**SCHEDULING STATUS:**

S4

## 1. NAME OF THE MEDICINE:

LONQUEX 6 mg solution for injection in pre-filled syringe

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each pre-filled syringe contains 6 mg of lipegfilgrastim* in 0,6 ml solution.

Each ml of solution for injection contains 10 mg of lipegfilgrastim.

The active substance is a covalent conjugate of filgrastim** with methoxy polyethylene glycol (PEG) via a carbohydrate linker.

* This is based on protein content only. The concentration is 20,9 mg/ml (i.e. 12,6 mg per pre-filled syringe) if the PEG moiety and the carbohydrate linker are included.

** Filgrastim (recombinant methionyl human granulocyte-colony stimulating factor [G-CSF]) is produced in *Escherichia coli* cells by recombinant DNA technology.

The potency of this medicine should not be compared to the potency of another pegylated or non-pegylated protein of the same therapeutic class. For more information, see **section 5.1**.

*Excipients with known effect:*

Each pre-filled syringe contains 30 mg sorbitol.

Sodium.

For the full list of excipients, see **section 6.1**.

## 3. PHARMACEUTICAL FORM:

Solution for injection in pre-filled syringe (injection)

LONQUEX is a clear, colourless solution.

## 4. CLINICAL PARTICULARS:

### 4.1 Therapeutic indications:

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

### 4.2 Posology and method of administration:

LONQUEX treatment should be initiated and supervised by medical practitioners experienced in oncology or haematology.

**Posology:**

A single pre-filled syringe of LONQUEX (one 6 mg dose of lipegfilgrastim) is recommended for each chemotherapy cycle, given approximately 24 hours after cytotoxic chemotherapy.

**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.

***Patients with renal impairment:***

Currently available data are described in **section 5.2**, but no recommendation on a posology can be made.

***Patients with hepatic impairment:***

Currently available data are described in **section 5.2**, but no recommendation on a posology can be made.

**Paediatric population:**

The safety and efficacy of LONQUEX in children and adolescents aged up to 17 years have not yet been established. Currently available data are described in **sections 4.8**, **5.1** and **5.2**.

**Method of administration:**

The solution is injected subcutaneously (SC). The injections should be given into the abdomen, upper arm or thigh.

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 should be performed under direct medical supervision.

For instructions on handling of the medicine before administration, see **section 6.6**.

## 4.3 Contraindications:

Hypersensitivity to lipegfilgrastim or to any of the excipients listed in **section 6.1**.

## 4.4 Special warnings and precautions for use:

***Traceability:***

In order to improve traceability of biological medicines, the trade name and batch number of the administered product should be clearly recorded (or stated) in the patient file.

***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 dose regimens.

***Allergic reactions and immunogenicity:***

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

Most biological medicines 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 LONQUEX does not preclude thrombocytopenia and anaemia caused by myelosuppressive chemotherapy. LONQUEX may also cause reversible thrombocytopenia (see **section 4.8**). Regular monitoring of the platelet count and haematocrit are recommended. Special care should be taken when administering single or combination chemotherapeutic medicine that are known to cause severe thrombocytopenia.

Leukocytosis may occur (see **section 4.8**). No adverse events directly attributable to leukocytosis have been reported. Elevation in white blood cells (WBC) is consistent with the pharmacodynamic effects of LONQUEX. 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 $10^9$/l after the expected nadir, LONQUEX 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 (see **section 4.3**).

***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 medicine, in combination with chemotherapy and/or radiotherapy in breast and lung cancer patients. A similar association is not known between LONQUEX 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:***

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

***Pulmonary adverse reactions:***

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

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**). In such circumstances LONQUEX should be discontinued at the discretion of the medical practitioner and appropriate treatment given.

*Vascular adverse reactions:*

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

***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 (see **section 4.8**). Medical practitioners 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 LONQUEX with splenic enlargement and vaso-occlusive crisis.

***Aortitis:***

Aortitis has been reported after G-CSF administration in healthy subjects and in cancer patients. The symptoms experienced included fever, abdominal pain, malaise, back pain and increased inflammatory markers (e.g. C-reactive protein and white blood cell count). In most cases aortitis was diagnosed by CT scan and generally resolved after withdrawal of G-CSF. See also **section 4.8**.

***Hypokalaemia:***

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

***Glomerulonephritis:***

Glomerulonephritis has been reported in patients receiving filgrastim, lenograstim or pegfilgrastim. Generally, events of glomerulonephritis resolved after dose reduction or withdrawal of filgrastim, lenograstim or pegfilgrastim. Urinalysis monitoring is recommended (see **section 4.8**).

***Excipients with known effect:***

LONQUEX contains sorbitol. Patients with hereditary fructose intolerance (HFI) should not use LONQUEX.

LONQUEX contains less than 1 mmol sodium (23 mg) per pre-filled syringe, i.e. essentially sodium-free.

**4.5 Interaction with other medicines and other forms of interaction:**

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 LONQUEX with any chemotherapeutic medicine 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 potential for interaction with lithium, which also promotes the release of neutrophils, has not been specifically investigated. There is no evidence that such an interaction would be harmful.

### 4.6 Fertility, pregnancy and lactation:

**Pregnancy:**

There are very limited data (less than 300 pregnancy outcomes) on the use of LONQUEX in pregnant women. Safety and efficacy in pregnant women have therefore not been established. The use of LONQUEX should be avoided during pregnancy.

**Breastfeeding:**

It is unknown whether the active ingredient, lipegfilgrastim, or its metabolites are excreted in human milk. A risk to the breastfed child cannot be excluded. Breastfeeding should be discontinued during treatment with LONQUEX.

**Fertility:**

No data are available. Animal studies with G-CSF and derivatives do not indicate harmful effects with respect to fertility (see **section 5.3**).

### 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 Undesirable effects:

### a. Summary of the safety profile:

The most frequent undesirable effects are musculoskeletal pain and nausea.

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 (see **section 4.4** and **section 4.8**).

### b. Tabulated summary of adverse reactions:

The safety of LONQUEX 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 1 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 1: 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*, aortitis* |
| *Respiratory, thoracic and mediastinal disorders* | Common | Haemoptysis |
| | Uncommon | Pulmonary adverse reactions*, Pulmonary haemorrhage |
| *Gastrointestinal disorders* | Very common | Nausea* |
| *Skin and subcutaneous tissue disorders* | Common | Skin reactions* |
| | Uncommon | Injection site reactions* |
| *Musculoskeletal and connective tissue disorders* | Very common | Musculoskeletal pain* |
| *General disorders and administration site conditions* | Common | Chest pain |
| *Investigations* | Uncommon | Increased blood alkaline phosphatase*, increased blood lactate dehydrogenase* |
| *See section "Description of selected adverse reactions" below | | |

**c. Description of selected adverse events:**

Thrombocytopenia and leukocytosis have been reported (see **section 4.4**).

Splenomegaly, generally asymptomatic, has been reported (see **section 4.4**).

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

Hypokalaemia has been reported (see **section 4.4**).

Pulmonary adverse reactions, in particular interstitial pneumonia, have been reported (see **section 4.4**). These pulmonary adverse reactions may also include pulmonary oedema, pulmonary infiltrates, pulmonary fibrosis, respiratory failure or ARDS (see **section 4.4**).

Nausea was very commonly observed in patients receiving chemotherapy.

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 include musculoskeletal pains such as bone pain and myalgia. Musculoskeletal pain is generally of mild to moderate severity, transient and can be controlled in most patients with standard analgesics. However, cases of severe musculoskeletal pain (mainly bone pain and back pain) have been reported, including cases that led to hospitalisation.

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 LONQUEX, but are generally accepted as being attributable to G-CSF and derivatives:

***Blood and lymphatic system disorders:***

- Splenic rupture including some fatal cases (see **section 4.4**)

- Sickle cell crisis in patients with sickle cell anaemia (see **section 4.4**)

***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 medicines or undergoing apheresis (see **section 4.4**).

- Aortitis (see **section 4.4**)

***Skin and subcutaneous tissue disorders:***

- Acute febrile neutrophilic dermatosis (Sweet's syndrome)

- Cutaneous vasculitis

***Renal and urinary disorders:***

- Glomerulonephritis (see **section 4.4**)

**d. Paediatric population:**

The experience in children is limited to a single-dose phase 1 study in 21 paediatric patients aged 2 to <18 years (see **section 5.1**), which did not indicate a difference in the safety profile of LONQUEX in children compared to that in adults. Treatment-related adverse events were back pain, bone pain and increased neutrophil count (1 event each).

***Reporting of suspected adverse reactions:***

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the **6.04 Adverse Drug Reaction Reporting Form**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

**4.9 Overdose:**

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

**5. PHARMACOLOGICAL PROPERTIES:**

**5.1 Pharmacodynamic properties:**

Pharmacotherapeutic group: Immunostimulants, colony stimulating factors, ATC code: L03AA14

LONQUEX is a biological medicine.

- ***Mechanism of action:***

Lipegfilgrastim is a covalent conjugate of filgrastim with a single methoxy polyethylene glycol (PEG) molecule via a carbohydrate linker consisting of glycine, N-acetylneuraminic acid and N-acetylgalactosamine. The average molecular mass is approximately 39 kDa of which the protein moiety constitutes approximately 48 %.

Human granulocyte colony-stimulating factor (G-CSF) is a glycoprotein that regulates the production and release of functional neutrophils from the bone marrow. Filgastrim 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 the human G-CSF receptor like filgrastim and pegfilgrastim.

- ***Pharmacodynamic 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 efficacy and safety:***

Once-per-cycle dosing of lipegfilgrastim 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 lipegfilgrastim or 6 mg pegfilgrastim. The study showed non-inferiority of 6 mg lipegfilgrastim to 6 mg pegfilgrastim for the primary endpoint, duration

of severe neutropenia (DSN) in the first cycle of chemotherapy (see table 2).

*Table 2: DSN, severe neutropenia (SN) and febrile neutropenia (FN) in cycle 1 of study XM22-03 (ITT):*

| | Pegfilgrastim 6 mg (n = 101) | Lipegfilgrastim 6 mg (n = 101) |
|---|---|---|
| **DSN** | | |
| Mean ± SD (d) | 0,9 ± 0,9 | 0,7 ± 1,0 |
| Δ LS mean | -0,186 | |
| 95 % CI | -0,461 to 0,089 | |
| **SN** | | |
| Incidence (%) | 51,5 | 43,6 |
| **FN** | | |
| Incidence (%) | 3,0 | 1,0 |

ITT = Intent-to-treat population (all randomised patients)

SD = standard deviation

d = days

CI = confidence interval

Δ LS mean (least square mean difference lipegfilgrastim – 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 lipegfilgrastim or placebo. The results of the study are presented in table 3. When the main study was finalised, the incidence of death was 7,2 %

(placebo) and 12,5 % (6 mg lipegfilgrastim) although after the 360-day follow-up period the overall incidence of death was similar between placebo and lipegfilgrastim (44,8 % and 44,0 %; safety population).

*Table 3: DSN, SN and FN in cycle 1 of study XM22-04 (ITT):*

| | Placebo (n = 125) | Lipegfilgrastim 6 mg (n = 250) |
|---|---|---|
| **FN** | | |
| Incidence (%) | 5,6 | 2,4 |
| 95 % CI | 0,121 to 1,260 | |
| p-value | 0,1151 | |
| **DSN** | | |
| Mean ± SD (d) | 2,3 ± 2,5 | 0,6 ± 1,1 |
| Δ LS mean | -1,661 | |
| 95 % CI | -2,089 to -1,232 | |
| p-value | < 0.0001 | |
| **SN** | | |
| Incidence (%) | 59,2 | 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<br>Odds ratio (lipegfilgrastim/placebo), CI and p-value out of multivariate | | |

| |
|---|
| logistic regression analysis |

A post-authorisation safety study XM22-ONC-40041 was conducted to collect data of disease progression and mortality in patients with advanced squamous or non-squamous cell lung cancer receiving lipegfilgrastim in addition to the platinum-based chemotherapy. Increased risk of disease progression or death was not observed with lipegfilgrastim.

***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.

**Paediatric population:**

In a phase 1 study of 21 children aged between 2 and 16 years with Ewing family of tumours or rhabdomyosarcoma, lipegfilgrastim was administered as a single subcutaneous dose of 100 µg/kg (up to a maximum of 6 mg, which is the fixed dose for adults) 24 hours after the end of the last chemotherapy treatment in week 1 of the regimen. The incidence of FN varied according to age (from 14,3 % to 71,4 %), with the highest frequency in the oldest age group. The use of three different chemotherapy regimens, with varying myelosuppressive effects and age distributions, complicated the comparison of efficacy across age groups (see **section 4.2**).

## 5.2 Pharmacokinetic properties:

**General:**

***Healthy volunteers:***

In healthy volunteers, the maximum blood concentration is reached after a median of 30 to 36 hours and the average terminal half-life range 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.

**Biotransformation:**

Lipegfilgrastim is metabolised via intra- or extracellular degradation by proteolytic enzymes. Lipegfilgrastim is internalised by neutrophils (non-linear process), then degraded within the cell by endogenous proteolytic enzymes. The linear pathway is likely due to extracellular protein degradation by neutrophil elastase and other plasma proteases.

***Medicine interactions:***

*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. Therefore, lipegfilgrastim is not likely to affect metabolism via human cytochrome P450 enzymes.

**Special populations:**

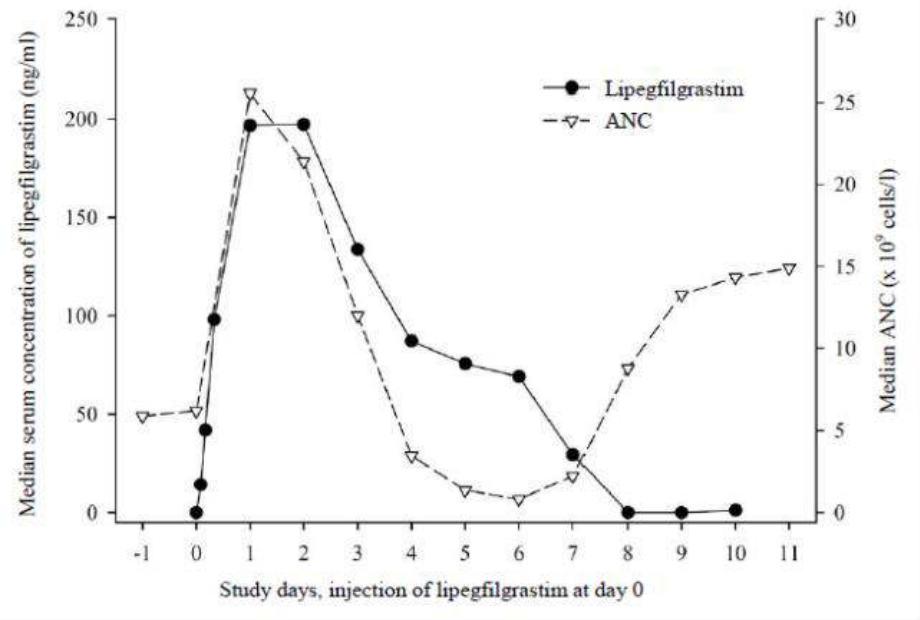
***Cancer patients:***

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 absolute neutrophil count (ANC) in chemotherapy-treated patients after a single 6 mg injection of lipegfilgrastim:*




***Patients with renal or hepatic impairment:***

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.

***Paediatric population:***

In a phase 1 study (see **section 5.1**), using a 10 mg/ml solution for subcutaneous injection specifically developed for the paediatric studies, the mean maximum blood concentrations ($C_{max}$) were 243 ng/ml in the 2 to < 6-year group, 255 ng/ml in the 6 to < 12-year group and 224 ng/ml in the 12 to < 18-year group after a single subcutaneous injection of 100 µg/kg (maximum 6 mg) lipegfilgrastim with the first cycle

of chemotherapy. The maximum blood concentrations were reached after a median time ($t_{max}$) of 23,9 hours, 30,0 hours and 95,8 hours, respectively. See **section 4.2**.

***Overweight patients:***

A trend towards a decrease in lipegfilgrastim exposure was observed with increase in weight. This may result in lowered pharmacodynamic responses in heavy patients (> 95 kg). Consequent decrease in efficacy in these patients cannot be excluded on current data.

### 5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single and repeated dose toxicity and local tolerance.

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.

## 6. PHARMACEUTICAL PARTICULARS:

### 6.1 List of excipients:

Acetic acid

Polysorbate 20

Sodium hydroxide (for pH-adjustment)

Sorbitol (E420)

Water for injection

**6.2 Incompatibilities:**

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

**6.3 Shelf life:**

3 years

**6.4 Special precautions for storage:**

Store in a refrigerator (2 °C – 8 °C).

Do not freeze.

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

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 medicine must be used within this period or disposed of.

**6.5 Nature and contents of container:**

LONQUEX is available in a pre-filled type I glass syringe containing 0,6 ml of solution, with a plunger stopper consisting of poly(ethylene-co-tetrafluoroethylene)-coated bromobutyl rubber and a fixed injection needle (stainless steel, 29G [0,34 mm] or 27G [0,4 mm] x 12,7 mm). Pre-filled syringes with

or without an additional safety device, which prevents needle stick injury and re-use, are available.

Pack sizes of 1 pre-filled syringe with or without safety device.

### 6.6 Special precautions for disposal and other handling:

The solution should be visually inspected before use. Only clear, colourless solutions without particles should be used.

The solution should be allowed to reach a comfortable temperature (15 °C – 25 °C) for injection.

Vigorous shaking should be avoided. Excessive shaking may aggregate lipegfilgrastim, rendering it biologically inactive.

LONQUEX does not contain any preservative. In view of the possible risk of microbial contamination, LONQUEX syringes are for single use only.

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

## 7. HOLDER OF CERTIFICATE OF REGISTRATION:

Teva Pharmaceuticals (Pty) Ltd

Maxwell Office Park, Magwa Crescent West

Waterfall City

Midrand

Gauteng

South Africa

2090

## 8. REGISTRATION NUMBER(S):

48/8.5/0745

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION:

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