperature for more than 72 hours should be discarded.

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

6.5 Nature and contents of container

Pre-filled Syringe with automatic needle guard:

Each carton contains 1 ready to use pre-filled syringe with automatic needle guard containing 6 mg of pegfilgrastim in 0.6 mL (10 mg/mL) solution for SC injection.

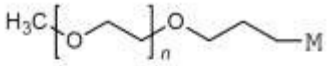
6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physicochemical properties

Chemical structure

$C_{849}H_{1347}N_{223}O_{244}S_{9,}(C_2H_4O)_n$



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MEELGMAPAL QPTQGAMPAF ASAFQRRAGG VLVASHLQSF

LEVSYRVLRH LAQP

CAS number

208265-92-3

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 - Prescription Only Medicine

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9 DATE OF FIRST APPROVAL

06 September 2019

10 DATE OF REVISION

Not applicable

Internal document code
zie060919i based on Neulasta Australian PI dated 25 September 2018