# Summary Report of Benefit-Risk Assessment

## LONQUEX SOLUTION FOR INJECTION IN PRE-FILLED SYRINGE 6MG/0.6ML

## NEW DRUG APPLICATION

| | |
|---|---|
| **Active Ingredient(s)** | Lipegfilgrastim |
| **Product Registrant** | Drug Houses of Australia Pte Ltd |
| **Product Registration Number** | SIN16019P |
| **Application Route** | Abridged Evaluation |
| **Date of Approval** | 25 September 2020 |

# Table of Contents

## A INTRODUCTION

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

Lipegfilgrastim is a long-acting recombinant human granulocyte colony stimulating factor [G-CSF]). The active substance 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. It binds to G-CSF receptor and results in stimulation of proliferation of haematopoietic progenitor cells, differentiation into mature cells and release into the peripheral blood. The PEGylation reduces renal clearance and improves the half-life of lipegfilgrastim.

Lonquex is available as a pre-filled syringe containing 6mg of lipegfilgrastim in 0.6ml solution. Other ingredients in the pre-filled syringe are glacial acetic acid, sorbitol, polysorbate and sodium hydroxide.

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## B ASSESSMENT OF PRODUCT QUALITY

The drug substance, lipefilgrastim, is manufactured at [redacted]. The drug product, Lonquex Solution for Injection in Pre-filled Syringe 6mg/0.6ml, is manufactured at Teva Pharmaceutical Industries Ltd, Kfar Saba, Israel.

**Drug substance:**

Adequate controls have been presented for the cell banks. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate. The drug substance manufacturer is compliant with Good Manufacturing Practice (GMP). Process validation was conducted on three consecutive production-scale batches.

The characterisation of the drug substance and its impurities are in accordance with ICH guidelines. Potential and actual impurities are adequately controlled.

The drug substance specifications are established in accordance with ICH Q6B and the impurity limits are considered appropriately qualified. The analytical methods used are adequately described and non-compendial methods are appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing was presented.

The stability data presented for [redacted] were adequate to support the approved storage condition and shelf life. The packaging is PFA bottles, closed with PFA caps. The drug substance is approved for storage at 2-8$^{o}$C with a shelf life of 6 months.

**Drug product:**
The manufacturing process utilises aseptic processing.

All manufacturing sites involved are compliant with Good Manufacturing Practice (GMP). Proper development and validation studies were conducted. It has been demonstrated that the

manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications are established in accordance with ICH Q6B and impurity limits are considered adequately qualified. The analytical methods used are adequately described and non-compendial methods were appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data submitted were adequate to support the approved shelf-life of 24 months when stored at 2-8ºC and a maximum single period of up to 3 days at below 25ºC after removal from the refrigerator. The container closure system is a pre-filled syringe with a staked needle and rigid needle shield, with or without a safety device.

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## C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of lipegfilgrastim for reduction in the duration of neutropaenia and the incidence of febrile neutropaenia in patients treated with cytotoxic chemotherapy for malignancy was primarily based on one Phase II dose escalation study (XM22-02-INT) and two pivotal Phase III studies (XM22-03 and XM22-04).

Study XM22-02-INT was a Phase II, dose-finding study which demonstrated a dose-dependent trend with 6 mg lipegfilgrastim dose for the primary efficacy endpoint of duration of severe neutropaenia (DSN- absolute neutrophil count [ANC] <0.5 x $10^9$/L) in cycle 1 compared to 4.5 mg or 3 mg doses. No dose-dependent trend was observed for lipegfilgrastim for any of the safety parameters. Based on these observations, 6mg dose was chosen for the pivotal phase III studies.

Study XM22-03 was a phase III, multicentre, randomised (1:1), active-controlled, double-blind, parallel-group study that evaluated the efficacy and safety of 6 mg lipegfilgrastim compared to 6 mg pegfilgrastim in patients with breast cancer scheduled to receive doxorubicin 60 mg/$m^2$ i.v./docetaxel 75 mg/$m^2$ i.v. as routine chemotherapy (CTX). Study drug (6 mg lipegfilgrastim or 6 mg pegfilgrastim) was given as a subcutaneous injection on day 2, approximately 24 hours after start of CTX and CTX was repeated every 3 weeks (unless a dose delay was necessary) for a maximum of 4 cycles.

The primary objective of the study was to demonstrate non-inferiority of lipegfilgrastim to pegfilgrastim for the primary efficacy endpoint of mean DSN in cycle 1 in all treated population (ATP). The non-inferiority margin was confirmed if the upper limit of the two-sided 95% CI for the difference of the expected DSN difference was less than 1 day. The key secondary efficacy endpoints included incidence of febrile neutropaenia (FN) in cycles 1, 2, 3, 4 and across all cycles, DSN in cycles 2, 3 and 4, depth of ANC nadir in cycles 1, 2, 3 and 4, time to ANC nadir, time to ANC recovery in cycles 1, 2, 3 and 4, time to ANC recovery from ANC nadir in cycles 1, 2, 3 and 4, incidence of severe neutropaenia and of very severe neutropaenia in cycles 1, 2, 3 & 4, duration of very severe neutropaenia (DVSN) in cycles 1, 2, 3 and 4, incidence of treatment with i.v. antibiotics, CTX intensity and density.

A total of 202 patients were randomised to receive 6 mg pegfilgrastim (N=101) or 6mg lipegfilgrastim (N=101). Majority of patients (95.5%) completed the study and of the 9 patients who prematurely discontinued, 3 were in the pegfilgrastim group and 6 were in the

lipegfilgrastim group. The demographics and baseline characteristics were balanced between the two arms. All patients were Caucasian females with a mean age of 51.1 and 49.9 years in pegfilgrastim and lipegfilgrastim arms respectively. Majority of patients received CTX as adjuvant therapy (73.3% for pegfilgrastim and 74.3% for lipegfilgrastim) and the remaining received chemotherapy in the metastatic setting (26.7% for pegfilgrastim and 25.7% for lipegfilgrastim). Most of the patients had stage III or high-risk stage II disease; only 19.8% of pegfilgrastim patients and 13.9% of lipegfilgrastim patients had stage IV disease. The patients had an ECOG performance status of either 1 (53.5% for pegfilgrastim and 55.4% for lipegfilgrastim) or 0 at baseline (remaining patients).

The primary efficacy endpoint was met with the demonstration of non-inferiority of lipegfilgrastim to pegfilgrastim for the mean DSN in cycle 1 as the upper limit of the 2-sided 95% CI was less than 1(95% CI of -0.498 to 0.062; p=0.1260). The mean DSN (SD) in Cycle 1 was 0.8±0.9 days in the pegfilgrastim group and 0.7±0.9 days in the lipegfilgrastim group. There were numerically higher number of subjects without severe neutropaenia in lipegfilgrastim arm (56.4%) compared to pegfilgrastim arm (48.9%).

The results for the analyses of secondary efficacy endpoints were consistent with those of the primary efficacy endpoint, with lipegfilgrastim demonstrating comparable or numerically better efficacy compared to pegfilgrastim. The DSN in each cycle was comparable in the two treatment groups and as expected, the mean DSN was consistently shorter in cycles 2 to 4 than in cycle 1 in both treatment groups. Three patients had investigator-assessed FN during the study in ATP group, where all 3 cases occurred in the pegfilgrastim group during cycle 1. There was one case of FN in the intent to treat population (ITT) for lipegfilgrastim arm which was fatal. The incidence of very severe neutropaenia over all cycles was 11.7% in pegfilgrastim arm and 6.4% in lipegfilgrastim arm (p=0.2066). The DVSN in each cycle was very short (≤0.1 day) in both the treatment arms. The depth of ANC nadir was comparable between the two arms in each cycle. The delay in CTX treatments was comparable between the two arms (12.9% vs 13.8%). The incidence of dose reduced or omitted was none in lipegfilgrastim arm and ranged from 2.2-4.3% in pegfilgrastim arm. There were no relevant differences between the two arms for quality of life assessments based on EORTC QLQ-C30 and QLQ-BR23. Subgroup analyses revealed no relevant differences between the treatment groups or between subgroups. Overall, the efficacy was comparable between pegfilgrastim and lipegfilgrastim arms with some parameters numerically favouring the lipegfilgrastim arm.

**Summary of key efficacy endpoints (Study XM22-03)**

| | **Pegfilgrastim 6mg (N=94)** | **Lipegfilgrastim 6mg (N=94)** |
|---|---|---|
| **Primary endpoint** | | |
| DSN (days) in cycle 1 (ATP) | | |
| Mean ±SD | 0.8 ±0.9 | 0.7 ±0.9 |
| Median | 1.0 | 0.0 |
| Range | 0.0 to 4.0 | 0.0 to 4.0 |
| Poisson regression, LS mean (95%CI), p-value | -0.218 (-0.418, 0.062), 0.1260 | |
| **Secondary endpoints** | | |
| FN (all cycles) (ATP) | 3 | 0 |
| DSN (days) in cycle 2 (Mean±SD) | 0.3±0.6 | 0.1±0.5 |
| DSN (days) in cycle 3 (Mean±SD) | 0.2±0.4 | 0.1±0.3 |
| DSN (days) in cycle 4 (Mean±SD) | 0.2±0.5 | 0.2±0.6 |
| DVSN (days) in cycle 1 (Mean±SD) | 0.11±0.32 | 0.11±0.32 |

| | Pegfilgrastim 6mg (N=94) | Lipegfilgrastim 6mg (N=94) |
|---|---|---|
| Incidence of severe neutropaenia (all cycles) | 58.5% | 50.0% |
| Incidence of very severe neutropaenia (all cycles) | 11.7% | 6.4% |
| DVSN (days) in cycle 1 (Mean±SD) | 0.1±0.3 | 0.0±0.2 |
| DVSN (days) in cycle 2 (Mean±SD) | 0.0±0.1 | 0.0±0.1 |
| DVSN (days) in cycle 3 (Mean±SD) | 0.0±0.0 | 0.0±0.1 |
| DVSN (days) in cycle 4 (Mean±SD) | 0.0±0.1 | 0.0±0.3 |
| Depth of ANC nadir [$10^9$/L] (cycle 1) | 1.0±1.3 | 1.2±1.3 |
| Time to ANC recovery (cycle 1) | 7.4±3.6 | 5.9±3.4 |

Study XM22-04 was a phase III, multicentre, randomized (2:1), placebo-controlled, double-blind, parallel-group study that evaluated the efficacy and safety of subcutaneous treatment of 6 mg lipegfilgrastim compared to placebo in patients with non-small cell lung cancer (NSCLC) scheduled to receive cisplatin 80 mg/m$^2$ i.v./ etoposide 120 mg/m$^2$ i.v. as CTX for 4 cycles. The primary objective was to demonstrate superiority of lipegfilgrastim to placebo for the primary efficacy endpoint of incidence of febrile neutropaenia after cycle 1. The key secondary efficacy endpoints included incidence of FN in cycles 2, 3, and 4 and across all cycles, DSN, incidence of severe neutropaenia, DVSN, incidence of very severe neutropaenia, depth of ANC nadir, time to ANC nadir, time to ANC recovery, incidence of treatment with intravenous antibiotics due to FN or connected infections, percentage of actually delivered vs. scheduled cumulative CTX dose, proportion of patients with CTX doses reduced, omitted, or delayed, overall quality of life.

The study randomised (2:1) 376 patients and a total of 250 (66.7%) patients completed the study (placebo: 81 [64.8%]; lipegfilgrastim:169 [67.6%]). Discontinuations due to progression of disease were comparable between both the arms (8.8% in both the arms). Discontinuations due to deaths were higher in lipegfilgrastim arm compared to the placebo arm (9.6% vs 5.6% in placebo arm). The demographics were comparable between the two groups with majority being males (84% vs 88%) and mean age of 58 years (58.7 vs. 58.2 years). Majority of patients received CTX as treatment for metastatic disease (104 [83.2%] placebo, 215 [86.0%] lipegfilgrastim). There were slight imbalances noted in the two arms regarding some baseline characteristics. These included numerically lower incidence of squamous cell carcinoma in placebo (57.6%) compared to lipegfilgrastim arm (67%), more patients in placebo arm had prior surgery compared to lipegfilgrastim arm (21% vs 14%) and numerically higher percentage in lipegfilgrastim arm (11%) had ECOG status of 2 than placebo (8%).

The study failed to demonstrate superiority for the primary efficacy endpoint as the difference in the incidence of FN in cycle 1 was not statistically significant, with p=0.1151. However, the incidence of FN in cycle 1 was numerically lower in the lipegfilgrastim group (2.4%) compared to the placebo group (5.6%), with an odds ratio of 0.39 (95% CI: 0.121, 1.260). The incidence of FN was numerically lower in lipegfilgrastim arm compared to placebo in cycles 2,3 and 4. The results for all other neutropaenia-related secondary endpoints consistently indicated that treatment with lipegfilgrastim was numerically superior to placebo. The DSN in cycle 1 was shorter in the lipegfilgrastim group (Mean±SD: 0.6±1.1 days) than in the placebo group (2.3±2.5 days). The DSN in cycles 2, 3 and 4 was consistently shorter in the lipegfilgrastim treatment group compared to placebo. In each of cycles 2 to 4 around 80% of lipegfilgrastim-treated patients had no severe neutropaenia compared to 40% in the placebo arm. The mean ANC nadir in cycle 1 was higher and the time to ANC nadir was also shorter for the

lipegfilgrastim group. In cycle 1, a higher incidence of hospitalisation due to FN was observed in the placebo group compared to the lipegfilgrastim group (3.2 vs. 0.4%, p=0.0262). The mean CTX delay was higher in the placebo group (12.8 ± 10.2 days) compared to the lipegfilgrastim group (6.4 ± 7.6 days). The proportion of patients with delays in the administration of CTX was higher for the placebo group in each of cycles 2 to 4 (p<0.05 in each case). Most patients in both treatment groups received their planned chemotherapy dose in each cycle, with only 0.9 to 3.3% of placebo patients and 1.1 to 2.3% of lipegfilgrastim patients having CTX dose reduced or treatments omitted.

**Summary of key efficacy endpoints (Study XM22-04)**

| | **Lipegfilgrastim 6mg (N=250)** | **Placebo (N=125)** |
|---|---|---|
| **Primary endpoint** | | |
| FN in cycle 1 (ATP) | | |
| Incidence (%) | 2.4% | 5.6% |
| Odds ratio (95% CI) | 0.390 (0.121-1.260) | |
| p-value | 0.1151 | |
| **Secondary endpoints** | | |
| Incidence of FN (cycle 2) | 0.5% | 0 |
| Incidence of FN (cycle 3) | 0.5% | 1.1% |
| Incidence of FN (cycle 4) | 1.2% | 2.5% |
| DSN (days) in cycle 1 (Mean±SD) | 0.6±1.1 | 2.3 ±2.5 |
| DSN (days) in cycle 2 (Mean±SD) | 0.3±0.7 | 2.2 ±2.6 |
| DSN (days) in cycle 3 (Mean±SD) | 0.4±0.9 | 2.0 ±2.4 |
| DSN (days) in cycle 4 (Mean±SD) | 0.5±1.1 | 2.3 ±2.5 |
| Incidence of severe neutropaenia (all cycles) | 41.4% | 80% |
| Incidence of very severe neutropaenia (all cycles) | 16.1% | 26.4% |
| Depth of ANC nadir [$10^9$/L] (cycle 1) | 1.60±1.64 | 0.67±0.85 |
| Time to ANC recovery (days) (cycle 1) | 6.8 (±5.1) | 13.0 (±7.2) |

Overall, study XM22-03 demonstrated non-inferiority of lipegfilgrastim to pegfilgrastim for the primary efficacy endpoint of DSN. Analysis of secondary efficacy endpoints further supported the non-inferiority of lipegfilgrastim to pegfilgrastim with a trend in favour of lipegfilgrastim. Although, study XM22-04 failed to demonstrate superiority of lipegfilgrastim to placebo for the primary efficacy endpoint of FN, there was a numerical reduction in the incidence of FN in cycle 1 in the lipegfilgrastim (2.4%) compared to the placebo group (5.6%), with an odds ratio of 0.39 (95% CI: 0.121, 1.260).The actual incidences of FN in this study were lower than those anticipated for placebo, based on the results of published lung cancer studies using the same chemotherapy combination with similar cisplatin and etoposide dosages, and were higher than that anticipated for lipegfilgrastim. Secondary endpoints favoured lipegfilgrastim over placebo which included the incidence of FN in all cycles and DS. Taken together, the efficacy of lipegfilgrastim in reducing febrile neutropaenia and duration of severe neutropaenia was considered comparable to pegfilgrastim.

## D ASSESSMENT OF CLINICAL SAFETY

The clinical safety data supporting the use of lipegfilgrastim for the proposed indication comprised 575 patients from the two-phase III pivotal studies (Study XM22-03 and XM22-04)

and a phase IV safety study (XM22-ONC-4041). The two-phase III pivotal studies included 349 patients in the 6mg lipegfilgrastim arm, 101 to pegfilgrastim 6 mg arm and 125 to placebo.

In Study XM22-03, treatment emergent adverse events (TEAEs) were experienced by 99 (98.0%) patients in the pegfilgrastim group and by 100 (99.0%) patients in the lipegfilgrastim group. The most common AEs that were of higher incidence in lipegfilgrastim arm compared to pegfilgrastim arm were nausea (60.4%, 51.5%), bone pain (13.9%, 9.9%), leukopenia (11.9%,7.9%), alopecia (92.1%,85.1%), and vomiting (9.9%,4.0%). Severe TEAEs were reported in 35 (34.7%) pegfilgrastim-treated patients and 26 (25.7%) lipegfilgrastim-treated patients. These included neutropenia (21.8% vs 15.8%), alopecia (9.9%vs 8.9%), (3.0% vs 5.0%), febrile neutropaenia (3.0%vs 1.0%), anaemia (1.0% vs 2.0%) in pegfilgrastim- and lipegfilgrastim-treated patients respectively. Frequencies of serious TEAEs were higher in the pegfilgrastim group compared to the lipegfilgrastim group (6.9 vs. 3%). There were 2 pegfilgrastim- and 1 lipegfilgrastim-treated patient who had febrile neutropenia that were classified as serious TEAE. A single patient, treated with lipegfilgrastim, died in this study due to enterocolitis and was considered not related to the study medication. Adverse events of special importance included bone pain related symptoms (16.8% in pegfilgrastim arm and 23.8% in lipegfilgrastim arm) and diarrhoea-like symptoms (11.9% in pegfilgrastim arm and 9.9% in lipegfilgrastim arm).

**Overview of Safety Profile: Study XM22-03**

| | **Lipegfilgrastim 6mg (N=101)** | **Pegfilgrastim 6mg (N=101)** |
|---|---|---|
| **AE** | | |
| Treatment-related AE | 100 (99.0%) | 99 (98.0%) |
| Serious adverse events (SAEs) (any) | 7(6.9%) | 3 (3.0%) |
| SAEs (related) | 1 | 1 |
| Discontinuations due to AEs (all) | 4 | 5 |
| Discontinuations due to AEs (related) | 0 | 0 |
| Deaths (all) | 1 | 0 |
| Deaths (related) | 0 | 0 |

In Study XM22-04, TEAEs were experienced by 115 (92.0%) patients in the placebo group and by 221 (89.1%) patients in the lipegfilgrastim group. The most commonly AEs reported at a higher frequency in lipegfilgrastim arm compared to placebo were alopecia (33.6% placebo, 40.7% lipegfilgrastim), anaemia (24.0%, 25.4%), nausea (21.6%, 23.8%), thrombocytopaenia (8.0%, 12.9%), hypokalaemia (2.4%, 8.1%), disease progression (4.0%, 6.5%), non-small cell lung cancer (3.2%, 6.5%), hypophosphatemia (1.6%, 4.8%), decreased weight (1.6%, 4.8%), arthralgia (1.6%, 3.6%), bone pain (0.8% , 2%), fatigue (4.8%, 6.5%), back pain (1.6% vs 2.4%), dizziness (3.2% vs 3.6%), headache (3.2% vs 3.6%), tachycardia (1.6% vs 2%) and upper abdominal pain (0.8%, 2.0%). Severe TEAEs were reported in 59 (47.2%) patients who received placebo and 104 (41.9%) lipegfilgrastim-treated patients. Severe TEAEs occurring at least 1% more frequently in the lipegfilgrastim group were alopecia, anaemia, non-small cell lung cancer, disease progression, hypokalaemia, cardio-respiratory arrest, fatigue, and pain. Bone-pain-related symptoms were reported in 8 (6.4%) and21 (8.5%) patients in the placebo and lipegfilgrastim arm, respectively.

Serious TEAEs were reported in 22 (17.6%) patients and 58 (23.4%) patients in the placebo and lipegfilgrastim arm, respectively. Serious TEAEs with higher frequency in lipegfilgrastim arm were anaemia (1.6% placebo, 3.2% lipegfilgrastim), non-small cell lung cancer (0.8%, 3.2%), disease progression (0%, 2.4%), cardio-respiratory arrest (0%,1.2%), thrombocytopaenia (0%, 1.2%), renal failure (0% vs 0.8%), pulmonary haemorrhage (0% vs 0.8%). TEAEs leading to discontinuation of study participation were reported in 33 (26.4%) placebo patients and in 57 (23.0%) lipegfilgrastim patients. The most frequent TEAEs leading to discontinuation were disease progression and non-small cell lung cancer. The TEAEs leading to discontinuation of study participation were assessed as unrelated to the study medication in all but 3 patients in the placebo arm and 3 patients in the lipegfilgrastim arm.

**Overview of Safety Profile: Study XM22-04**

| | **Lipegfilgrastim 6mg (N=248)** | **Placebo (N=125)** |
|---|---|---|
| **AE** | | |
| Treatment-related AE | 221 (89.1%) | 115 (92.0%) |
| Serious adverse events (SAEs) (any) | 58 (23.4%) | 22 (17.6%) |
| SAEs (related) | 3 | 0 |
| Discontinuations due to AEs (all) | 57 (23.0%) | 33 (26.4%) |
| Discontinuations due to AEs (related) | 3 | 3 |
| Deaths (all) | 31 (12.5%) | 9 (7.2%) |
| Deaths (related) | 1 | 0 |

In study XM22-04, the incidence of deaths was higher in lipegfilgrastim arm (7.2%) compared to the placebo arm (12.5%) mainly due to disease progression (1.6% in the placebo group and 5.6% in the lipegfilgrastim group) at 24 weeks. There were some imbalances observed in terms of baseline characteristics including lower incidence of squamous cell carcinoma or ECOG 2 patients, which may have favoured the placebo arm in terms of disease progression but could not be established with certainty. The incidence of mortality was comparable between the two treatment arms (44.4% in lipegfilgrastim arm and 44.8% in placebo arm), when the subjects were followed for 1 year. Furthermore, study XM22-ONC-40041 conducted in lung cancer was submitted to evaluate the risk of disease progression associated with lipegfilgrastim in comparison to placebo and pegfilgrastim.

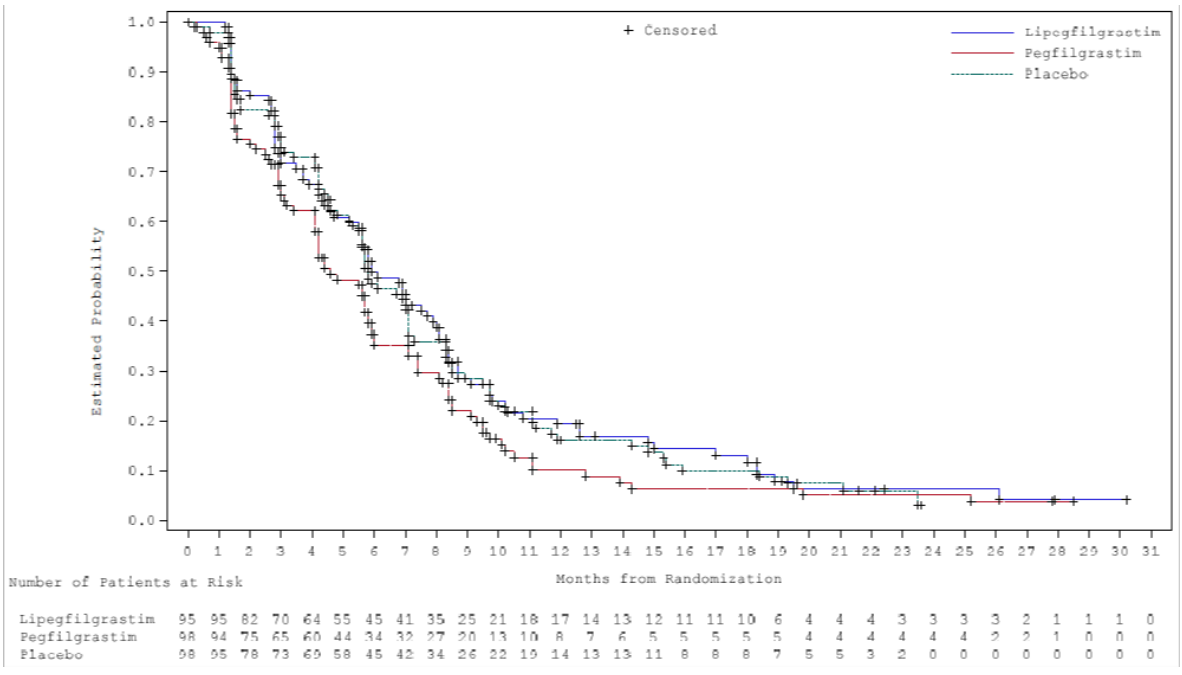
Study XM22-ONC-40041 was a phase IV, multinational, multicentre, randomised, double-blind study to compare disease progression and mortality data for lipegfilgrastim, pegfilgrastim, and placebo in adults with advanced squamous or non-squamous NSCLC Stage IIIB/IV who received moderately myelosuppressive CTX (combination of pemetrexed and cisplatin, cisplatin and paclitaxel, or cisplatin and docetaxel)for 6 cycles (21 days per cycle). The key inclusion criteria were 18 to 75-year-old patients with histologically or cytologically confirmed, unresectable, advanced or metastatic squamous or non-squamous NSCLC. The primary safety objective was progression-free survival (PFS), measured according to the Response Evaluation Criteria in Solid Tumours version 1.1 criteria (RECIST1.1), using data from an Independent centralised assessment of images. The secondary efficacy endpoints were DSN, FN, incidence of very severe neutropaenia, and incidence of severe neutropaenia in Cycle 1. Other safety endpoints included overall survival (OS) and objective response rates (ORR).

A total of 303 patients were randomly assigned to three groups (101 patients to lipegfilgrastim, 101 patients to pegfilgrastim, and 101 patients to the placebo treatment group); 291 (96%) patients received at least 1 dose and were evaluable for safety; and 168 (55%) patients

completed the treatment period of the study (at least 6 cycles of CTX). A total of 264 (87%) patients discontinued the study; the proportion was similar across the 3 treatment groups (lipegfilgrastim 86%, pegfilgrastim 89%, placebo 86%). The most common reason for discontinuation was death (overall 66%), followed by withdrawal by patients (10%), and lost to follow-up (9%). Similar proportion of discontinuation were seen across all the three arms and the proportion of deaths were comparable between the three arms. The baseline and demographic characteristics were balanced across the three groups. The average age of the patients was 59.6 years (range 36 to 75 years), majority males (81%) and all were Caucasians.

The median PFS was similar between the lipegfilgrastim, placebo and pegfilgrastim treatment groups (5.9 months [95% CI=5.20, 7.9] vs 5.8 months [95% CI=5.20, 7.10] vs 4.6 months [95% CI=4.10, 5.80]). The incidence of disease progression or death was similar between treatment groups; (lipegfilgrastim 85 [89%] patients; pegfilgrastim 89 [91%], and placebo 88 [90%]). The log-rank test comparing disease progression or death between groups, showed no statistically significant difference between the lipegfilgrastim versus placebo treatment groups (p=0.8114) and the lipegfilgrastim versus pegfilgrastim treatment groups (p=0.0865) over time. The Kaplan-Meier (KM) survival analysis estimated that the 18-month survival rates for the lipegfilgrastim, pegfilgrastim, and placebo treatment groups were 12%, 6% and 10%, respectively. The log-rank test comparing disease progression or death between groups, showed no statistically significant difference between the lipegfilgrastim versus placebo treatment groups (p=0.8114) and the lipegfilgrastim versus pegfilgrastim treatment groups (p=0.0865) over time.

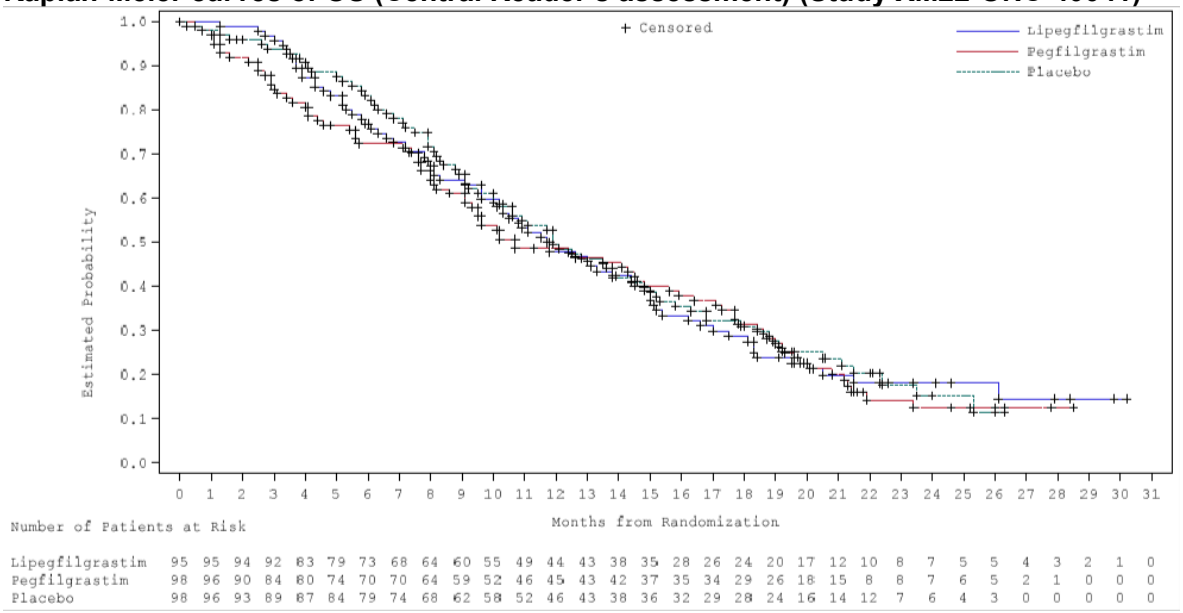
**Kaplan-Meier curves of PFS (Central reader's assessment) (Study XM22-ONC-40041)**




The incidence of deaths was similar between the lipegfilgrastim, placebo and pegfilgrastim treatment groups (75 [79%] patients vs 76 [78%] patients vs 81 [83%]). The median OS was similar in the three arms (11.7 months [95% CI:9.60, 14.50] vs 11.9 months [95% CI:10.00,

14.80] vs10.7 months [95% CI:9.10, 14.80]) in lipegfilgrastim, placebo and pegfilgrastim arms respectively). The ORR according to the central reader assessment was 43%, 37% and 40% in the lipegfilgrastim, pegfilgrastim, and placebo treatment groups respectively.

**Kaplan-Meier curves of OS (Central Reader's assessment) (Study XM22-ONC-40041)**




**Summary of key safety endpoints (Study XM22-ONC-40041)**

| | **Lipegfilgrastim 6 mg (N=95)** | **Placebo (N=98)** | **Pegfilgrastim 6 mg (N=98)** |
|---|---|---|---|
| **Primary endpoint** | | | |
| PFS per IRC | | | |
| PFS events, n (%) | 85 (89%) | 88 (90%) | 89 (91%) |
| Median PFS (months) (95% CI) | 5.9 (5.20, 7.90) | 5.8 (5.20, 7.10) | 4.6 (4.10, 5.80) |
| Log rank p-value (lipegfilgrastim vs placebo) | 0.8114 | | N/A |
| Log rank p-value (lipegfilgrastim vs pegfilgrastim) | 0.0865 | N/A | |
| **Secondary endpoints** | | | |
| OS events, n (%) | 75 (79) | 76 (78) | 81 (83) |
| Median OS (months) (95% CI) | 11.7 (9.60, 14.50) | 11.9 (10.00, 14.80) | 10.7 (9.10, 14.80) |
| Hazard ratio (95% CI) | | | |
| Lipegfilgrastim/Pegfilgrastim | 0.95 (0.696, 1.305) | N/A | |
| Lipegfilgrastim/Placebo | 1.04 (0.756, 1.432) | | N/A |
| Pegfilgrastim/Placebo | N/A | | 1.09 (0.798, 1.494) |
| ORR-IRC, n (%) | 41 (43%) | 39 (40%) | 36 (37%) |

In Study XM-ONC-40041, a total of 288 (99%) patients were reported with at least 1 adverse event during the study, 94 (99%) received lipegfilgrastim, 97 (99%) received pegfilgrastim, and 97 (99%) received placebo. The most frequently reported adverse events (overall) were: NSCLC (81% of patients) followed by anaemia (41%), nausea (34%), and alopecia (32%). Only a few adverse events reported during the study were considered by the investigator to be related to the treatment (lipegfilgrastim: 14 [15%] patients; pegfilgrastim: 13 [13%]; placebo 11 [11%]). The treatment-related adverse events were mainly of grade 1 or 2 with 6 patients having grade 3. The adverse events reported were thrombocytopaenia, bone pain, and syncope (lipegfilgrastim group; 1 patient each), neutropaenia (pegfilgrastim group; 1 patient each), and anaemia (placebo group; 1 patient). No grade 4 AEs reported.

A total of 232 patients (80%) were reported with an adverse event leading to death, 75 patients (79%) receiving lipegfilgrastim, 81 patients (83%) receiving pegfilgrastim, and 76 patients (78%) receiving placebo. Most of the adverse events leading to death were due to the underlying disease (67 [71%] patients; 68 [69%]; 69 [70%]). None of the deaths in lipegfilgrastim arm were considered related to study drug.

A total of 247 (85%) patients were reported with at least 1 serious adverse event, 81 (85%) patients receiving lipegfilgrastim, 86 (88%) receiving pegfilgrastim, and 80 (82%) receiving placebo. All serious adverse events were reported with similar frequencies across all treatment groups and majority (76% of all patients) were due to the underlying disease.

**Overview of Safety Profile: Study XM22-ONC-40041**

| AE<br>n (%) | Lipegfilgrastim 6mg<br>(N=95) | Pegfilgrastim 6mg<br>(N=98) | Placebo<br>(N=98) |
|---|---|---|---|
| Any TEAE | 94 (99%) | 97 (99%) | 97 (99%) |
| Treatment-related TEAE | 14 (15%) | 13 (13%) | 11 (11%) |
| SAE | 81 (85%) | 86 (88%) | 80 (82%) |
| Treatment-related SAE | 0 | 0 | 2 (2%) |
| Discontinuations due to AE | 69 (73%) | 79 (81%) | 74 (76%) |
| Treatment-related discontinuations | 0 | 0 | 3 (3%) |
| Deaths | 75 (79%) | 81 (83%) | 76 (78%) |
| Deaths due to treatment | 0 | 0 | 2 (2%) |

AE: adverse event; SAE: serious adverse event; TEAE: treatment-emergent adverse event

No subject had neutralising antibodies against lipegfilgrastim.

Overall, the safety of lipegfilgrastim was comparable to that of pegfilgrastim with some higher incidence of bone related events which were mild to moderate in intensity. The adverse reactions observed were typical for G-CSFs which included musculoskeletal related events (bone pain, arthralgia, myalgia), nausea, anaemia, thrombocytopaenia, diarrhoea, hypokalaemia, asthenia etc., which could be managed. Other rare known AEs like pulmonary events, leucocytosis, capillary leak syndrome, spleen related events, Sweets syndrome were not observed in the studies. There was higher incidence of deaths in lipegfilgrastim arm compared to placebo noted in study XM22-04 mainly due to disease progression. This

observation raised concerns on whether there is a potential increased risk of disease progression associated with lipegfilgrastim. There were some imbalances in the baseline characteristics which may have favoured the placebo arm, but the uncertainty about stimulation of non-haematopoietic malignant cells could not be ruled out. Follow-up data for up to 1 year which showed that the incidence of deaths was comparable between the lipegfilgrastim and placebo arms provided some assurance (44.4% vs 44.8%). Furthermore, study XM22-ONC-40041 which was submitted to support safety in the same NSCLC population did not show any difference in PFS or OS between lipegfilgrastim, pegfilgrastim and placebo. Taken together, the data suggested that lipegfilgrastim may not be associated with increased risk of disease progression or death compared to pegfilgrastim or other G-CSFs. Overall, the safety profile was considered consistent with that known for GCSFs.

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## E ASSESSMENT OF BENEFIT-RISK PROFILE

Lipegfilgrastim is a long-acting G-CSF similar to pegfilgrastim with slight difference in the PEG moiety. Study XM22-03, a study conducted in breast cancer patients, demonstrated non-inferiority of 6 mg lipegfilgrastim to pegfilgrastim for the primary efficacy endpoint of DSN in cycle 1. This was supported by the secondary efficacy endpoints. Study XM22-04, conducted in NSCLC patients did not demonstrate statistical superiority of lipegfilgrastim over placebo for the primary efficacy endpoint of incidence of FN. Nonetheless, the results were numerically favouring lipegfilgrastim and were supported by the secondary efficacy endpoints.

The safety of lipegfilgrastim was comparable to that of pegfilgrastim with slightly higher incidence of bone related AEs. The adverse reactions observed were typical for G-CSFs and were manageable. There was a higher incidence of deaths in study XM22-04 in lipegfilgrastim arm due to disease progression at about 24 weeks but were comparable when followed up to 1 year. Study XM22-ONC-40041 also demonstrated that lipegfilgrastim did not impact disease progression in NSCLC patients.

Overall, the benefit risk profile was similar to that known for other G-CSF products and considered favourable for the proposed indication of reduction of chemotherapy induced FN and duration of severe neutropaenia in adult patients with solid tumours.

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## F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of Lonquex for the reduction in the duration of neutropaenia and the incidence of febrile neutropaenia in patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes) was deemed favourable and approval of the product registration was granted on 24 September 2020.

## APPROVED PACKAGE INSERT AT REGISTRATION

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

## 1. NAME OF THE MEDICINAL PRODUCT

LONQUEX PRE-FILLED SYRINGE 6MG/0.6ML

## 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.
Sodium.

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 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

One 6 mg dose of lipegfilgrastim (a single pre-filled syringe of Lonquex) 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 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 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 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. Patients with rare hereditary problems of fructose intolerance should not use this medicinal product.

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*<br>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 | 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 painis 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 postmarketing 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 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 lipegfilgrastim 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 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 national reporting system..

### 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<br>Odds ratio (lipegfilgrastim / placebo), CI and p-value out of multivariate logistic regression analysis | | |

A post-authorisation safety study was conducted to collect comparative data of disease progression and mortality in patients with advanced squamous or non-squamous non-small cell lung cancer. Study XM22-ONC-40041 was an active-and placebo-controlled study in 303 patients with non-small cell lung cancer receiving up to 6 cycles of chemotherapy combination of pemetrexed and cisplatin, cisplatin and paclitaxel, or cisplatin and docetaxel and included a planned follow-up period in which patients were followed for tumor progression and survival until 225 deaths were observed. Patients were randomised 1:1:1 to receive 6 mg lipegfilgrastim or 6 mg pegfilgrastim or placebo. The median time to disease progression or death was 5.8 months (95 % CI = 5.20, 7.10) in the placebo treatment group, 5.9 months (95 % CI = 5.20, 7.90) in the lipegfilgrastim treatment group and 4.6 months (95 % CI = 4.10, 5.80) in the pegfilgrastim treatment group. The risk of experiencing disease progression or death in lipegfilgrastim versus placebo treatment groups or lipegfilgrastim versus pegfilgrastim treatment groups was similar. The incidence of death was 78 % (placebo), 79 % (lipegfilgrastim) and 83 % (pegfilgrastim). The median time to death was 11.9 months (95 % CI = 10.00, 14.80) in the placebo treatment group, 11.7 months (95% CI = 9.60, 14.50) in the lipegfilgrastim treatment group and 10.7 months (95% CI = 9.10, 14.80) in the pegfilgrastim treatment group.

*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

The European Medicines Agency has deferred the obligation to submit the results of studies with Lonquex in all subsets of the paediatric population in the treatment of chemotherapy-induced neutropenia and prevention of chemotherapy-induced febrile neutropenia (see section 4.2 for information on paediatric use). 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 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.

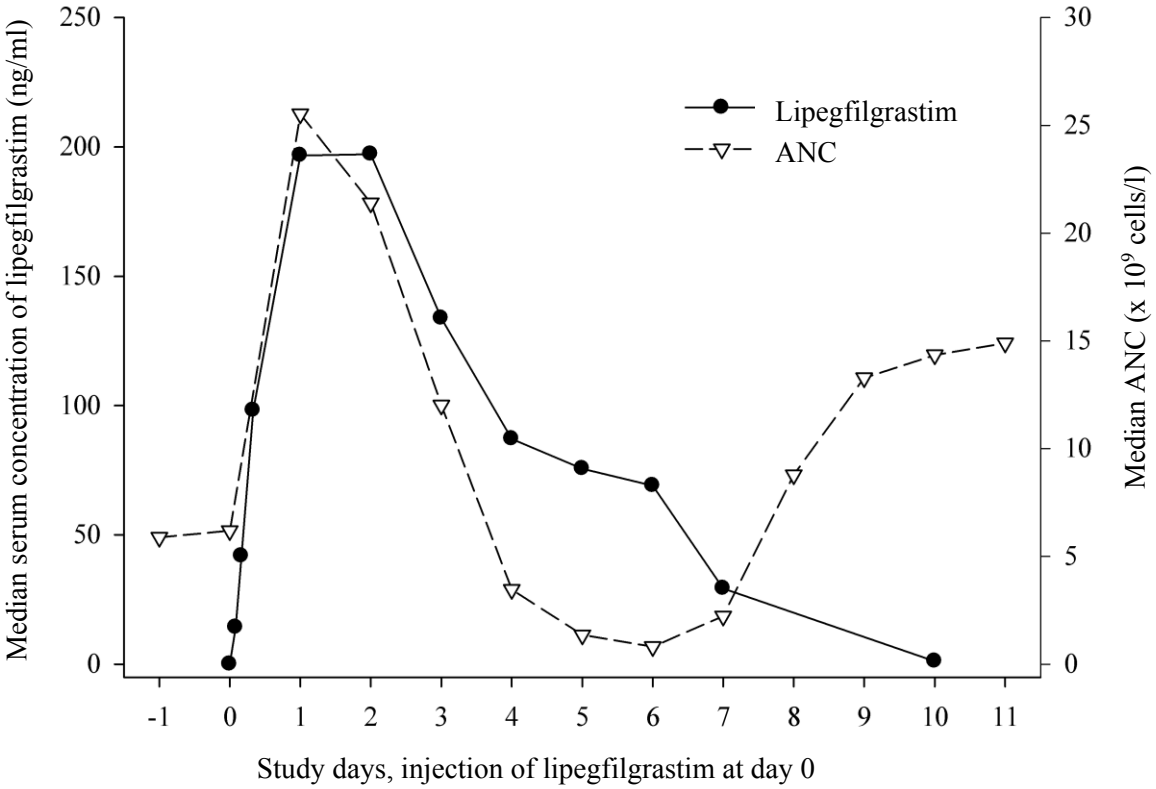
Special populations

*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 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

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 pre-filled syringe with or without safety device (which prevents needle stick injury and re-use).

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. MANUFACTURER

TEVA Pharmaceutical Industries, Ltd
18, Eli Hurvitz St., Industrial Zone
Kfar Saba, 4410202, Israel

## 8. MARKETING AUTHORISATION NUMBER(S)

SINXXXXX

## 9. DATE OF REVISION OF THE TEXT

XX-XXXX