1. NAME OF THE MEDICINAL PRODUCT

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 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 5.1.

Excipients with known effect

Each pre-filled syringe contains 30 mg sorbitol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled syringe (injection)

Clear, colourless solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Lonquex is indicated in adults and in children 2 years of age and older for reduction in the duration of neutropenia and the incidence of febrile neutropenia in 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 physicians experienced in oncology or haematology.

Posology

Adults
The recommended dose is 6 mg (a single pre-filled syringe) of Lonquex for each chemotherapy cycle, given approximately 24 hours after cytotoxic chemotherapy.

Children 2 years of age and older

For children weighing 45 kg and more, the recommended dose is 6 mg (a single pre-filled syringe) of Lonquex for each chemotherapy cycle, given approximately 24 hours after cytotoxic chemotherapy.

For children weighing less than 45 kg, Lonquex is also available as a vial presentation which can be dosed according to body weight (please refer to the Summary of Product Characteristics of the vial presentation).

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 lipegfilgrastim. 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 patients (children less than 2 years)
The safety and efficacy of Lonquex in children below 2 years of age have not been established. No data are available.

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 medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the trade name and batch number of the administered medicinal product should be clearly recorded 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 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). 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). No adverse events directly attributable to leukocytosis have been reported. Elevation in white blood cells (WBC) is consistent with the pharmacodynamic 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 10^9/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.

Splenic adverse reactions

Generally asymptomatic cases of splenomegaly have been reported after administration of lipegfilgrastim (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 lipegfilgrastim (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 physician 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, hypoalbuminaemia, 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). 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.

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 underling 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

This medicinal product contains sorbitol. The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account.

This medicinal product contains less than 1 mmol sodium (23 mg) per pre-filled syringe, i.e. essentially ‘sodium-free’.

4.5 Interaction with other medicinal products 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 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 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 lipegfilgrastim in pregnant women. Animal studies have shown reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of Lonquex during pregnancy.

Breast-feeding

It is unknown whether lipegfilgrastim/metabolites are excreted in human milk. A risk to the breast-fed child cannot be excluded. Breast-feeding 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

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).

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

Description of selected adverse reactions

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 lipegfilgrastim, 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 medicinal products 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)

Paediatric population

The safety assessment in paediatric patients is limited to the clinical trial data from the following studies:
- a phase I study with 21 paediatric patients aged 2 to 16 years with Ewing family of tumours or rhabdomyosarcoma receiving lipegfilgrastim after a single cycle of chemotherapy (see also section 5.1)
- a phase II study with 21 paediatric patients aged 2 to 18 years with Ewing family of tumours or rhabdomyosarcoma receiving one dose of lipegfilgrastim per chemotherapy cycle, for 4 consecutive cycles (see also section 5.1).

Overall, the safety profile in paediatric patients appeared similar to that observed in adult clinical trials. Some blood and lymphatic system disorders (anaemia, lymphopenia, thrombocytopenia) and gastrointestinal disorders (vomiting) were observed with a higher frequency in paediatric patients than those in adult clinical trials (see also section 5.1).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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 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.

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 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

Two clinical studies (XM22-07 and XM22-08) were conducted in paediatric populations using lipegfilgrastim for the treatment of chemotherapy-induced neutropenia and the prevention of chemotherapy-induced febrile neutropenia. In both studies, lipegfilgrastim was supplied in glass vials containing 10 mg of lipegfilgrastim in a 1 ml solution for subcutaneous injection.

In the phase I study (XM22-07), 21 children aged between 2 and 16 years with Ewing family of tumours or rhabdomyosarcoma received lipegfilgrastim 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 chemotherapy regimens consisted of: vincristine, ifosfamide, doxorubicin and etoposide (VIDE); vincristine, actinomycin D and cyclophosphamide (VAC); or ifosfamide, vincristine, and actinomycin D (IVA). 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.

In the phase II study (XM22-08), 42 children aged between 2 and < 18 years with Ewing family of tumours or rhabdomyosarcoma received for 4 consecutive chemotherapy cycles in a randomised 1:1 ratio either lipegfilgrastim at a dose of 100 µg/kg (up to a maximum of 6 mg, 1 dose per cycle) or

filgrastim at a dose of 5 µg/kg (once daily for at least 5 consecutive days per cycle [maximum of 14 days]). The chemotherapy regimens consisted of: VIDE; VAC; IVA; vincristine, doxorubicin, and cyclophosphamide alternating with ifosfamide and etoposide (VDC/IE); or ifosfamide, vincristine, actinomycin D and doxorubicin (IVADo). The primary endpoint was the duration of severe neutropenia (DSN) in cycle 1. DSN (mean [standard deviation]) in cycle 1 was 2.7 (2.25) days in the lipegfilgrastim group and 2.5 (2.09) days in the filgrastim group (Per Protocol [PP] Analysis set). The overall incidence of febrile neutropenia was 35 % in the lipegfilgrastim group and 42% in the filgrastim group (PP Analysis Set). The study was not powered for formal hypothesis testing. Therefore, results from this study should be interpreted with caution.

5.2 Pharmacokinetic properties

General

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.

Metabolism

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.

Drug interactions
In vitro data indicate that lipegfilgrastim is 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

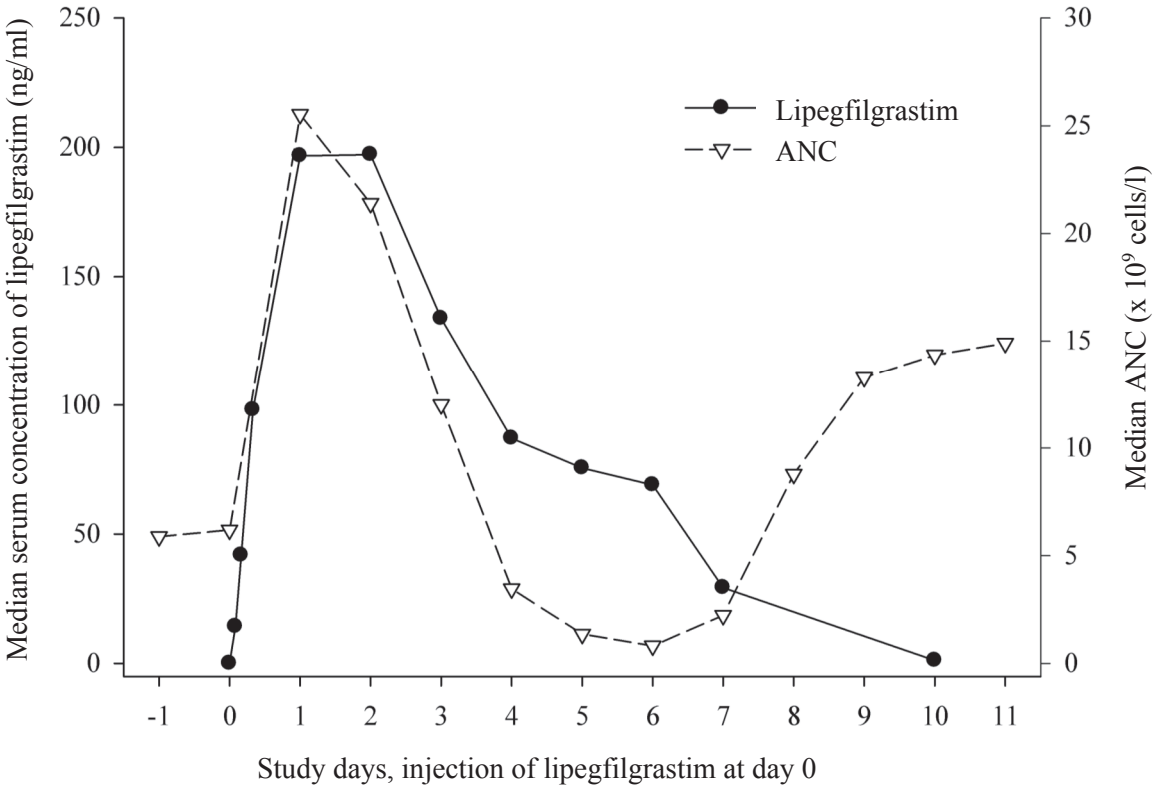
Cancer patients
In 2 studies (XM22-02 and XM22-03) in patients with breast cancer receiving chemotherapy consisting of doxorubicin and docetaxel, mean maximum blood concentrations of 227 and 262 ng/ml were reached after median times to maximum concentration (t_{max}) of 44 and 48 hours. The mean terminal 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 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 I study (see section 5.1) the geometric 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.

Pharmacokinetic and pharmacodynamic (PK-PD) modelling of paediatric data (aged 2 to <18 years with administered doses of 100 ug/kg), including additional data from the phase II study (see section 5.1) and combined with previous adult PK data, support that comparable lipegfilgrastim serum exposures were achieved in paediatric patients as compared to adult patients, and that PK and PD

parameters were comparable across the paediatric weight bands studied and support the dose recommendation by body weight ranges for paediatric patients.

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

Glacial acetic acid
Sodium hydroxide (for pH-adjustment)
Sorbitol (E420)
Polysorbate 20
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

2 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 3 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

Pre-filled syringe (type I glass) with a plunger stopper [poly(ethylene-co-tetrafluoroethylene)-coated bromobutyl rubber] and a fixed injection needle (stainless steel, 29G [0.34 mm] or 27G [0.4 mm] x 0.5 inch [12.7 mm]).

Each pre-filled syringe contains 0.6 ml of solution.

Pack sizes of 1 and 4 pre-filled syringes with safety device (which prevents needle stick injury and re-use) or 1 pre-filled syringe without safety device.

Not all pack sizes may be marketed.

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

7. MARKETING AUTHORISATION HOLDER

Teva B.V.
Swensweg 5
2031 GA Haarlem
Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/856/001
EU/1/13/856/002
EU/1/13/856/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 July 2013.
Date of latest renewal: 08 May 2018

10. DATE OF REVISION OF THE TEXT

22/07/2022

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.