AUSTRALIAN PRODUCT INFORMATION – FILPEGLA (pegfilgrastim) solution for injection

1 NAME OF THE MEDICINE

FILPEGLA contains pegfilgrastim, a long-acting form of recombinant human Granulocyte Colony-Stimulating Factor (G-CSF).

FILPEGLA is a biosimilar medicine to Neulasta®. The evidence for comparability supports the use of FILPEGLA for the listed indication[s]

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

FILPEGLA is composed of filgrastim (recombinant methionyl human G-CSF) with a 21,000 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*. FILPEGLA has a total molecular weight of 40,000 daltons.

Each single-use pre-filled syringe with automatic needle guard of FILPEGLA contains 6 mg of pegfilgrastim (based on protein mass only).

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

3 PHARMACEUTICAL FORM

Solution for injection (injection).

FILPEGLA is a sterile, clear and colourless preservative-free solution for injection for subcutaneous (SC) administration.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

FILPEGLA 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 FILPEGLA is a single SC injection of 6 mg administered once per chemotherapy cycle. FILPEGLA 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

FILPEGLA contains no antimicrobial agent. FILPEGLA is for single use in one (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.

Traceability

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

4.3 Contraindications

Pegfilgrastim 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

Splenomegaly and splenic rupture

Cases of splenic rupture, including some fatal cases, have been reported following 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 pegfilgrastim 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 pegfilgrastim, 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.

Myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML) in breast and lung cancer patients

In the post-marketing observational study setting, myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML) have been associated with the use of pegfilgrastim in conjunction with chemotherapy and/or radiotherapy in breast and lung cancer patients. Monitor patients for signs and symptoms of MDS/AML in these settings.

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, e.g. 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

Thrombocytopenia has been reported in patients receiving pegfilgrastim. Platelet counts should be monitored closely.

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 (i.e. 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 pegfilgrastim 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 haemopoietic 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. Pegfilgrastim 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 pegfilgrastim 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 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 incidence ≥ 1%

	Percentage of Patients Reporting Events	
Body System and Preferred Terms	**Pegfilgrastim (n = 465)**	**Filgrastim 5 µg/kg/day (n = 331)**
Application site		
Injection site pain	3	3
Body as a whole		
Pain	2	1
Pain chest	1	1
Oedema periorbital	1	< 1
Fever	1	1
CNS/PNS		
Headache	4	4
Musculo-skeletal		
Pain skeletal	21	27
Myalgia	7	8
Arthralgia	6	6
Pain back	4	8
Pain limb	3	2
Pain musculo-skeletal	1	1
Pain neck	1	1

Table 2. Most frequently reported treatment-related adverse events in randomised clinical trials with placebo control

	Number and Percentage of Patients Reporting Events	
Body System and Preferred Terms	**Placebo (N=463)**	**Pegfilgrastim (N = 465)**
Gastrointestinal disorders		
Diarrhoea	10 (2%)	9 (2%)
General disorders and administration site conditions	9 (2%)	8 (2%)
Pyrexia		
Infections and infestations		
Influenza	5 (1%)	6 (1%)
Musculoskeletal and connective tissue disorders	41 (9%)	62 (13%)
Bone Pain		

Arthralgia	20 (4%)	31 (7%)
Myalgia	23 (5%)	26 (6%)
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	9 (2%)	8 (2%)
Alopecia		

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. FILPEGLA 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.

Cases of thrombocytopenia have been reported commonly (≥ 1/100 and < 1/10) in patients receiving pegfilgrastim.

Cases of myelodysplastic syndrome and acute myeloid leukaemia have been reported in breast and lung cancer patients receiving chemotherapy and/or radiotherapy.

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 FILPEGLA with Neulasta®

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

In the Phase 1 PK/PD study (EGF/USV/P1/001) in healthy volunteers, the pattern and nature of adverse events (AEs) reported after administration of FILPEGLA were consistent with the safety profile of the reference medicine (Neulasta®). Most commonly observed adverse events were extremity pain, musculoskeletal pain, headache and back pain.

Study PEGF/USV/P3/003 was assessor-blind, active-controlled, randomised, parallel-group, multi-center study conducted in female patients with breast cancer receiving established myelosuppressive chemotherapy. Patients were randomised to either FILPEGLA 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 and study drug administration was 6 mg dose SC in every cycle.

In the Study PEGF/USV/P3/003 among patients with breast cancer, FILPEGLA was generally well tolerated and the safety profile was similar to EU-Neulasta®. Table 3 provides a summary of related TEAEs reported by ≥5% of patients across all 6 cycles. The most commonly reported related TEAE by preferred term was bone pain in both FILPEGLA and Neulasta® arm.

Table 3. Summary of adverse events in patients with breast cancer by preferred term – study PEGF/USV/P3/003 (Safety Analysis Set)

System Organ Class / Preferred term	FILPEGLA (N=166) n (%)	EU-Neulasta (N=82) n (%)
Blood and lymphatic system disorders	145 (87.3	70 (85.4)
Neutropenia	130 (78.3)	63 (76.8)
Leukopenia	74 (44.6)	36 (43.9)
Thrombocytopenia	25 (15.1)	8 (9.8)
Anaemia	15 (9.0)	9 (11.0)
Febrile neutropenia	9 (5.4)	2 (2.4)
Leukocytosis	6 (3.6)	5 (6.1)
Gastrointestinal disorders	109 (65.7)	54 (65.9)
Nausea	79 (47.6)	38 (46.3)
Diarrhoea	33 (19.9)	20 (24.4)
Vomiting	17 (10.2)	7 (8.5)
Abdominal pain upper	12 (7.2)	9 (11.0)
Abdominal pain	9 (5.4)	2 (2.4)
General disorders and administration site conditions	80 (48.2)	38 (46.3)
Asthenia	35 (21.1)	18 (22.0)
Fatigue	21 (12.7)	12 (14.6)
Injection site reaction	16 (9.6)	8 (9.8)
Infections and infestations	10 (6.0)	2 (2.4)
Investigations	12 (7.2)	3 (3.7)
Musculoskeletal and connective tissue disorders	59 (35.5)	31 (37.8)
Bone pain	54 (32.5)	27 (32.9)
Spinal pain	13 (7.8)	8 (9.8)
Nervous system disorders	68 (41.0)	33 (40.2)
Headache	46 (27.7)	18 (22.0)
Dizziness	36 (21.7)	15 (18.3)
Respiratory, thoracic and mediastinal disorders	9 (5.4)	3 (3.7)
Skin and subcutaneous tissue disorders	64 (38.6)	31 (37.8)
Alopecia	62 (37.3)	30 (36.6)

Comparability of FILPEGLA with Neulasta® in terms of immunogenicity

Immunogenicity of FILPEGLA and Neulasta® 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 both treatment groups. There was one subject wherein antibody against pegfilgrastim was found to have neutralizing capacity however the titre of antibody for screening as well neutralization assay were low (<2). Antibody appearance was transient as antibody was detected only at one timepoint - at cycle 4 day -3 and it was not detected at other time points. This isolated and transient NAbs (neutralizing antibodies) case has no impact on the efficacy and safety of FILPEGLA.

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

Reporting of suspected adverse effects

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 FILPEGLA with Neulasta®

Pharmacodynamic (PD) similarity of FILPEGLA was demonstrated in a randomised, single-dose, two-period crossover study in healthy subjects with a single SC administration of FILPEGLA and Neulasta®.

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

PD similarity between FILPEGLA and Neulasta® 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 and E_{max} being entirely contained within the pre-defined margins of 90.00-111.11%.

Table 4: Summary of the PD similarity of the primary ANC PD parameters – Study EGF/USV/P1/001 (PD analysis set)

PD Parameters	Geometric Mean [a]		Ratio [b]	95% CI
	FILPEGLA n = 142	Neulasta® n = 142		
AUEC (× 10^9/L/h)	4420	4440	99.66	(97.46, 101.91)
E_{max} (× 10^9/L/h)	31.84	31.73	100.35	(97.47, 103.31)

ANC; absolute neutrophil count

a. Adjusted geometric mean from analysis of covariance model

b. Ratio of adjusted geometric means defined as USV pegfilgrastim/Neulasta®

Clinical trials

Clinical Trials with Neulasta®

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

	Study 1: 6 mg		Study 2: 100 µg/kg	
Endpoint	**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 cycles)	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 antiinfective 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 FILPEGLA with Neulasta®

The efficacy and safety of FILPEGLA were assessed in a randomised active-control, assessor-blind, parallel group, multicentre, clinical Phase III study in 254 patients ≥ 18 years of age with breast cancer receiving established myelosuppressive chemotherapy (Study PEGF/USV/P3/003). Patients were randomised to either FILPEGLA or Neulasta® 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 this study, study drug administration was 6 mg dose SC in every cycle and treatment duration was up 18 weeks.

In study PEGF/USV/P3/003, the primary objective was to compare FILPEGLA and Neulasta® 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 primary analysis model demonstrated that FILPEGLA is equivalent to the reference medicine (Neulasta®) because the 95% CI was contained within the defined range of 0.65-1.55 for study (Table 6 and Table 7).

Table 6: Primary efficacy variable: Duration of severe neutropenia (DSN) in days in Cycle 1 (FAS set)

DNS (days)	PEGF/USV/P3/003	
	FILPEGLA	Neulasta®
N	166	82
Mean (± SD)	1.58 (1.207)	1.65 (1.231)
Median (range)	2.0 (0-5)	2.0 (0-4)

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

Table 7: Summary of Efficacy Results for the Duration of severe neutropenia (DSN) in Cycle 1, Estimated with generalized linear model accounting for treatment effect following treatment with FILPEGLA and Neulasta® (FAS set)

DSN (days)	FILPEGLA (N=166)	Neulasta® (N=82)	Ratio (FILPEGLA vs. Neulasta®)
LS Mean	1.58	1.65	0.96
95% Cl	1.40 - 1.79	1.39 - 1.95	0.78 - 1.18

LS: Least Square; CI: Confidence Interval

The results of DSN data in Cycle 1 show the similarity in efficacy of FILPEGLA and Neulasta® (0.78 - 1.18) since the 95% CI are within the equivalence range of 0.65 to 1.55 for treatment comparisons.

5.2 Pharmacokinetic properties

Absorption

After a single SC dose of pegfilgrastim in man, the time to peak serum concentration of pegfilgrastim was variable, ranging from 8 to 120 hours. After a 6 mg SC dose, the range was from 15.9 to 120.5 hours with a median value of 39.9 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.

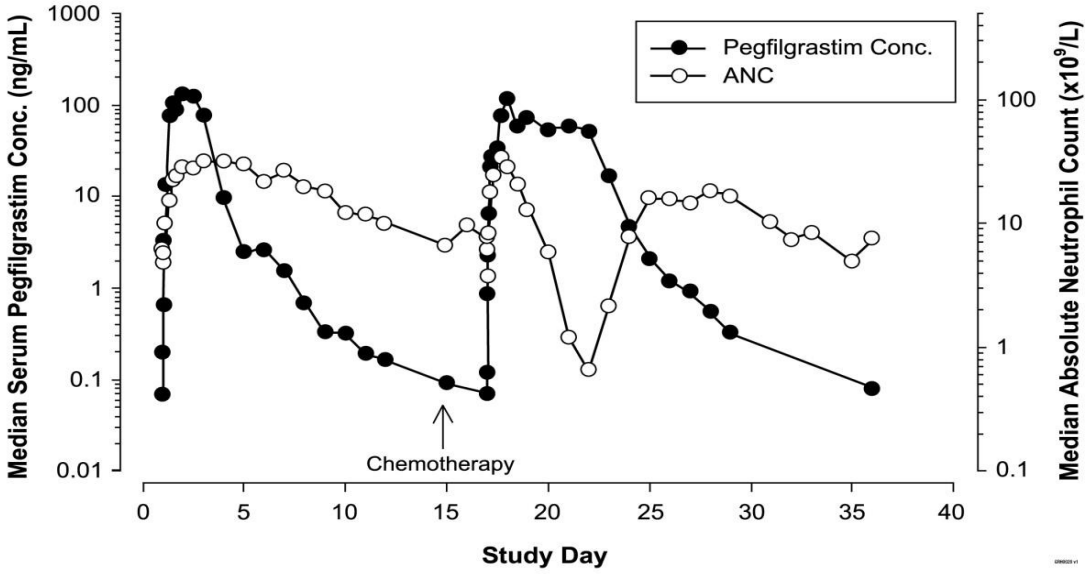
Metabolism

The metabolic pathway of pegfilgrastim has not been characterised.

Excretion

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



Special populations

Hepatic impairment

No studies have been conducted in patients with hepatic failure; however, the pharmacokinetics of pegfilgrastim 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 pegfilgrastim.

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-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.

Comparability of FILPEGLA with Neulasta®

Pharmacokinetic (PK) profiles of FILPEGLA and Neulasta® were compared in a single dose, randomized, double-blind, two treatments, two period, two sequence crossover, phase 1 PK/PD study in 156 healthy male and female volunteers (PEGF/USV/P1/001). A single, fixed SC dose of 6 mg was administered over two 28-day periods with a 4 week washout. The 90% CI of the primary PK endpoint parameters ($AUC_{(last)}$, $AUC_{(0\text{-}inf)}$ and C_{max} for pegfilgrastim) were contained within the pre-defined acceptance range of 80-125%, demonstrating the biosimilarity of FILPEGLA to the reference product, Neulasta®.

Table 8 shows the PK results following the administration of FILPEGLA and Neulasta®. The ratios of the geometric means for the test/reference (FILPEGLA/Neulasta®) were within the pre-defined acceptance range of 80 – 125% for $AUC_{(last)}$, $AUC_{(0\text{-}inf)}$ and C_{max}.

Table 8: Assessment of Comparability – Pharmacokinetic Parameters for FILPEGLA and Neulasta®: Pharmacokinetic Dataset

Parameter (Unit)	Geometric Mean[a]		Ratio [b]	90% Confidence Interval [c]
	FILPEGLA [c] n = 142	Neulasta® n = 142		
$AUC_{(last)}$ (pg·h/mL)	3540000	3480000	101.70	(92.86, 111.38)
$AUC_{(0\text{-}inf)}$ (pg·h/mL)	3570000	3510000	101.70	(92.95, 111.27)
C_{max} (pg/mL)	107000	109000	98.32	(89.38, 108.15)

AUC_{last} = The area under the curve (AUC - calculated by the linear trapezoidal rule) from time zero up to the sampling time for which the last non-zero concentration; AUC_{inf} = The AUC from time zero to infinity; C_{max} = The maximum observed concentration of pegfilgrastim over the sampling interval;

a. Adjusted geometric mean from analysis of variance model
b. Ratio of adjusted geometric means defined as FILPEGLA/Neulasta®
c. Confidence Interval for the ratio of adjusted geometric means

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*.

Carcinogenicity

No carcinogenicity testing has been conducted for pegfilgrastim.

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The product is formulated at pH 3.8 to 4.3 with 0.35 mg glacial acetic acid, 30.0 mg sorbitol, 0.02 mg polysorbate 20, 0.035 mg sodium hydroxide in water for injections 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.

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.

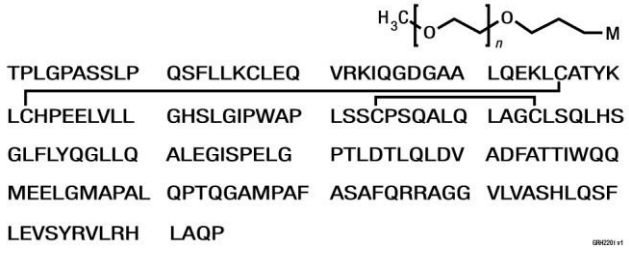
6.6 Special precautions for disposal

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

6.7 Physicochemical properties

Chemical structure

$C_{849}H_{1347}N_{223}O_{244}S_9,(C_2H_4O)_n$



CAS number

208265-92-3

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

19.08.2022

10 DATE OF REVISION

[Item to be completed at the time of approval]

Summary table of changes

Section changed	Summary of new information
NA	NA

NA: Not Applicable.