NEW ZEALAND DATA SHEET

PELGRAZ (PEGFILGRASTIM) SOLUTION FOR INJECTION

1 PRODUCT NAME

Pelgraz 6 mg/0.6mL solution for injection.

Pelgraz is a biosimilar medicinal product.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 6 mg of pegfilgrastim in 0.6 mL solution for injection. The concentration is 10 mg/mL based on protein only.

Pelgraz is a biosimilar medicine. The prescribing physician should be involved in any decision regarding interchangeability. Refer to www.medsafe.govt.nz/profs/RIss/Biosimilars.asp for further information. Refer to **Section 5.1 Pharmacodynamic Properties** for data comparing Pelgraz with Neulastim.

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

Filgrastim is a 175 amino acid protein manufactured by recombinant DNA technology. Filgrastim is produced by *Escherichia coli (E.coli)* bacteria into which 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 39,000 daltons.

Excipients with known effect

Each pre-filled syringe contains 30 mg sorbitol.

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

3 PHARMACEUTICAL FORM

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

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Reduction in the duration of neutropenia, the incidence of febrile neutropenia and the incidence of infection as manifested by febrile neutropenia in patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes).

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage (Dose and Interval)

The recommended dosage of Pelgraz is a single SC injection of 6 mg administered once per chemotherapy cycle. Pelgraz 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).**

Paediatric Population

The safety and efficacy of pegfilgrastim in children aged below 18 years have not yet been established. Currently available data are described in **Section 5.2 Pharmacokinetic Properties** but no recommendation on a dosage can be made.

Method of Administration

Subcutaneous injection.

For instructions on handling the medicine before administration, see **section 6.6 Special precautions for disposal and other handling**.

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.

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 anti-metabolites. 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.

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.

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.

Stevens-Johnson Syndrome

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

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 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.

Thrombocytopenia

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

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 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.

All Patients

The needle cover on the single-use pre-filled syringe contains dry natural rubber (a derivative of latex), which may cause allergic reactions and should not be handled by individuals who are sensitive to latex.

Use in Hepatic Impairment

See **Section 5.2 Pharmacokinetic Properties.**

Use in Renal Impairment

See **Section 5.2 Pharmacokinetic Properties.**

Use in Elderly Patients

See **Section 5.2 Pharmacokinetic Properties.**

Paediatric Use

See **Section 5.2 Pharmacokinetic Properties.**

Effects on Laboratory Tests

None known.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

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.

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

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 have not been assessed.

4.8 UNDESIRABLE EFFECTS

Safety data for pegfilgrastim 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%

Body System and Preferred Terms	Percentage of Patients Reporting Events	
	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
Musculoskeletal		
Pain Skeletal	21	27
Myalgia	7	8
Arthralgia	6	6
Pain Back	4	8
Pain Limb	3	2
Pain Musculoskeletal	1	1
Pain Neck	1	1

Table 2. Most Frequently Reported Treatment-Related Adverse Events in Randomised Clinical Trials with Placebo Control

Body System and Preferred Terms	Number and Percentage of Patients Reporting Events	
	Placebo (n=463)	Pegfilgrastim (n=465)
Gastrointestinal Disorders		
Diarrhoea	10 (2%)	9 (2%)
General Disorders & Administration Site Conditions		
Pyrexia	9 (2%)	8 (2%)
Infections & Infestations		
Influenza	5 (1%)	6 (1%)
Musculoskeletal & Connective Tissue Disorders		
Bone Pain	41 (9%)	62 (13%)
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 & 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]).

Comparability of Pelgraz with Neulastim®

Adverse Effects

In both clinical studies conducted, Pelgraz was well tolerated, and the safety profile of Pelgraz was similar to that of Neulastim®.

In the PK/PD study (APO-Peg-02) with 66 healthy subjects, both Pelgraz and Neulastim® were well tolerated. The overall safety profile of Pelgraz was consistent with Neulastim® in terms of adverse events.

During the Phase III clinical study (APO-Peg-03), 589 subjects with breast cancer were exposed to pegfilgrastim. The safety profile of pegfilgrastim observed in this clinical study was consistent with that reported for the reference products used in this study. The pattern of treatment-emergent adverse events and serious adverse events was comparable between treatment groups and consistent with the safety profile of Neulastim®.

Results from the Phase III efficacy and safety clinical study (APO-Peg-03) demonstrated similar safety profile between treatment arms. This is shown in Table 3.

Table 3. Common Adverse Events (AEs) (≥10% of Subjects) Reported in Phase III Study (APO-Peg-03) – Treatment Period[#] (Safety Analysis Set)*

PREFERRED TERM	NUMBER OF PATIENTS WITH AEs, n (%)			
	Pelgraz (N=294)	US-Neulastim® (N=148)	EU-Neulastim® (N=147)	Total (N=589)
Any AE	265 (90.1)	138 (93.2)	136 (92.5)	539 (91.5)
Neutropenia	149 (50.7)	85 (57.4)	77 (52.4)	311 (52.8)
Bone Pain	139 (47.3)	73 (49.3)	78 (53.1)	290 (49.2)
Nausea	138 (46.9)	67 (45.3)	72 (49.0)	277 (47.0)
Asthenia	72 (24.5)	44 (29.7)	37 (25.2)	153 (26.0)
Alopecia	75 (25.5)	37 (25.0)	39 (26.5)	151 (25.6)
Leukopenia	62 (21.1)	41 (27.7)	41 (27.9)	144 (24.4)
Headache	66 (22.4)	38 (25.7)	32 (21.8)	136 (23.1)
Diarrhoea	51 (17.3)	32 (21.6)	37 (25.2)	120 (20.4)
Dizziness	58 (19.7)	27 (18.2)	28 (19.0)	113 (19.2)
Fatigue	43 (14.6)	18 (12.2)	32 (21.8)	93 (15.8)
Vomiting	43 (14.6)	18 (12.2)	28 (19.0)	89 (15.1)
Myalgia	28 (9.5)	19 (12.8)	15 (10.2)	62 (10.5)

[#]Randomization scheme 2:1:1 applied to Pelgraz: US-Neulastim®: EU-Neulastim®

*Safety Analysis Set: Included all enrolled subjects who received at least one dose of the active treatment.

Immunogenicity

Samples from the clinical studies were tested in an assay using a multi-tiered approach to first screen, then confirm and provide a relative anti-pegfilgrastim Anti-drug Antibody (ADA) concentration (titre). Any confirmed positive samples were then further characterized to determine if the anti-pegfilgrastim antibodies present in a sample were specific for the protein moiety (G-CSF) or PEG moiety by competition with Pelgraz (G-CSF) and PEG, respectively. Lastly, the assay was also used to determine whether the confirmed anti-pegfilgrastim antibodies bind to the endogenous counterpart of the drug. The confirmed positive samples were also tested in a neutralizing antibody assay.

In the PK/PD study (APO-Peg-02), of the samples tested for Anti-Drug Antibody (ADA), 10 samples (6 subjects) out of 190 samples (66 subjects) were confirmed ADA positive and as having treatment-emergent ADAs. Within these 6 subjects, 3 were from Pelgraz and the other 3 from Neulastim® treated groups. Two subjects were confirmed ADA negative following Period 2 of the study. All confirmed ADA positive samples tested negative for neutralizing antibodies. There is no evidence to support a significant impact of ADA development on the PK or PD of Pelgraz or Neulastim®.

In the Phase III efficacy and safety study (APO-Peg-03), 3.1% of subjects (18 out of 589) assessed for immunogenicity were confirmed to be positive for ADAs at one or more time points. Incidence of treatment-emergent induced ADAs was low and similar between the three treatment groups: 1.0% in Pelgraz, 0.7% in US-Neulastim® and 0.7% in EU-Neulastim® treatment arms. The samples from the 18 patients with confirmed ADA positive results were tested in the cell based assay to evaluate the presence of antibodies with neutralizing activity.

Neutralizing activity could have been specific to pegfilgrastim or endogenous rhuG-CSF. Neither Pelgraz nor Neulastim® exposure resulted in the induction of neutralizing antibodies to pegfilgrastim. Neutralizing antibodies to endogenous rhuG-CSF were detected in 3 subjects (0.5%). Two of these subjects were positive at the screening visit, of which one was negative at all post-dosing time points and one was positive for rhuG-CSF neutralizing antibodies at one other time point (Week 20). The third subject was positive for rhuG-CSF neutralizing antibodies at two post-treatment time points. The rhuG-CSF neutralizing antibodies were transient and all 3 subjects were negative for neutralizing antibodies at their last time points tested. The presence of neutralising antibodies did not have any impact on PD activity and was unrelated to any adverse events. There were no instances of anaphylaxis or other immunologically-related adverse events.

Collectively, these findings confirmed the low immunogenic potential of Pelgraz.

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. Pegfilgrastim 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 (≥ 1/1,000 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 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.

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 medicine. Healthcare professionals are asked to report any suspected adverse reactions at https://pophealth.my.site.com/carmreportnz/s/.

4.9 Overdose

There is no experience with overdose of pegfilgrastim in humans. In subjects administered doses of up to 300 mcg/kg, adverse events were similar to those observed in subjects administered lower doses of pegfilgrastim.

For risk assessment and advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

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.

Comparability of Pelgraz with Neulastim®

Comparability assessments, between Pelgraz and Neulastim®, of primary pharmacodynamics (PD) have been conducted *in vitro* in M-NFS-60 cells (a murine myeloblastic cell line) and *in vivo* in neutropaenic mice on receptor binding and biological activity, respectively. In addition, pharmacokinetics (PK) and PD from a Phase 1 clinical study in healthy subjects support similar/equivalent pharmacological activity of Pelgraz and Neulastim®.

In the Phase 1 clinical study (APO-Peg-02) in healthy subjects, the 95% CI of the relative mean of each of the primary PD endpoint parameters for Absolute Neutrophil Count (ANC), $AUEC_t$, and E_{max} were contained within the pre-defined acceptance margins of 80-125%. While not defined as a primary PD endpoint parameter, the 95% CI for the relative mean of the T_{max} parameter was also contained within these acceptance limits, demonstrating the biosimilarity of Pelgraz to the reference product, Neulastim®.

The results from APO-Peg-02, following SC administration of a single 6 mg dose of Pelgraz or Neulastim®, are summarised in Table 4.

Table 4. Summary of Absolute Neutrophil Count (ANC) Pharmacodynamic Population Results Following a Fixed Single Subcutaneous Administration of 6 mg/0.6 mL Pelgraz or Neulastim® in Healthy Subjects

ANC Pharmacodynamic Parameter	Mean (SD)		Relative Mean [%]	95% CI [%]
	Pelgraz n=56	Neulastim® n=56		
$AUEC_t$ (cells x 10^9*h/L)	4749.85 (1247.09)	4817.55 (1314.54)	98.8	96.0 – 101.6
E_{max} (cells x 10^9/L)	29.75 (7.99)	30.94 (8.72)	96.3	92.6 – 100.1
T_{max} (h)	63.43 (16.54)	60.86 (18.94)	103.8	96.1 – 111.4

ANC : Absolute Neutrophil Count; SD = Standard Deviation; CI : Confidence Interval
$AUEC_t$: Area Under the Effect Curve from time zero, measured up to the last sampling time
E_{max} : Maximum effect on ANC observed over the sampling interval
T_{max} : Sampling time at which E_{max} occurred

Clinical trials

Clinical Trials with the Reference Biological Product

Three pivotal, randomised, double-blind clinical studies have been conducted using Neulastim® 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 versus placebo (1% versus 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% versus 14%, p <0.001; and 2% versus 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 Pelgraz with Neulastim®

Therapeutic equivalence of Pelgraz and Neulastim® was demonstrated in a comparative phase III efficacy

and safety study (APO-Peg-03). A single, fixed SC dose of 6 mg/0.6 mL was administered on Day 2 of each chemotherapy cycle. There were 589 subjects (all female of median age 52 years, range 22-80 years) dosed in the following treatment arms: Pelgraz (n=294), EU-approved Neulastim® (n=147) and US-licensed Neulastim® (n=148). The dose was administered to early-stage breast cancer patients undergoing 6 cycles of (each cycle 21 days apart) of TAC chemotherapy (docetaxel 75mg/m^2, doxorubicin 50mg/m^2, cyclophosphamide 500mg/m^2) in an adjuvant setting.

The primary efficacy endpoint was Duration of Severe Neutropenia (DSN) in cycle 1. Equivalence of Pelgraz and Neulastim® was considered to be demonstrated if the two-sided 95% CI for the difference in mean DSN in Cycle 1 was within the equivalence range [-0.5 day, +0.5 day].

The results of DSN in Cycle 1 are described in Table 6 and the results of the treatment comparisons are described in Table 7:

Table 6. Study APO-Peg-03: Summary of Efficacy Results for the Duration of Severe Neutropenia[a] (DSN) in Cycle 1 in Cancer Subjects (FAS-As Treated)*

Statistics	Pelgraz n=298	US-Neulastim® n=147	EU-Neulastim® n=144
Mean Days (SD)	1.6 (1.48)	1.4 (1.17)	1.6 (1.34)
Median Days	1.5	1.0	2.0

SD: Standard Deviation

[a] Severe neutropenia was defined as occurrence of ANC below 0.5 x 10^9/L

* FAS-As Treated (Full Analysis Set-As Treated) includes all enrolled subjects who were randomized, received at least one dose of active treatment and who had any follow-up data for the primary target variables. Treatment assignment for subjects was based on the treatment they received (As Treated allocation).

Table 7. Study APO-Peg-03: Summary of Efficacy Results for the Duration of Severe Neutropenia (DSN) in Cycle 1, Estimated with ANOVA accounting for Treatment Effect following treatment with Pelgraz, US-Neulastim® and EU-Neulastim® (FAS-As Treated)*

DSN (days)	Pelgraz	US-Neulastim®	EU-Neulastim®	Pelgraz – US-Neulastim®	Pelgraz – EU-Neulastim®
LS Mean	1.62	1.39	1.63	0.23	-0.01
95% CI	1.46 to 1.77	1.17 to 1.61	1.41 to 1.86	-0.04 to 0.50	-0.29 to 0.26

LS: Least Square; CI: Confidence Interval

* FAS-As Treated (Full Analysis Set-As Treated) includes all enrolled subjects who were randomized, received at least one dose of active treatment and who had any follow-up data for the primary target variables. Treatment assignment for subjects was based on the treatment they received (As Treated allocation).

The results of DSN data in Cycle 1 show the similarity in efficacy of Pelgraz and US-Neulastim® (-0.04 to 0.50) as well as of Pelgraz and EU-Neulastim® (-0.29 to 0.26) since the 95% CI are within the equivalence range of -0.5 to 0.5 days for both comparisons.

The results for secondary efficacy endpoints are presented below:

In Cycle 1, blood samples were collected for complete blood counts with differentials on Day 0, 1, 3, 5, 6, 7, and every day until post-nadir ANC recovery to ≥2 x 10^9/L or up to Day 15, if recovery did not occur earlier. The mean day to reach the peak ANC was Day 3.4, 3.1 and 3.1 in the Pelgraz, US- Neulastim® and EU-Neulastim® arms, and the mean peak values were similar across the treatment arms: 28.4, 29.9 and 28.7 x 10^9/L, respectively. Mean day to reach the ANC nadir was Day 7.1, 7.1 and 7.3 in the Pelgraz, US-Neulastim® and EU-Neulastim® arms and mean recovery of ANC (≥2.0 x 10^9/L) was reached on Day 9.4, 9.5 and 9.2, respectively. The mean depth of the nadir was comparable across the treatment arms: 0.6, 0.4 and 0.4 x 10^9/L in the Pelgraz, US-Neulastim® and EU-Neulastim® arms, respectively.

The frequency of Grade 3 neutropenia (ANC below 1.0 x 10^9/L) across all cycles was reported in 24 subjects (8.2%) for Pelgraz, 18 subjects (12.2%) for US-Neulastim® and 14 subjects (9.5%) for EU-Neulastim® arms. The frequency of Grade 4 neutropenia (ANC below 0.5 x 10^9/L) across all cycles

was reported as 233 subjects (79.3%) for Pelgraz, 116 subjects (78.4%) for US-Neulastim® and 117 subjects (79.6%) for EU-Neulastim® arms, respectively.

The rates of Febrile Neutropenia (FN) by cycle and across the cycles (defined as: single temperature: ≥38.3°C measured orally or ≥38.0°C for over 1 hour; neutropenia: ANC $<0.5 \times 10^9$/L or $<1 \times 10^9$/L and a predicted decline to $\leq 0.5 \times 10^9$/L over the next 48 hours) was assessed. Overall during the treatment phase, FN occurred in 5.8%, 4.7% and 3.4% of subjects in the Pelgraz, US-Neulastim® and EU-Neulastim® treatment arms, respectively. For the majority of subjects, FN occurred in Cycle 1: 5.1% in the Pelgraz arm, 4.1% in the US-Neulastim® arm and 3.4% in the EU-Neulastim® arm.

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.

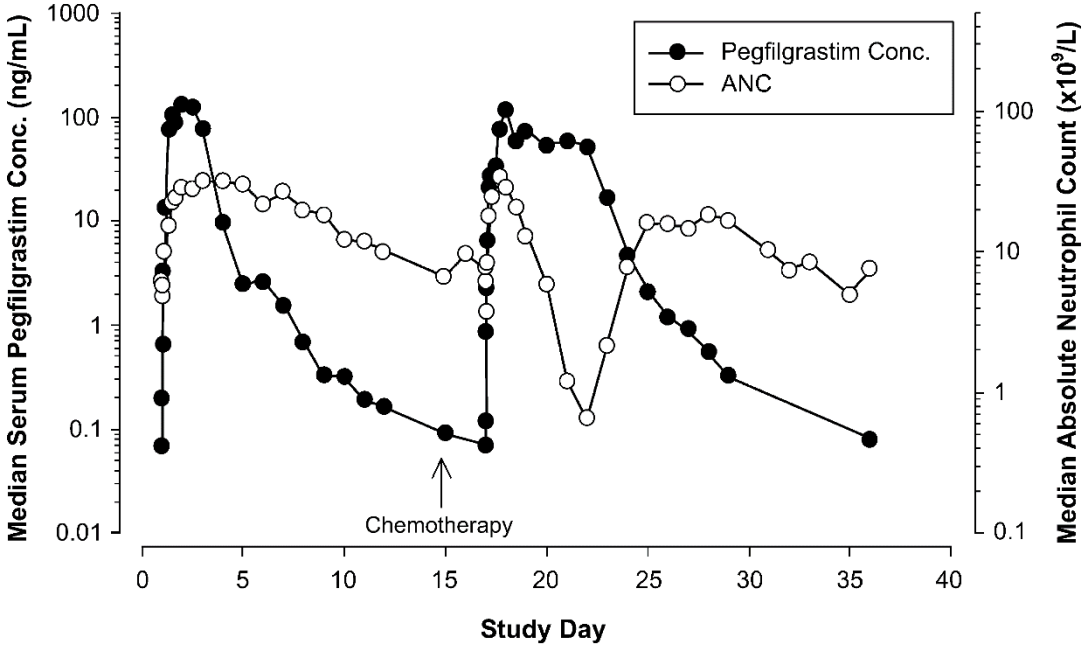
Metabolism

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 Pelgraz with Neulastim®

Pharmacokinetic (PK) profiles of Pelgraz and Neulastim® were compared in a single-dose, randomized, two-way crossover, assessor-blinded, active controlled, phase 1 PK/PD study in 66 healthy male and female volunteers (APO-Peg-02). A single, fixed SC dose of 6 mg was administered over two 28-day periods with an 8 week washout. The 90% CI of the primary PK endpoint parameters (AUC_t and C_{max} for pegfilgrastim) were contained within the pre-defined acceptance range of 80-125%, demonstrating the biosimilarity of Pelgraz to the reference product, Neulastim®.

Table 8 shows the PK results following the administration of Pelgraz and US-Neulastim®. The ratios of the geometric means for the test/reference (Pelgraz/Neulastim®) were within the pre-defined acceptance range of 80 – 125% for AUC_t, AUC_{inf} and C_{max}. In addition, the 90% confidence interval of the geometric mean ratio for AUC_{inf} was also contained within this acceptance range whereas the upper bound of the AUC_t ratio was 125.5%. The marginally high upper bound is a consequence of a smaller drug content in the US-Neulastim® dose (less than 95% of the label claim) administered during the study, as supported by the results from the potency corrected data in Table 9 below.

Table 8. Mean (CV %) Pharmacokinetic Parameters Following a Fixed Single SC Injection of 6 mg Pelgraz or US-Neulastim® to Healthy Subjects (PK Population) – Measured Data

Pegfilgrastim (6 mg) Geometric Mean Arithmetic Mean (CV %)				
Endpoint	**Pelgraz * (N=56)**	**US-Neulastim® [t] (N=56)**	**Ratio of Means [%] [b]**	**90% Confidence Interval [%]**
AUC_t (ng*h/mL)	6725 8282 (64)	6027 7622 (74)	111.6	99.2 − 125.5
AUC_{inf}[a] [ng*h/mL]	6741 8224 (67)	6186 7890 (72)	109.0	95.5 − 124.3
C_{max} [ng/mL]	159 193 (60)	150 183 (66)	105.7	
T_{max} [h] [§]	25.82 (31)	24.18 (38)	105.2	
$T_{1/2}$[a] [h] [§]	58.03 (39)	55.09 (30)	103.2	

AUC_t = 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;
T_{max} = Time at which C_{max} is observed; $T_{1/2}$ = Terminal elimination half-life.
* 6 mg/0.6 mL (Accord) – measured concentration 6.1 mg/0.6 mL
t 6 mg/0.6 mL (Amgen Inc. USA) – measured concentration 5.7 mg/0.6 mL
§ Expressed as the arithmetic mean (CV %) only
a $T_{1/2}$ and AUC_{inf} were not determined in subjects if the log-linear terminal phase was not clearly defined. N = 50 for Pelgraz and N = 53 for Neulastim®.
b Based on the least square estimates of the geometric means of AUC_t, C_{max}, AUC_{inf}. Based on the least square estimates of the arithmetic means for T_{max} and $T_{1/2}$.

Table 9 shows results from the potency corrected pegfilgrastim concentration data for both Pelgraz and US-Neulastim®. For the primary pharmacokinetic endpoint of AUC_t, the 90% confidence interval of the Pelgraz/Neulastim® ratio of geometric means was contained within the acceptance range of 80 - 125%.

Table 9. Mean (CV %) Pharmacokinetic Parameters Following a Fixed Single Subcutaneous Injection of 6 mg Pelgraz or US-Neulastim to Healthy Subjects (PK Population) – Potency Corrected Data

Pegfilgrastim (6 mg) Geometric Mean Arithmetic Mean (CV %)				
Endpoint	**Pelgraz * (N=56)**	**US-Neulastim® t (N=56)**	**Ratio of Means [%] b**	**90% Confidence Interval [%]**
AUC_t [ng*h/mL]	6631 8166 (64)	6425 8126 (74)	103.2	91.7 – 116.1
AUC_{inf} a [ng*h/mL]	6647 8109 (67)	6595 8410 (72)	100.8	88.3 – 115.0
C_{max} [ng/mL]	157 190 (60)	160 195 (66)	97.7	
T_{max} [h] §	25.82 (31)	24.18 (38)	105.2	
$T_{1/2}$ a [h] §	58.03 (39)	55.09 (30)	103.2	

AUC_t = 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;
T_{max} = Time at which C_{max} is observed;
$T_{1/2}$ = Terminal elimination half-life.
* 6 mg/0.6 mL (Accord)
t 6 mg/0.6 mL (Amgen Inc. USA)
§ Expressed as the arithmetic mean (CV%) only
a $T_{1/2}$ and AUC_{inf} were not determined in subjects if the log-linear terminal phase was not clearly defined. N = 50 for Pelgraz and N = 53 for Neulastim®.
b Based on the least square estimates of the geometric means of AUC_t, C_{max}, AUC_{inf}. Based on the least square estimates of the arithmetic means for T_{max} and $T_{1/2}$.

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

Glacial acetic acid
Sorbitol
Polysorbate-20
Sodium hydroxide
Water for injections

6.2 INCOMPATIBILITIES

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

6.3 SHELF LIFE

36 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at 2°C to 8°C (Refrigerate. Do not freeze). Avoid shaking. Protect from light.

Pelgraz may be exposed to room temperature (up to 25°C) for a maximum single period of up to 15 days that ends within the labelled expiry date. Once Pelgraz has been out at room temperature it should not be put back into the refrigerator. Pelgraz left at room temperature for more than 15 days should be discarded.

Freezing should be avoided; however, if accidentally frozen, Pelgraz should be allowed to thaw in the refrigerator before administration and administered within the labelled expiry date. If frozen a second time, Pelgraz should be discarded.

6.5 NATURE AND CONTENTS OF CONTAINER

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

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

Pelgraz contains no antimicrobial agent. Pelgraz is for single-use in one patient only.

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 needle guard to reach room temperature before injecting.

Pelgraz is supplied in single-use, pre-filled syringes with a needle guard to prevent accidental needle stick injury. When the pre-filled syringe is emptied of all the medication, the needle-guard mechanism pushes over the needle, withdrawing it from the skin and covering it completely. The pre-filled syringe should be disposed of by placing it into an approved puncture-proof container.

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

7 MEDICINE SCHEDULE

Prescription Only Medicine

8 SPONSOR

Pharmacy Retailing (NZ) Limited Trading as Healthcare Logistics
58 Richard Pearse Drive
Airport Oaks
Auckland 2022
New Zealand

Phone: 0800 004 375

9 DATE OF FIRST APPROVAL

01 September 2022

10 DATE OF REVISION

12 December 2025

Version 2.0

Summary table of changes

Section Changed	Summary of new information
4.4	Addition of Stevens-Johnson Syndrome
4.8	Update adverse reactions website