AUSTRALIAN PI – LONQUEX® (LIPEGFILGRASTIM) SOLUTION FOR INJECTION

1 NAME OF THE MEDICINE

Lipegfilgrastim.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Lonquex® is the Teva Pharmaceuticals Ltd. trademark for lipegfilgrastim (rbe), a long-acting form of recombinant human granulocyte colony-stimulating factor (G-CSF).

Lonquex® contains the active substance lipegfilgrastim (rbe). Lipegfilgrastim is a covalent conjugate of a 19,000 dalton E.Coli produced r-metHuG-CSF and a 20,000 dalton polyethylene glycol (PEG) moiety. The theoretical molecular mass of r-metHuG-CSF is 18,798.9 Da. The molecular mass of the final glycoPEGylated human N-methionyl granulocyte-colony stimulating factor is approximately 39,000 Da. The PEG moiety is attached enzymatically through a glycolinker (glycyl-sialyl-GalNac) to the amino acid Thr134 (which corresponds to the glycosylation site Thr133 in endogenous G-CSF).

Lipegfilgrastim is a covalent conjugate of filgrastim with a single methoxy polyethylene glycol (PEG) molecule via a carbohydrate linker consisting of L-Glycine, N-acetylneuraminic acid (Sialic Acid) and a N-acetylgalactosamine (GalNAc) moiety to Threonine134. The average molecular mass is approximately 39,000 dalton of which the protein moiety constitutes approximately 48%.

The potency of this medicinal product should not be compared to the potency of another pegylated or non-pegylated protein of the same therapeutic class. For more information, see **Section 5, PHARMACOLOGICAL PROPERTIES.**

Each single-use pre-filled syringe of Lonquex® contains 6 mg of lipegfilgrastim in 0.6 mL solution. Each mL of solution for injection contains 10 mg of lipegfilgrastim.

This medicinal product contains 30 mg sorbitol per pre-filled syringe. Patients with rare hereditary problems of fructose intolerance should not use this medicinal product.

This medicinal product contains less than 1 mmol sodium (0.14 mg) per pre-filled syringe, i.e. essentially ‘sodium-free’.

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

3 PHARMACEUTICAL FORM

Lonquex® is a sterile, clear, colourless, preservative-free aqueous liquid for subcutaneous (SC) administration, presented in a 1 mL prefilled syringe.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage and administration

Lonquex® treatment should be initiated and supervised by physicians experienced in oncology or haematology.

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.

The recommended dosage of Lonquex® is a single subcutaneous injection of 6 mg administered once per chemotherapy cycle.

Dosage

One 6 mg dose of Lonquex® (a single pre-filled syringe of Lonquex) is recommended for each chemotherapy cycle, given approximately 24 hours after cytotoxic chemotherapy. The maximum amount of Lonquex® that can be safely administered as a single dose has not been determined.

Preparation and Administration of Lonquex®

Lonquex® does not contain any preservative. In view of the possible risk of microbial contamination, Lonquex® syringes are for single use in one patient only. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Only clear, colorless solutions without particles should be used. Do not use this medicine if you notice any particulate matter or discoloration.

Avoid vigorous shaking. Excessive shaking may aggregate lipegfilgrastim, rendering it biologically inactive.

Allow the ready to use pre-filled syringe to reach a comfortable temperature (15°C - 25°C) before injecting.

Method of administration

The solution is injected subcutaneously (SC). The injections should be given into the abdomen, upper arm or thigh. Lonquex® should not be injected into an area that is tender, red, bruised, or hard, or that has scars or stretch marks.

Self-administration of Lonquex® should only be performed by patients who are well motivated, adequately trained and have access to expert advice. The first injection of Lonquex® should be performed under direct medical supervision.

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

Special populations

Elderly patients

In clinical studies with a limited number of elderly patients, there was no relevant age-related difference with regard to the efficacy or safety profiles of Lonquex®. Therefore, no adjustment of the dose is necessary for elderly patients.

No alternative dosage regimes are currently recommended for patients affected by renal or hepatic impairment (see **Section 5, PHARMACOLOGICAL PROPERTIES**).

Paediatric population

The safety and efficacy of Lonquex® in children and adolescents aged less than 18 years have not yet been established. No data are available.

4.3 CONTRAINDICATIONS

Lonquex® is contraindicated in patients with known hypersensitivity to lipegfilgrastim and any other component of the product or other G-CSF products including lenograstim, pegfilgrastim and filgrastim.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

The safety and efficacy of Lonquex® have not been investigated in patients receiving high dose chemotherapy. Lonquex® should not be used to increase the dose of cytotoxic chemotherapy beyond established dosage regimens.

In order to improve the traceability, the trade name and batch number of the administered medicinal product should be clearly recorded in the patient file.

Allergic reactions and immunogenicity

Patients who are hypersensitive to G-CSF or derivatives are also at risk of hypersensitivity reactions to lipegfilgrastim due to possible cross-reactivity. No lipegfilgrastim therapy should be commenced in these patients because of the risk of cross-reaction.

Most biological medicinal products elicit some level of anti-drug antibody response. This antibody response can, in some cases, lead to undesirable effects or loss of efficacy. If a patient fails to respond to treatment, the patient should undergo further evaluation.

If a serious allergic reaction occurs, appropriate therapy with close patient follow-up over several days should be administered.

Haematopoietic system

Treatment with lipegfilgrastim does not preclude thrombocytopenia and anaemia caused by myelosuppressive chemotherapy. Lipegfilgrastim may also cause reversible thrombocytopenia (see **Section 4.8, ADVERSE EFFECTS (UNDESIRABLE EFFECTS**)). Regular monitoring of the platelet count and haematocrit is recommended. Special care should be taken when administering single or combination chemotherapeutic medicinal products that are known to cause severe thrombocytopenia.

Leukocytosis may occur (see **Section 4.8, ADVERSE EFFECTS (UNDESIRABLE EFFECTS)**). No adverse events directly attributable to leukocytosis have been reported. Elevation in white blood cells (WBC) is consistent with the pharmacodynamics effects of lipegfilgrastim. A WBC count should be performed at regular intervals during therapy owing to the clinical effects of lipegfilgrastim and the potential for leukocytosis. If WBC counts exceed 50 x 109/l after the expected nadir, lipegfilgrastim should be discontinued immediately.

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

Patients with myeloid leukaemia or myelodysplastic syndromes

Granulocyte-colony stimulating factor can promote growth of myeloid cells and some non-myeloid cells *in vitro*.

The safety and efficacy of Lonquex have not been investigated in patients with chronic myeloid leukaemia, myelodysplastic syndromes or secondary acute myeloid leukaemia; it should therefore not be used in such patients. Particular care should be taken to distinguish the diagnosis of blast transformation of chronic myeloid leukaemia from acute myeloid leukaemia.

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

In an observational post-marketing study, myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML) were associated with the use of pegfilgrastim, an alternative G-CSF, in combination with chemotherapy and/or radiotherapy in breast and lung cancer patients. A similar association is not known between lipegfilgrastim and MDS/AML. Nevertheless, patients with breast cancer and patients with lung cancer should be monitored for signs and symptoms of MDS/AML.

Splenic adverse reactions

Frequent but generally asymptomatic cases of splenomegaly and infrequent cases of splenic rupture, including fatal cases, have been reported after administration of G-CSF or derivatives (see Section 4.8, ADVERSE EFFECTS). Spleen size should therefore be carefully monitored (e.g. clinical examination, ultrasound). A diagnosis of splenic rupture or enlarged spleen should be considered in patients reporting left upper abdominal pain or shoulder tip pain.

Pulmonary adverse reactions

Pulmonary adverse reactions, in particular interstitial pneumonia, have been reported after administration of lipegfilgrastim (see **Section 4.8, ADVERSE EFFECTS (UNDESIRABLE EFFECTS)**). Patients with a recent history of pulmonary infiltrates or pneumonia may be at higher risk.

Adult respiratory distress syndrome (ARDS)

The onset of pulmonary symptoms such as cough, fever and dyspnoea in association with radiological signs of pulmonary infiltrates and deterioration in pulmonary function together with an increased neutrophil count may be preliminary signs of Acute Respiratory Distress Syndrome (ARDS) (see **Section 4.8, ADVERSE EFFECTS (UNDESIRABLE EFFECTS)**). In such circumstances Lonquex® should be discontinued at the discretion of the physician and appropriate treatment given.

Pulmonary Haemorrhage and Haemoptysis

Pulmonary haemorrhage manifesting as pulmonary infiltrates and haemoptysis requiring hospitalization have been reported in patients and donors receiving human G-CSF. Haemoptysis resolved with discontinuation of human G-CSF.

Vascular adverse reactions

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

Capillary leak syndrome has been reported after administration of G CSF or derivatives and is characterised by hypotension, hypoalbuminaemia, oedema and haemoconcentration. Patients who develop symptoms of capillary leak syndrome should be closely monitored and receive appropriate symptomatic treatment, which may include a need for intensive care (see **Section 4.8, ADVERSE EFFECTS (UNDESIRABLE EFFECTS)**).

Glomerulonephritis

Glomerulonephritis has been reported in patients receiving filgrastim. Generally, events of glomerulonephritis resolved after dose reduction or withdrawal. Urinalysis monitoring is recommended.

Patients with sickle cell anaemia

Sickle cell crisis has been associated with the use of G-CSF or derivatives in patients with sickle cell anaemia. Physicians should therefore exercise caution when administering Lonquex® in patients with sickle cell anaemia, monitor appropriate clinical parameters and laboratory results and be attentive to the possible association of lipegfilgrastim with splenic enlargement and vaso-occlusive crisis.

Hypokalaemia

Hypokalaemia may occur (see **Section 4.8, ADVERSE EFFECTS (UNDESIRABLE EFFECTS)**). For patients with increased risk on hypokalaemia due to underling disease or co-medications, it is recommended to monitor the serum potassium level carefully and to substitute potassium if necessary.

Use in renal impairment

See **Section, 5.2, Pharmacokinetic Properties, Special Populations.**

Use in the elderly

Of the 399 patients treated with lipegfilgrastim 6mg in the cancer studies, 69 (17.3%) were 65 years of age and older. No overall differences in safety or effectiveness were observed between patients aged 65 and older and younger patients.

Paediatric use

The safety and efficacy of Lonquex® in children and adolescents aged less than 18 years have not yet been established.

Effects on laboratory tests

No data are available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No formal clinical drug interaction studies between lipegfilgrastim and other drugs have been performed.

In vitro data indicate that lipegfilgrastim has little or no direct or immune system-mediated effects on CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4/5 activity.

Due to the potential sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy, Lonquex® should be administered approximately 24 hours after administration of cytotoxic chemotherapy. Concomitant use of lipegfilgrastim with any chemotherapeutic medicinal product has not been evaluated in patients. In animal models, concomitant administration of G-CSF and 5-fluorouracil (5-FU) or other antimetabolites has been shown to potentiate myelosuppression.

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

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

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data are available. Animal studies with G-CSF and derivatives do not indicate harmful effects with respect to fertility.

Use in pregnancy – Pregnancy Category B3

There are very limited data (less than 300 pregnancy outcomes) on the use of lipegfilgrastim in pregnant women. Animal studies have shown reproductive toxicity. Lonquex® has not been studied in pregnant women and should not be used during pregnancy until further evidence is available.

In a study of toxicity to reproduction and development in rabbits, an increased incidence of post-implantation loss and abortion has been observed at high doses of lipegfilgrastim, likely owing to an exaggerated pharmacodynamic effect specific for rabbits. There is no evidence that lipegfilgrastim is teratogenic. These findings are consistent with results from G-CSF and derivatives. Published information on G-CSF and derivatives reveal no evidence of adverse effects on fertility and embryo-foetal development in rats or pre-/postnatal effects other than those related to maternal toxicity as well. There is evidence that filgrastim and pegfilgrastim may be transported at low levels over the placenta in rats, although no information is available for lipegfilgrastim. The relevance of these findings for humans is not known.

Use in lactation.

Lonquex® has not been studied in lactating women and should not be used while breastfeeding until further evidence is available.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Reporting 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 www.tga.gov.au/reporting-problems.

Summary of the safety profile

The most frequent undesirable effects are musculoskeletal pains. Musculoskeletal pains are generally of mild to moderate severity, transient and can be controlled in most patients with standard analgesics.

Capillary leak syndrome, which can be life threatening if treatment is delayed, has been reported mostly in cancer patients undergoing chemotherapy after administration of G-CSF or derivatives.

Adverse events in clinical studies

The following event data in **Table 1** compares the frequency of treatment-emergent adverse events for Lonquex® 6 mg (target dose) and the active control, pegfilgrastim 6 mg, in patients with breast cancer. **Table 2** compares the frequency of treatment-emergent adverse events for Lonquex® 6mg and placebo in patients with non-small cell lung cancer (NSCLC).

Table 1 Adverse Events with an incidence ≥5% of patients in either treatment group in Study XM22-03 (breast cancer patients)

MedDRA Preferred Term	pegfilgrastim 6 mg (N=101)		Lonquex® 6 mg (N=101)	
	n	%	n	%
Alopecia	86	85.1	93	92.1
Nausea	52	51.5	61	60.4

MedDRA Preferred Term	pegfilgrastim 6 mg (N=101)		Lonquex® 6 mg (N=101)	
	n	%	n	%
Asthenia	29	28.7	28	27.7
Neutropenia	32	31.7	26	25.7
Bone pain	10	9.9	14	13.9
Erythema	12	11.9	12	11.9
Leukopenia	8	7.9	12	11.9
Diarrhoea	12	11.9	10	9.9
Vomiting	4	4.0	10	9.9
Anaemia	9	8.9	9	8.9
Myalgia	6	5.9	9	8.9
Headache	5	5.0	9	8.9
Decreased appetite	9	8.9	7	6.9
Dizziness	2	2.0	6	5.9
Fatigue	7	6.9	5	5.0
Stomatitis	7	6.9	5	5.0
Arthralgia	2	2.0	5	5.0
Dysgeusia	5	5.0	3	3.0

Note: This table is sorted by descending frequency in the Lonquex® group. Multiple mentions per patient are possible.

Table 2 Adverse Events with an incidence ≥2% of patients in either treatment group in Study XM22-04 (NSCLC patients)

MedDRA Preferred Term	Placebo (N=125)		Lonquex® 6 mg (N=248)	
	n	%	n	%
Alopecia	42	33.6	101	40.7
Anaemia	30	24.0	63	25.4
Nausea	27	21.6	59	23.8
Neutropenia	44	35.2	51	20.6
Thrombocytopenia	10	8.0	32	12.9
Asthenia	23	18.4	28	11.3
Vomiting	15	12.0	28	11.3
Decreased appetite	12	9.6	23	9.3
Hypokalaemia	3	2.4	20	8.1
Leukopenia	14	11.2	16	6.5
Fatigue	6	4.8	16	6.5
Disease progression	5	4.0	16	6.5
Non-small cell lung cancer	4	3.2	16	6.5
Chest pain	8	6.4	14	5.6
Pyrexia	6	4.8	12	4.8
Hypophosphataemia	2	1.6	12	4.8
Weight decreased	2	1.6	12	4.8
Febrile neutropenia	10	8.0	11	4.4
Dyspnoea	9	7.2	11	4.4
Dizziness	4	3.2	9	3.6
Headache	4	3.2	9	3.6
Arthralgia	2	1.6	9	3.6
Haemoptysis	5	4.0	7	2.8
Diarrhoea	4	3.2	7	2.8
Back pain	2	1.6	6	2.4
Cough	3	2.4	5	2.0

MedDRA Preferred Term	Placebo (N=125)		Lonquex® 6 mg (N=248)	
Tachycardia	2	1.6	5	2.0
Abdominal pain upper	1	0.8	5	2.0
Blood phosphorus decreased	1	0.8	5	2.0
Bone pain	1	0.8	5	2.0
Hyperkalaemia	1	0.8	5	2.0
Pain	1	0.8	5	2.0
Pneumonia	4	3.2	4	1.6
Atrial fibrillation	5	4.0	3	1.2
Lung neoplasm malignant	3	2.4	3	1.2
Pain in extremity	3	2.4	3	1.2
Insomnia	3	2.4	2	0.8
Wheezing	3	2.4	2	0.8

Note: This table is sorted by descending frequency in the Lonquex® group. Multiple mentions per patient are possible. TEAEs with onset after start of prophylactic open-labeled Lonquex® treatment are not included.

Tabulated list of adverse reactions

The safety of lipegfilgrastim has been evaluated based on results from clinical studies including 506 patients and 76 healthy volunteers treated at least once with lipegfilgrastim.

The adverse reactions listed below in **Table 3** are classified according to System organ class. Frequency groupings are defined according to the following convention:

Very common: ≥ 1/10
Common: ≥ 1/100 to < 1/10
Uncommon: ≥ 1/1,000 to < 1/100
Rare: ≥ 1/10,000 to <1/1,000
Very rare: < 1/10,000
Not known: cannot be estimated from the available data.
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 3 Adverse reactions

System organ class	Frequency	Adverse reaction
Blood and lymphatic system disorders	Common	Thrombocytopenia*
	Uncommon	Leukocytosis* Splenomegaly*
Immune system disorders	Uncommon	Hypersensitivity reactions*
Metabolism and nutrition disorders	Common	Hypokalaemia*
Nervous system disorders	Common	Headache
Vascular disorders	Not known	Capillary leak syndrome*
Respiratory, thoracic and mediastinal disorders	Uncommon	Pulmonary adverse reactions*
Skin and subcutaneous tissue disorders	Common	Skin reactions*
	Uncommon	Injection site reactions*

Musculoskeletal and connective tissue disorders	Very common	Musculoskeletal pains*
General disorders and administration site conditions	Common	Chest pain
Investigations	Uncommon	Blood alkaline phosphatase increased*, Blood lactate dehydrogenase increased*
*See subsection "Description of selected adverse reactions" below		

Post-marketing experience

Adverse reactions reported during the post-marketing period are derived from spontaneous reports including reports from healthcare professionals, consumers, competent authorities and from solicited case reports including those from non-interventional studies.

Among adverse reactions reported post-marketing, the majority of reported ADRs belonged to SOC Musculoskeletal and connective tissue disorders and Blood and lymphatic system disorders.

A review of these case reports does not demonstrate any new events of interest or potential safety signals, no new relevant post-marketing safety information was identified to alter the known benefit-risk profile of Lonquex®.

Description of selected adverse reactions

Cases of pulmonary haemorrhage and haemoptysis have been reported in post-marketing experience after administration of G-CSF.

Thrombocytopenia and leukocytosis have been reported.

Hypersensitivity reactions such as allergic skin reactions, urticaria, angioedema and serious allergic reactions may occur.

Hypokalaemia has been reported.

Pulmonary adverse reactions, in particular interstitial pneumonia, have been reported. These pulmonary adverse reactions may also include pulmonary oedema, pulmonary infiltrates, pulmonary fibrosis, respiratory failure or ARDS.

Skin reactions such as erythema and rash may occur.

Injection site reactions such as injection site induration and injection site pain may occur.

The most frequent adverse reactions are musculoskeletal pains such as bone pain and myalgia. Musculoskeletal pains are generally of mild to moderate severity, transient and can be controlled in most patients with standard analgesics.

Reversible, mild to moderate elevations in alkaline phosphatase and lactate dehydrogenase may occur, with no associated clinical effects. Elevations in alkaline phosphatase and lactate dehydrogenase most likely originate from the increase in neutrophils.

Certain adverse reactions have not yet been observed with lipegfilgrastim, but are generally accepted as being attributable to G-CSF and derivatives:

Blood and lymphatic system disorders

- Splenic rupture including some fatal cases
- Sickle cell crisis in patients with sickle cell anaemia

Vascular disorders

- Capillary leak syndrome

Cases of capillary leak syndrome have been reported in post-marketing experience after administration of G-CSF or derivatives. These have generally occurred in patients suffering from advanced malignant diseases, having sepsis, taking multiple chemotherapy medications or undergoing apheresis.

- Aortitis

Rare cases of Aortitis have been reported in post-marketing experience after administration of G-CSF.

Skin and subcutaneous tissue disorders

- Acute febrile neutrophilic dermatosis (Sweet's syndrome)
- Cutaneous vasculitis

4.9 OVERDOSE

There is no experience with overdose of lipegfilgrastim. In the case of overdose, WBC and platelet count should be performed regularly and spleen size should be carefully monitored (e.g. clinical examination, ultrasound).

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Immunostimulants, Colony stimulating factors, ATC code: L03AA14.

Mechanism of action

Human G-CSF is a glycoprotein that regulates the production and release of functional neutrophils from the bone marrow. Filgrastim is an un-glycosylated recombinant methionyl human G-CSF. Lipegfilgrastim is a sustained duration form of filgrastim due to decreased renal clearance. Lipegfilgrastim binds to human the G-CSF receptor like filgrastim and pegfilgrastim.

Pharmacodynamics effects

Lipegfilgrastim and filgrastim induced a marked increase in peripheral blood neutrophil counts within 24 hours, with minor increases in monocytes and/or lymphocytes. These results suggest that the G-CSF moiety of lipegfilgrastim confers the expected activity of this growth factor: stimulation of proliferation of haematopoietic progenitor cells, differentiation into mature cells and release into the peripheral blood. This effect includes not only the neutrophil lineage but extends to other single lineage and multilineage progenitors and pluripotent haematopoietic stem cells. G-CSF also increases the antibacterial activities of neutrophils including the phagocytosis.

Clinical trials

Clinical efficacy and safety

Once-per-cycle dosing of Lonquex® was investigated in two pivotal randomised, double-blind clinical studies in patients undergoing myelosuppressive chemotherapy.

The first pivotal (phase III) clinical study XM22-03 was an active-controlled study in 202 patients with stage II-IV breast cancer receiving up to 4 cycles of chemotherapy consisting of doxorubicin and docetaxel. Patients were randomised 1:1 to receive 6 mg Lonquex® or 6 mg pegfilgrastim. The study showed non-inferiority of 6 mg Lonquex® to 6 mg pegfilgrastim for the primary endpoint, duration of severe neutropenia (DSN) in the first cycle of chemotherapy (see **Table 4**).

Table 4 DSN, severe neutropenia (SN) and febrile neutropenia (FN) in cycle 1 of study XM22-03 (ITT)

	Pegfilgrastim 6 mg (n = 101)	Lonquex® 6 mg (n = 101)
DSN		
Mean ± SD (d)	0.9 ± 0.9	0.7 ± 1.0
Median	0.0	1.0
Δ LS mean	-0.186	
95 % CI for difference	-0.461 to 0.089	
SN		
Incidence (n(%))	52 (51.5%)	44 (43.6%)
Odds ratio	0.758	
95 % CI	0.423 to 1.361	
FN		
Incidence (n(%))	3 (3.0%)	1 (1.0%)
Odds ratio	0.321	
95 % CI	0.040 to 2.562	

ITT = Intent-to-treat population (all randomised patients)
SD = standard deviation
d = days
CI = confidence interval
Δ LS mean (least square mean difference Lonquex® – pegfilgrastim) and CI out of multivariate Poisson regression analysis

The second pivotal (phase III) clinical study XM22-04 was a placebo-controlled study in 375 patients with non-small cell lung cancer receiving up to 4 cycles of chemotherapy consisting of cisplatin and

etoposide. Patients were randomised 2:1 to receive either 6 mg Lonquex® or placebo. The results of the study are presented in **Table 5**. When the main study was finalised, the incidence of death was 7.2% (placebo) and 12.5% (6 mg Lonquex®) although after the 360-day follow-up period the overall incidence of death was similar between placebo and Lonquex® (44.8% and 44.0%; safety population).

Table 5 DSN, SN and FN in cycle 1 of study XM22-04 (ITT)

	Placebo (n = 125)	Lipegfilgrastim 6 mg (n = 250)
FN		
Incidence (n(%))	7 (5.6%)	6 (2.4%)
Odds ratio	0.390	
95 % CI	0.121 to 1.260	
p-value	0.1151	
DSN		
Mean ± SD (d)	2.3 ± 2.5	0.6 ± 1.1
Median	2.0	0.0
Δ LS mean	-1.661	
95 % CI for difference	-2.089 to -1.232	
p-value	< 0.0001	
SN		
Incidence (n(%))	74 (59.2%)	80 (32.1%)
Odds ratio	0.325	
95 % CI	0.206 to 0.512	
p-value	< 0.0001	
Δ LS mean (least square mean difference lipegfilgrastim – placebo), CI and p-value out of multivariate Poisson regression analysis Odds ratio (lipegfilgrastim / placebo), CI and p-value out of multivariate logistic regression analysis		

Immunogenicity

An analysis of anti-drug antibodies of 579 patients and healthy volunteers treated with lipegfilgrastim, 188 patients and healthy volunteers treated with pegfilgrastim and 121 patients treated with placebo was performed. Drug-specific antibodies emerging after start of treatment were detected in 0.86% of the subjects receiving lipegfilgrastim, in 1.06% of the subjects receiving pegfilgrastim and in 1.65% of the subjects receiving placebo. No neutralising antibodies against lipegfilgrastim were observed.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Following initial sc administration of lipegfilgrastim in healthy subjects, a lag in absorption of approximately 1 hour is observed with maximum serum concentrations being attained at approximately 35 hours after dose administration. Given its molecular weight, lipegfilgrastim is believed to be primarily absorbed via the lymphatic system then drained into the vascular system.

Following repeated administration in patients (cycle 4), mean serum concentrations of lipegfilgrastim are consistently lower than after a single dose. Maximum serum concentrations after repeat doses were attained earlier (8 to 24 hours after dose administration) than after a single dose. The observed

differences in pharmacokinetics following repeated administrations of lipegfilgrastim are consistent with the presence of higher absolute neutrophil count (ANC).

Distribution

Lipegfilgrastim has a small, weight-dependent volume of distribution (V_c approximately 70 mL/kg), indicating that it is not distributed beyond the lymphatic/vascular system.

Metabolism

Lipegfilgrastim is metabolised via intra- or extracellular degradation by proteolytic enzymes. Following binding to the G-CSF receptors, intracellular degradation occurs with lipegfilgrastim being internalised by neutrophils (non-linear process), then degraded within the cell by endogenous proteolytic enzymes. A second, linear pathway, is likely due to extracellular protein degradation by neutrophil elastase and other plasma proteases.

Excretion

Lipegfilgrastim has two distinct clearance pathways. The first clearance pathway is linear and is likely comprised of degradation by proteolytic enzymes. The second pathway is non-linear neutrophil-mediated clearance (intracellular) that is dependent on ANC.

After administration of lipegfilgrastim, the nonlinear clearance in any given subject varies over time together with the ANC values and the drug concentration values. In general, low ANC values are associated with a high linear clearance percentage. Thus, at lower ANC values the linear clearance is the predominant pathway and at high ANC values nonlinear clearance predominates. Given the differences in ANC values between healthy subject and cancer patients, who are exposed to the effects of myelosuppressive CTX, the predominant pathway varies between populations. Of note, the predominant pathway appears to change from linear to nonlinear at an ANC value of approximately ≥5-10 cells x 10^9/L.

Median terminal half-life of lipegfilgrastim is approximately 33 hours and median MRT is approximately 58 hours.

Of note, the PEG moiety which is cleaved from the amino acid backbone of the molecule via internal and external degradation is likely excreted unchanged in the urine due to its molecular size.

Healthy volunteers

In 3 studies (XM22-01, XM22-05, XM22-06) in healthy volunteers, the maximum blood concentration was reached after a median of 30 to 36 hours and the average terminal half-life ranged from approximately 32 to 62 hours after a single subcutaneous injection of 6 mg lipegfilgrastim.

After subcutaneous injection of 6 mg lipegfilgrastim at three different sites (upper arm, abdomen and thigh) in healthy volunteers, the bioavailability (peak concentration and area under the curve [AUC]) was lower after subcutaneous injection in the thigh compared to subcutaneous injection in the abdomen and in the upper arm. In this limited study XM22-06, bioavailability of lipegfilgrastim and observed differences among the injection sites were higher in male subjects compared to female subjects. Nevertheless, pharmacodynamic effects were similar and independent from gender and injection site.

Special populations

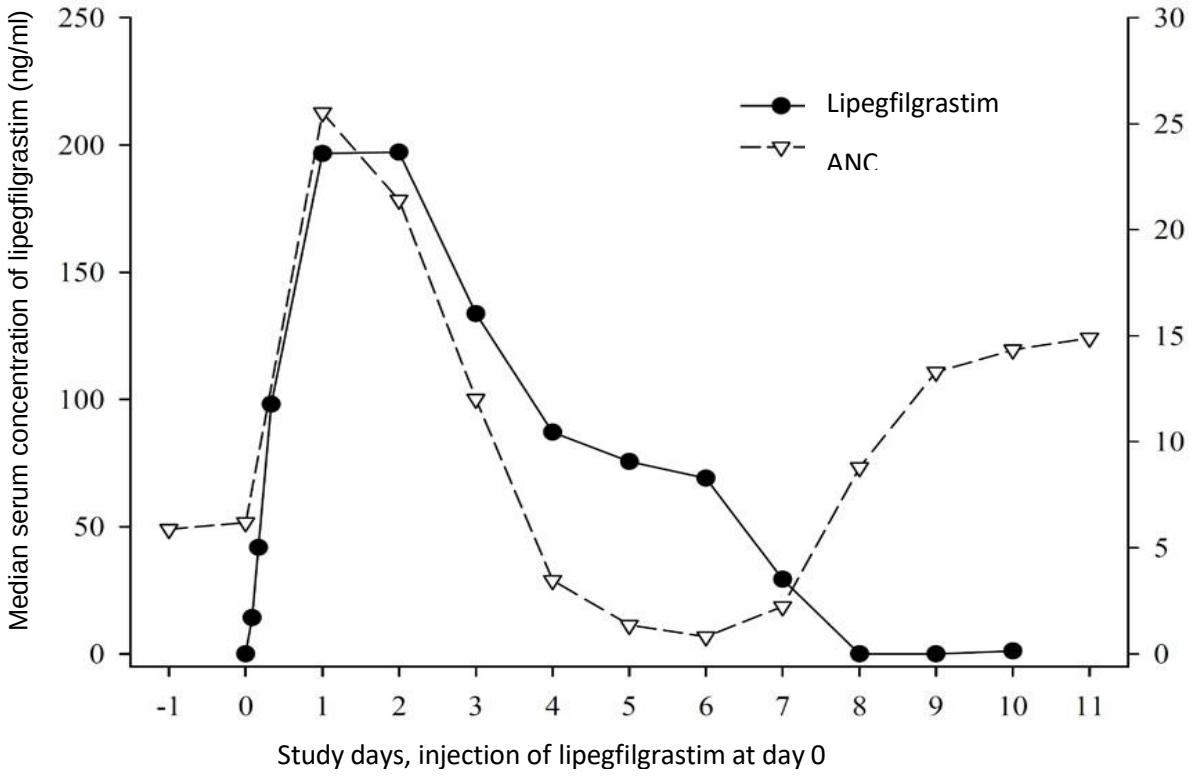
Cancer patients

In 2 studies (XM22-02 and XM22-03) in patients with breast cancer receiving chemotherapy consisting of doxorubicin and docetaxel, mean maximum blood concentrations of 227 and 262 ng/ml were reached after median times to maximum concentration (t_{max}) of 44 and 48 hours. The mean terminal half-lives were approximately 29 and 31 hours after a single subcutaneous injection of 6 mg lipegfilgrastim during the first cycle of chemotherapy. After a single subcutaneous injection of 6 mg lipegfilgrastim during the fourth cycle, the maximum blood concentrations were lower than observed in the first cycle (mean values 77 and 111 ng/ml) and were reached after median t_{max} of 8 hours. The mean terminal half-lives in the fourth cycle were approximately 39 and 42 hours.

In a study (XM22-04) in patients with non-small cell lung cancer receiving chemotherapy consisting of cisplatin and etoposide, the mean maximum blood concentration of 317 ng/ml was reached after a median t_{max} of 24 hours and the mean terminal half-life was approximately 28 hours after a single subcutaneous injection of 6 mg lipegfilgrastim during the first cycle of chemotherapy. After a single subcutaneous injection of 6 mg lipegfilgrastim during the fourth cycle, the mean maximum blood concentration of 149 ng/ml was reached after a median t_{max} of 8 hours and the mean terminal half-life was approximately 34 hours.

Lipegfilgrastim appears to be mainly eliminated by neutrophil-mediated clearance, which becomes saturated at higher doses. Consistent with a self-regulating clearance mechanism, the serum concentration of lipegfilgrastim declines slowly during the chemotherapy-induced transient neutrophil nadir and rapidly at the following onset of neutrophil recovery (see **Figure 1**).

Figure 1: Profile of median serum concentration of lipegfilgrastim and median ANC in chemotherapy-treated patients after a single 6 mg injection of lipegfilgrastim.



Patients with renal or hepatic impairment

There was no meaningful effect of mild renal impairment (CrCL: 62-87 mL/min; n = 20) on the pharmacokinetics of lipegfilgrastim in cancer patients. The impact of more severe renal impairment on the pharmacokinetics of lipegfilgrastim was not studied.

The impact of hepatic impairment on the pharmacokinetics of lipegfilgrastim in cancer patients was not studied.

Due to the neutrophil-mediated clearance mechanism, the pharmacokinetics of lipegfilgrastim is not expected to be affected by renal or hepatic impairment.

Elderly patients

Limited patient data indicate that the pharmacokinetics of lipegfilgrastim in elderly patients (65 - 74 years) is similar to that in younger patients. No pharmacokinetic data are available in patients ≥75 years.

Gender

No statistically significant differences in exposure were observed between men and women.

Race

Due to the limited data in the population studied, conclusions regarding the impact of race on the pharmacokinetics of lipegfilgrastim cannot be drawn.

Effect of body weight

A statistically significant difference in lipegfilgrastim exposure was observed between the heaviest (>80 kg) and the lightest (<60 kg) subjects studied. Exposure in the heaviest subjects was approximately 30% that of the exposure in lightest subjects. A decrease in efficacy cannot be excluded in patients >80 kg from currently available data.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Genotoxicity studies were not performed with Lonquex®.

Recombination products such as Lonquex® would not be expected to interact directly with deoxyribonucleic acid (DNA) or other chromosomal material. A mutagenic potential is not expected for Lonquex®.

The mutagenic potential of r-metHuG-CSF (filgrastim, Neupogen) was evaluated *in vivo* (mouse micronucleus test, intraperitoneal administration) as well as *in vitro* (Ames test, chromosomal aberration test). r-metHuG-CSF was found not to be mutagenic.

Carcinogenicity

Carcinogenicity studies with Lonquex® were not performed as there is no evidence for a genotoxic effect of these cytokines and although not being relevant for chronic toxicity studies in rats, during long-term administration carcinogenicity studies neutralising antibodies with G-CSF may develop and may restrict a meaningful result.

Moreover, cytotoxic chemotherapy as concomitant therapy of Lonquex in patients with cancer implies a genotoxic and carcinogenic risk that cannot be separated from potential effects of Lonquex®.

There is no indication for a potential carcinogenicity of Lonquex® from chronic toxicity studies.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The product is formulated at a concentration of 10 mg/ml in a 10 mM sodium acetate buffer (pH 5.0), 50 mg/mL sorbitol (30.0 mg) and polysorbate 20 (0.02 mg). Other excipients used in the formulation are acetic acid (0.36 mg), 1 M sodium hydroxide (0.14 mg) and water for injection (q.s. to 0.6 mL). The concentration of 10 mg/mL is based on protein content only. The concentration is 20.9 mg/mL (i.e. 12.6 mg per prefilled syringe) if the PEG moiety and the carbohydrate linker are included.

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 in a refrigerator between 2 - 8°C. Do not freeze.

Keep the prefilled syringe in the outer carton, in order to protect from light.

Avoid shaking.

Lonquex® may be removed from the refrigerator and stored below 25°C for a maximum single period of up to 7 days. Once removed from the refrigerator, the medicinal product must be used within this period or disposed of.

6.5 NATURE AND CONTENTS OF CONTAINER

Lonquex is supplied as a single use, preservative free, solution in a pre-filled syringe (type I glass) with a bromobutyl, latex free, plunger stopper and a fixed injection needle (stainless steel, 29G [0.34 mm] x 0.5 inch [12.7 mm]). It contains a solution volume of 0.6 mL with 6 mg of the active ingredient, lipegfilgrastim, for a 10 mg/mL solution. This is based on the protein content only.

Pack sizes of 1 pre-filled syringe with or without safety device (which prevents needle stick injury and re-use). For syringes without safety device, a plunger rod (polypropylene) is attached.

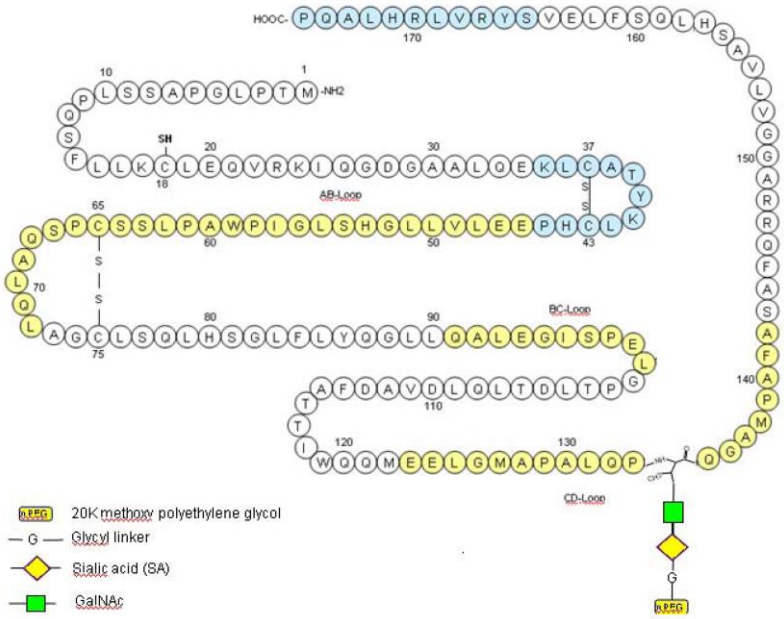
Each syringe is supplied in its own blister and carton.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



CAS number

1117844-87-7

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine.

8 SPONSOR

In **Australia**:

Teva Pharma Australia Pty Ltd
37 Epping Road
Macquarie Park NSW 2113
Australia

In **New Zealand**:

Teva Pharma New Zealand Ltd
PO Box 128 244, Remuera
Auckland 1541,
New Zealand

9 DATE OF FIRST APPROVAL

12 November 2015

10 DATE OF REVISION

15 November 2023

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
6.4	Storage conditions outside the refrigerator updated to 7 days.