Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Lipegfilgrastim (rbe)

Proprietary Product Name: Lonquex

Sponsor: Teva Pharma Australia Pty Ltd

February 2016

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
γ-GT	γ-glutamyl-transferase
ADA	Anti-drug-antibody
AE	Adverse Event
ALAT	Alanine aminotransferase
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ANOVA	Analysis of variance
aPPT	Activated partial thromboplastin time
ASAT	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
AUC	Area under the curve
AUC_{0-t}	Area under the curve from the time of dosing to the time of the last observation
AUC_{last}	Area under the curve from the time of dosing to the last measurable concentration
$AUC_{0-\infty}$	Area under the curve from the time of dosing extrapolated to infinity, based on the last observed concentration
BW	Body weight
CHMP	Committee of Human Medicinal Products
CI	Confidence interval
CK	Creatine kinase
CL	Total body clearance
C_{max}	Highest observed plasma concentration
CML	Chronic myelogenous leukemia
CPA/CTX	Cyclophosphamide
CYP450	Cytochrome P450
DNA	Deoxyribonucleic acid

Abbreviation	Meaning
DNS	Duration of severe neutropenia
DPF	Dose proportion factor
EC70	Effective concentration of drug substances that lead to a 70% viability of the NFS-60 cells
ECG	Electrocardiography
ECL	Electro-chemiluminescence
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
FN	Febrile neutropenia
G-CSF	Granulocyte colony stimulating factor
GalNAc	N-Acetylgalactosamine
GD	Gestation day
GLDH	Glutamate-dehydrogenase
HCT	Haematocrit
HD	High dose
HGB	Haemoglobin content
IA	Intra-arterial
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IM	Intramuscular
IP	Intraperitoneal
ISS	Integrated Summary of Safety
ITT	Intent-to-Treat
IV	Intravenous
LC/MS/MS	Liquid chromatography/tandem mass spectrometry
LD	Low dose
LDH	Lactate dehydrogenase
LDS	Loading-dye sample buffer
LI	Lobularity index
LLOD	Lower limit of detection

Abbreviation	Meaning
LLOQ	Lower limit of quantification
LOD	Limit of detection
LLOQ	Limit of quantification
LPS	Lipoplysaccharides
LS	Least square
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean corpuscular volume
MD	Medium dose
MedDRA	Medical Dictionary for Regulatory Activities
MFI	Median fluorescent intensity
mPEG	Methoxypolyethylene glycol
MSR	Minimal significant ratio
NFS60	Mouse myelogenous leukaemia cell line adapted to respond to recombinant G-CSF (lipegfilgrastim/Neulasta)
NMP	Normal monkey plasma
NOAEL	No Observed Adverse Effect Level
NRP	Normal rat plasma
NRS	Naïve rat serum
NZW	New Zealand white
PBS	Phosphate buffered saline
PCT	Number of platelets
PEG	Polyethylene glycol
PK	Pharmacokinetics
PNRS	Pooled naïve rat serum
PP	Per-Protocol
PRbS	Pregnant rabbit serum
PV	Paravenous
QC	Quality control

Abbreviation	Meaning
RBC	Red blood cells (erythrocytes)
r-metHuG-CSF	Recombinant N-methionyl granulocyte-colony stimulating factor
SC	Subcutaneous
SD	Standard deviation
SDS-PAGE	Sodium dodecylsulfate-polyacrylamide gel electrophoresis
SAE	Serious Adverse Event
SPR	Surface plasmon resonance
$T_{1/2}$	Terminal half-life-ln(2)/λ_z
$t_{1/2elim}$	Plasma elimination half-life
t_{max}	Time of C_{max}
TEAE	Treatment Emergent Adverse Event
TPT	Thromboplastin time
ULOQ	Upper limit of quantification
V_{ss}	Volume of distribution at steady state
V_z	Volume of distribution based on the terminal phase
WBC	White blood cell (leucocytes)
XM21	Recombinant human G-CSF, equivalent to Filgrastim, precursor of lipegfilgrastim
XM22	Glyco-pegylated recombinant human G-CSF, glycoPEG-XM21; Lipegfilgrastim

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Decision:	Approved
Date of decision:	29 October 2015
Date of entry onto ARTG	12 November 2015
Active ingredient(s):	Lipegfilgrastim (rbe)
Product name(s):	Lonquex
Sponsor's name and address:	Teva Pharma Australia Pty Ltd, 7 Clunies-Ross Ct, Eight Mile Plains, Queensland 4113
Dose form(s):	Solution for injection,
Strength(s):	6 mg/0.6 mL
Container(s):	Prefilled syringe
Pack size(s):	On pre-filled syringe with or without safety device (which prevents needle stick injury and re-use). For syringes without safety device, a plunger rod (polypropylene) is attached. Each syringe is supplied in its own blister and carton.
Approved therapeutic use:	*For reduction in the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes).*
Route(s) of administration:	Subcutaneous (SC) injection
Dosage:	One 6 mg dose of Lonquex (a single pre-filled syringe of Lonquex) is recommended for each chemotherapy cycle, given approximately 24 hours after cytotoxic chemotherapy. The maximum amount of Lonquex that can be safely administered as a single dose has not been determined.
ARTG number (s):	231016

Product background

This AusPAR describes the application by the sponsor, Teva Pharma Australia Pty Ltd, to register a new chemical entity, lipegfilgrastim (Lonquex®).

Lipegfilgrastim is a covalent conjugate of recombinant N-methionyl human granulocyte-colony stimulating factor (G-CSF) and a single polyethylene glycol (PEG) moiety and belongs to the pharmacotherapeutic group Immunostimulants, colony stimulating factors.

Human G-CSF is a glycoprotein that regulates the production and release of functional neutrophils from the bone marrow. Stimulating the G-CSF receptor can raise neutrophil count in some conditions and has been used in cancer to reduce neutropenia, a risk factor for infection and for increasing delay in the next chemotherapy cycle.

The sponsor has proposed the following indications for Lonquex:

> *Lonquex is indicated for the treatment of cancer patients following chemotherapy, to decrease the duration of severe neutropenia and so reduce the incidence of infection, as manifest by febrile neutropenia.*

The following is the EU approved indications:

> *Reduction in the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes).*

The TGA Delegate proposed the following indications:

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

The recommended dose is 6 mg for each chemotherapy cycle (3 weeks per cycle).

Filgrastim binds to the G-CSF receptor, promoting the proliferation and differentiation of progenitor cells within the bone marrow and the release of mature neutrophils into the peripheral blood. Pegfilgrastim (Neulasta) is filgrastim conjugated to polyethylene glycol (PEG) which increases its pharmacodynamic effect offering the option of a single injection per chemotherapy cycle.

Registration dates of other G-CSF stimulating factors on the Australian Register of therapeutic Goods (ARTG)

Table 1: List of tradenames and ARTG inclusion dates

Active ingredient	Trade names	Date of inclusion on the ARTG
Pegfilgrastim	Neulasta	18 May 2010
Filgrastim	Neupogen Tevagrastim Nivestim Zarzio	6 September 2001 29 August 2011 8 September 2011 7 May 2013
Lenograstim	Granocyte	12 February 2007

Lipegfilgrastim is a covalent conjugate of an E. coli produced G-CSF (equivalent to filgrastim) and a single PEG molecule. The difference between pegfilgrastim and lipegfilgrastim is between the linkage between the filgrastim and PEG molecules.

XM22 is the company code used in the sponsor dossier for lipegfilgrastim.

Regulatory status

This is an application to register a new chemical entity in Australia.

The overseas regulatory status of lipegfilgrastim is summarised in the following table.

Table 2: International regulatory status of lipegfilgrastim.

Regulator	Date submitted or approved	Registered indication
EU	Approved in July 2013 by centralised procedure	Reduction in the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes).
Swiss Medic	Submission withdrawn due to negative preliminary assessment	Not applicable.
Health Canada	Submitted July 2013	Not yet registered.
FDA	Submission withdrawn due to 'commercial reasons'	The sponsor has no plans to resubmit Lonquex in the US.
Russia	Approved June 2014	Same as EU
Israel	Approved January 2015	Same as EU
Brazil	Approved November 2013	Same as EU
Chile	Approved October 2014	Same as EU
Serbia	Approved Feb 2015	Same as EU

The sponsor states that submissions have been made to Korea (2013), South Africa (2013), Argentina (2014), Peru (2014), Kazakhstan (2014) and Ukraine (2014) but none of these had decisions at the time of this AusPAR.

The withdrawal of the submission to SwissMedic is discussed in the CER (Attachment 2). The Delegate has considered these reasons, below, and considers the issues surmountable.

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Quality findings

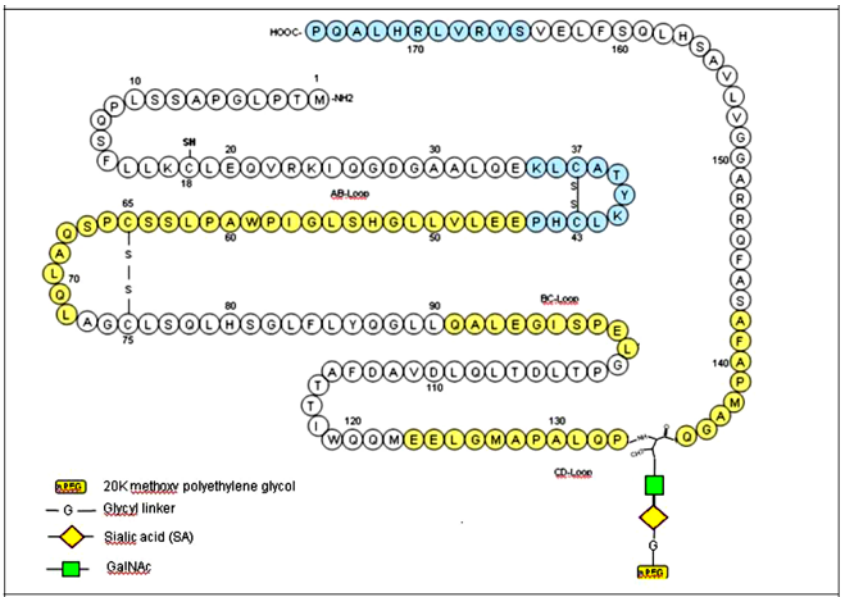
Drug substance (active ingredient)

Structure

Lipegfilgrastim (company code: XM22) is a covalent conjugate of recombinant human N-methionyl granulocyte-colony stimulating factor (G-CSF, Filgrastim, company code: XM21), a carbohydrate linker and a single methoxy polyethylene glycol (PEG) molecule (Figure 1). The average molecular mass of lipegfilgrastim is approximately 39,000 Dalton (Da) which comprises 18 798 Da of filgrastim augmented by 203 Da for GalNAc, 338 Da for glycylsialic acid and the mean of 20,000 Da for PEG (Figure 1).

The primary and higher order structure including disulphide bonds of XM21 and XM22 were fully characterised (Figure 1). The protein contains one sialic acid molecule which is included as a part of carbohydrate linker.

Figure 1: Chemical structure of lipegfilgrastim.

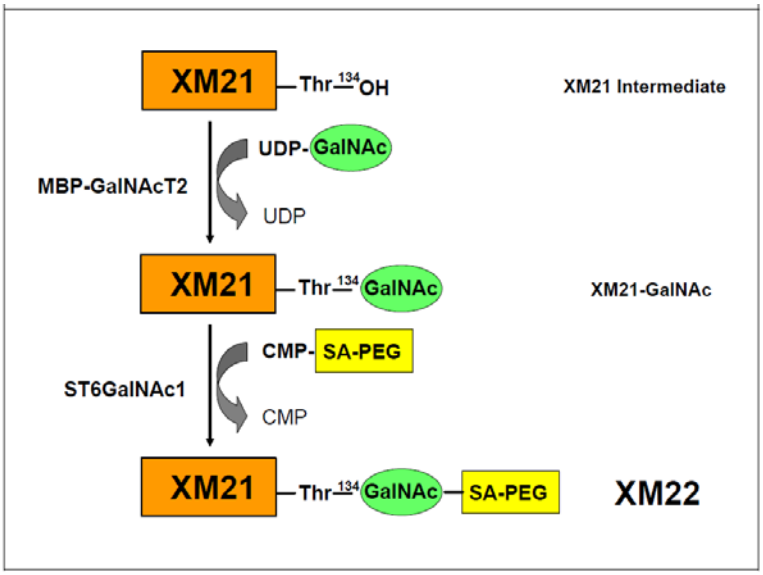


Filgrastim (XM21) is the drug substance intermediate for the manufacture of lipegfilgrastim. The XM21 is produced in *Escherichia coli (E.coli)* by recombinant Deoxyribonucleic acid (DNA) technology. The primary structure of XM21 is same as that of human granulocyte colony-stimulating factor plus one additional amino acid, an N-terminal methionine (r-met HU G-CSF). In contrast to its natural counterpart, filgrastim is not glycosylated. Filgrastim contains a free cysteine at position 18 and two disulphide bonds between Cys37-Cys43 and Cys65-Cys75. From the crystal structure analysis of recombinant G-CSF it is known that the molecule consists of a four-helix bundle with an up-up-down-down configuration.

Lipegfilgrastim is similar to another PEGylated filgrastim molecule currently marketed as Neulasta (International Nonproprietary Name (INN):pegfilgrastim). Pegfilgrastim is different on the molecular level from lipegfilgrastim in the way the PEG moiety is attached to filgrastim. In lipegfilgrastim, the PEG moiety is attached enzymatically through a glycolinker (glycyl-sialyl-GalNac) to the amino acid Threonine[134] whereas in pegfilgrastim the PEG moiety is bound chemically to the N-terminal methionine.

The manufacturing process of lipegfilgrastim consists of two parts; manufacture of filgrastim intermediate (XM21) and production of lipegfilgrastim (XM22) (Figure 2).

Figure 2: Overview of enzymatic pegylation reaction to manufacture XM22



All viral/prion safety issues have been addressed, including use of animal-derived excipients, supplements in the fermentation process and in cell banking.

Major product related impurities include methionine oxidised species, non-pegylated XM21-GalNac, deamidated species and XM22 multimers. Biological activities of impurities and charge variants were characterised. Impurity levels are effectively controlled by appropriate testing methods during the manufacture and at release. Potency of ipegfilgrastim determined by *in vitro* cell-based assay is approximately 50% lower than that of unmodified Filgrastim (XM21). This reduction of in vitro potency is caused PEG-moiety attached to filgrastim molecule. However, PEG moiety increases the half-life of the molecule, thereby allowing a less-frequent dosing schedule while maintaining an acceptable safety and efficacy profile.

Separate specifications for XM21 and XM22 were provided. The proposed specifications are adequate to control essential quality attributes including identity, content, potency, purity and other biological and physical properties of the drug substance relevant to the dose form. In-house test methods were validated according to relevant guidelines and the batch data indicated a consistent good quality of manufactured drug substance batches.

Stability data have been generated under real time and various stress conditions to characterise the stability/degradation profile of the drug substance.

Drug product

Lonquex is a sterile, preservative-free aqueous solution for subcutaneous administration, presented in a 1 mL pre-filled syringe. Each syringe contains 6 mg of lipegfilgrastim (based on protein content) in 0.6 mL acetate buffer at pH 5.0. The Drug Product is manufactured with a 5% overfill to ensure an extractable volume of 0.6 mL for each syringe. Formulation does not contain overage. The composition of the liquid formulation and the fill volume for the pre-filled syringe are provided in Table 3. A tray or blister containing one syringe is packaged in cardboard carton of the appropriate size, together with the leaflets.

Table 3: Composition of Drug Product in Pre-Filled Syringe

Ingredient	Content per dose	Function	Reference to Quality Standard
XM22 Drug Substance	6 mg	Active Ingredient	In-house
Excipients			
Acetic acid	0.36 mg	Buffer component	Ph.Eur., USP
Polysorbate 20	0.02 mg	Surfactant	Ph.Eur, NF
Sorbitol	30.0 mg	Stabiliser	Ph.Eur, NF
Sodium hydroxide (1 M)	0.14 mg (ad pH 5.0)	pH titration	Ph. Eur, USP
Water for Injection	q.s. to 0.6 mL	Vehicle	Ph.Eur. USP

The final drug product manufacture does not involve formulation as the drug substance is formulated at the end of down-stream manufacturing process of the drug substance. Manufacturing process of XM22 drug product pre-filled syringes involves pooling of already formulated XM22 drug substance, sterile filtration and filling, visual inspection, release testing and labelling and packaging.

The proposed release and shelf-life specifications provide adequate control of identity, potency, purity, dose delivery and other physical, chemical and microbiological properties relevant to the clinical use of the product. The analytical methods used for the quality control of final drug product are essentially the same as those used for the drug substance. The analytical procedures were adequately validated and the proposed specifications were justified.

Stability data have been generated under stressed and real time conditions to characterise the stability profile of the product. Photostability data indicates that the product is not photostable. The proposed shelf life is 24 months when stored at 5 ± 3 °C protected from light. The temperature excursion stability data indicate that the product can be exposed to up to 25°C for less than 48 hours during shipping. Frozen/melted products or products exposed to temperature above 25°C would have to be discarded. The product is for single use only so the storage conditions adequately control the in-use purposes.

Biopharmaceutics

Biopharmaceutic data are not required for this product because only one route of administration is used.

Quality summary and conclusions

The administrative, product usage, chemical, pharmaceutical, and microbiological data submitted in support of this application have been evaluated in accordance with the Australian legislation, pharmacopoeial standards and relevant technical guidelines adopted by the TGA.

The quality evaluator recommends that Lonquex, lipegfilgrastim (rbe) 6 mg/0.6 mL solution for injection, prefilled syringe should be approved.

Proposed conditions of registration: batch release testing

It is a condition of registration that, as a minimum, the first five independent batches of Lonquex lipegfilgrastim (rbe) 6 mg/0.6 mL solution for injection, prefilled syringe imported into Australia are not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA.

III. Nonclinical findings

Introduction

General comments

The sponsor has submitted an adequate dossier to support the registration of Lonquex. All toxicity studies were Good Laboratory Practice (GLP) compliant. The pharmacology of G-CSF has been well established and the submitted studies aimed to ascertain that lipegfilgrastim demonstrates the pharmacological activity of G-CSF with an extended action like other long acting products such as Neulasta and to establish its toxicity profile.

Pharmacology

Primary pharmacology

In vitro studies confirmed the expected potency of stimulating the proliferation of cells expressing the G-CSF receptor, although lipegfilgrastim has a 2 fold lower potency than the non-pegylated intermediate G-CSF molecule, XM21, in the production of lipegfilgrastim. Binding affinity of lipegfilgrastim and Neulasta to amine-coupled hG-CSF receptor were similar (Lipegfilgrastim K_D 481 nM; Neulasta: K_D 516 nM) but around 4 fold lower than the affinity of XM21 (K_D 121 nM).

Primary pharmacological activity was demonstrated in rats and monkeys. In a cyclophosphamide (CPA)-induced cytopenic rat model, lipegfilgrastim given 4 h post neutropenia induction prevented the depression of blood leucocyte counts. When lipegfilgrastim was administered 24 h post induction of neutropenia, a quick increase of leucocytes was observed. The effect was long lasting, similar to Neulasta; high blood leucocytes counts were still observable on Day 10. The dose-dependent increases of leucocytes (mainly neutrophilic granulocytes) were followed by transient depression 2 to 3 days after the lipegfilgrastim (and Neulasta) dose before a rebound from Day 4. The transient decrease in peripheral leucocytes was probably due to a combination of depletion of the bone marrow storage pool, depletion of white blood cell (WBC) precursors in the maturation phase and short half-life of neutrophils. Lipegfilgrastim, as for other G-CSFs, also induced elevations in monocyte counts and marginal increases in eosinophilis, basophilic granulocytes and large unstained cells. Lymphocytes were not affected.

The pharmacological activity of lipegfilgrastim was also demonstrated in normal rats and monkeys. Lipegfilgrastim, Neulasta or XM21 (100 µg/kg) resulted in a pronounced increase of blood leukocytes, principally neutrophilic granulocytes. Maximum increase in neutrophilic granulocytes was evident 24 to 48 h post-lipegfilgrastim administration. No differences were observed between lipegfilgrastim and Neulasta, with prolonged effects for both lipegfilgrastim and Neulasta in comparison to XM21. The prolonged activity corresponded the longer elimination half-life ($t_{1/2}$) of lipegfilgrastim (and Neulasta) compared to XM21 (see below under *Pharmacokinetics*). Repeat-dose studies in rats and monkeys with weekly lipegfilgrastim dosing also demonstrated significant, dose-dependent increases in leukocytes. Results from the 26 week study in rats revealed a time and dose dependent pharmacodynamic effect of lipegfilgrastim, with maximal induction observed at the end of the study (approximately 24 h post-final dose). Leukocyte levels returned to baseline by the end of the recovery period. Repeat-dose studies in monkeys demonstrated only variable increases in leucocytes with no specific dose-dependence despite a clear dose-dependent increase in plasma lipegfilgrastim concentration. The

leukocyte increase was already maximal at the low dose (100 µg/kg), and only marginal increments were observed at higher doses (500 to 1500 µg/kg), indicating a possible saturation of the response.

Overall, the nonclinical studies demonstrated that lipegfilgrastim induces proliferation and mobilisation of granulocytic cells in both normal and neutropenic animals, consistent with the pharmacological effects of G-CSF products. The magnitude and duration of the effects observed with lipegfilgrastim are similar to Neulasta.

Secondary and safety pharmacology

One secondary pharmacodynamic study evaluated the potential proliferative effects of lipegfilgrastim and three other G-CSF products (Neupogen, Neulasta and Granocyte) in human cancer cells. The tested G-CSF materials produced little to no effects on the proliferation and survival of 7 human cancer cell lines.

Two safety pharmacology studies investigated effects on central nervous system (CNS) (rats) and cardiovascular (Beagle dogs) functions. At up to 10 mg/kg SC, lipegfilgrastim had no effects on CNS or cardiovascular functions including blood pressure (BP) and electrocardiogram (ECG). ECG monitoring, blood pressure and heart rate measurements in repeat dose toxicity studies showed no treatment related abnormalities in monkeys. Serum lipegfilgrastim peak plasma concentration (C_{max}) in the 13 week monkey study was up to 36 times the clinical value. Lipegfilgrastim is unlikely to affect CNS and cardiovascular functions in patients.

Pharmacokinetics

The pharmacokinetic profile of lipegfilgrastim was studied in rats and monkeys, where blood neutrophilic granulocytes were also measured. In both species, lipegfilgrastim had a longer elimination $t_{1/2}$ than the non-pegylated moiety, XM21 (6.4 compared to 2.1 h in rats and 10.6 compared to 7.8 h in monkeys) and comparable half-life to Neulasta (6.9 h in rats and 10.5 h in monkeys) after a single SC dose of 100 µg/kg. Lipegfilgrastim resulted in pronounced increases in neutrophilic granulocyte and monocyte counts as well as marginal increases in eosinophilic and basophilic granulocyte and large unstained cell counts (discussed above). The absorption was slower for lipegfilgrastim and Neulasta than for XM21 (time to peak plasma concentration (T_{max}) 9 to 12 h compared to 1 to 4 h).

Tissue distribution and metabolism of lipegfilgrastim were not studied. This is acceptable considering the biological nature of the protein moiety and extensive clinical experience with the PEG molecule. In rats receiving lipegfilgrastim by the intravenous (IV) route, the volume of distribution (Vz) was calculated to be 28 mL/kg (at steady state (Vss) 52 mL/kg), similar to rat plasma volume, suggesting distribution within the intravascular space.

One metabolism study demonstrated that lipegfilgrastim was more resistant to degradation by human neutrophil elastase compared to XM21 and Neulasta, which were quickly degraded and lost activity. However, pharmacokinetic studies in rats and monkeys (discussed above) showed similar elimination $t_{1/2}$ between lipegfilgrastim and Neulasta. The findings suggest that degradation by neutrophil elastase plays a minor role in the clearance of G-CSFs.

One excretion study comparing clearance in intact and bilaterally nephrectomised rats showed that the contribution of renal clearance to total body clearance for lipegfilgrastim was very small (approximately 1%), compared with 38% for Neulasta and 82% for Neupogen. However, since there was morbidity and mortality in all nephrectomised animal groups the reliability of the study results was compromised.

The kinetics of lipegfilgrastim was non-linear in rats and monkeys at 100 to 1500 µg/kg and increased in a more than dose proportional manner, which is consistent with a saturable elimination pathway. Literature has reported neutrophil and receptor-mediated clearance of G-CSFs. However, as discussed above it appears that neutrophil elastase plays a minor role in the elimination of lipegfilgrastim as does renal clearance. The elimination pathway for lipegfilgrastim is unclear but cleavage of PEG from the protein and subsequent degradation of the G-CSF moiety by proteinases are probably responsible for the elimination of lipegfilgrastim.

The area under the plasma concentration versus time curve from time 0 to the last time point of sampling ($AUC_{0\text{-t last}}$) values in repeat-dose studies were generally lower after the last administration of the study than after the first dose, particularly in monkeys, which was associated with the emergence of anti-drug antibody (ADA) in monkeys. In rats the time-dependent decrease in plasma drug levels was small, consistent with low ADA positive incidences.

Overall, rat and monkey studies with lipegfilgrastim demonstrated the expected delay in absorption and prolonged clearance compared to the non-pegylated moiety and the pharmacokinetic profile of lipegfilgrastim was similar to the profile of Neulasta. Pharmacokinetics was characterised by a non-linear response at the dose range of 100 to 1500 µg/kg indicative of saturable elimination.

Pharmacokinetic drug interactions

One study investigated the direct effect of lipegfilgrastim on cytochrome P450 (CYP450) activities or indirect effects through the stimulation of cytokine production using human hepatocytes. In vitro incubation of hepatocytes with lipegfilgrastim (20 to 250 ng/mL) or human plasma from whole blood exposed to the drug (500 ng/mL) showed no effects on isozymes CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP3A4/5 activity. The study results indicate lipegfilgrastim is unlikely to affect the activity of CYP450 in humans.

Toxicology

There were no specific single dose toxicity studies. In safety pharmacology studies in rats and dogs, lipegfilgrastim was well tolerated at a single SC dose of 10 mg/kg. An IV dose of 250 µg/kg was also well tolerated in the renal excretion study in rats.

Three GLP compliant repeat-dose toxicity studies in rats for up to 26 weeks and two GLP studies in monkeys for up to 13 weeks have been conducted. In the 4 week studies the doses were 100 to 1500 µg/kg/week and 100 to 1000 µg/kg/week in longer term studies in both species. All studies had a recovery period of 4 or 8 weeks.

Relative exposure

The animal/human relative exposures achieved in the repeat-dose toxicity studies were high (up to 92 in rats and 76 in monkeys) at the highest dose based on AUC (see Table 4 below). Lower exposures and larger variability after repeated dosing, particularly in monkeys, after the first dose were most likely a result of the development of neutralising antibodies to lipegfilgrastim in some animals. Animal/human exposure ratios based on C_{max} were generally lower (≤ 2 fold) than the exposure ratio based on AUC.

Table 4: Relative exposure in repeat-dose toxicity studies

Species	Study period	Weekly dose (µg/kg)	$AUC_{0-t\ last}$ (µg·h/mL)				Exposure ratio#			
			Day 1		Last dose day		Day 1		Last dose day	
			Male	Female	Male	Female	Male	Female	Male	Female
Rat	4 weeks	100	3.69	5.49	1.11	3.55	0.8	1.2	0.2	0.8
		500	78.0	104.4	33.4	74.9	17	23	7.4	17
		1500	324	370	258	413	72	82	57	92
	13 weeks	100	2.89	4.65	0.95	2.48	0.6	1.0	0.2	0.6
		500	53.8	69.1	21.9	41.9	12	15	5	9
		1000	158	199	109	170	35	44	24	38
	26 weeks	100	2.97	5.53	0.169	1.55	0.7	1.2	<0.1	0.3
		500	43.9	48.3	8.92	63.2	10	11	2.0	14
		1000	149	152	47.5	133	33	34	11	30
Monkey	4 weeks	100	5.80	9.18	2.34	1.94	1.3	2.0	0.5	0.4
		500	90.1	716	67.9	18.3	20	16	15	4.1
		1500	191	250	147	138	42	56	33	31
	13 weeks	100	12.0	7.01	1.63	2.82	2.7	1.6	0.4	0.6
		500	129	122	39.6	17.4	29	27	8.8	3.9
		1000	229	299	1.74	176	51	67	0.4	39
Human healthy volunteers *	Single dose	6 mg (cycle 1)	13.5				–			

animal AUC × 3:human AUC_{0-last}; * Estimated AUC_{0-t} 13500 ng.h/mL and C_{max} 168 ng/mL after a single dose of 6 mg (100 µg/kg) from *Summary of Clinical Pharmacology Studies*, Table 11.

Treatment with lipegfilgrastim was well tolerated. Toxicity findings were associated with the pharmacological activity. Blood counts showed increased leukocytes, primarily of neutrophils in rats and monkeys at all doses. In addition, decreases in red cell count, haematocrit and haemoglobin, as well as a corresponding increase in reticulocytes occurred in both species. Associated with changes in blood counts were myeloid hyperplasia in several organs such as bone marrow, spleen, liver and lymph nodes, consisting primarily of neutrophilic granulocytes, as well as dose-dependent extramedullary haematopoiesis in spleen, enlarged spleen and increases in the myeloid/erythroid ratio of bone marrow. In rats, marked, dose dependent increases in plasma Alkaline phosphatase (ALP) (group mean values up to 7.7 fold compared to the control group) and slight increases in Gamma glutamyltransferase (GGT) (up to 2 fold) were observed in all dose groups, probably secondary to the effects on bone (bone effects

discussed below) and increased leukocytes.[1] Only minor increases in ALP (< 2 fold) were observed in monkeys. There were small increases in plasma globulin and total protein level (by up to 40%) in monkeys at ≥ 500 µg/kg/week in the 4 week study and only at 1000 µg/kg/week in the 13 week study.

Dose related atrophy of trabecular bone (reduction in the amount and density of trabecular bone near the cartilaginous growth plate in the spongiosa of the femur) was seen in high dose male rats (1000 µg/kg/week) in the 13 week study and in all treated male groups and the mid and high dose female groups in the 26 week rat study. This finding is a class effect of G-CSF products specific to rodents because of continuous bone remodelling. The same effects were not seen in monkeys. The bone effects in rats are unlikely to be relevant to adult humans.

There was a trend of decreased plasma cholesterol in both species, which have been previously described for other G-CSF products possibly attributable to cytokine induced activation of the liver.[2] All changes except the bone finding were completely reversible after a recovery period of 4 to 8 weeks. Atrophy of trabecular bone in rats was partially reversible.

Lipegfilgrastim was highly immunogenic in monkeys and rabbits with minimal immunogenicity observed in rats. ADA developed after repeated dosing in monkeys and rabbits and reduced both exposure and pharmacodynamic responses. The development of ADA limited the usefulness of monkeys for studying long term effects beyond 13 weeks. Immunogenicity was low in rats. ADA was detected in only a few treated animals in the rat studies. The low ADA did not affect exposure or pharmacological activity. Therefore, long term studies were conducted only in rats, which are considered adequate.

Overall, the toxicity profile is very similar to that of other G-CSFs and all findings were class effects of G-CSFs.

Genotoxicity and carcinogenicity

Genotoxicity and carcinogenicity were not investigated since mutagenic potential is not expected for lipegfilgrastim. The PEG moiety is common to many pegylated drug substances, and pegylation of filgrastim is not likely to alter the genotoxicity of the drug, which was shown to be negative in a battery of *in vitro* and *in vivo* genotoxicity studies. The lack of genotoxicity and carcinogenicity studies is acceptable. However, G-CSF has been reported to stimulate tumour growth and intratumoural vessel density in animal tumour models.[3]

[1] Okasaki K., Funato M., Kashima M., Nakama K., Inoue T., Hiura M., Kato Y. and NagataR. *Twenty-six-week repeat-dose toxicity study of a recombinant human granulocyte colony-stimulating factor derivative (Nartograstim) in Cynomolgus monkeys.* Toxicological Sciences. 2002;65:246-255.

[2] Keller P. and Smalling R. *Granulocyte colony stimulating faator: Animal studies for risk assessment.* International Review of Eperimental Pathology. 1993;34A:173-188; Okasaki K., Funato M., Kashima M., Nakama K., Inoue T., Hiura M., Kato Y. and NagataR. *Twenty-six-week repeat-dose toxicity study of a recombinant human granulocyte colony-stimulating factor derivative (Nartograstim) in Cynomolgus monkeys.* Toxicological Sciences. 2002;65:246-255.

[3] Okasaki K., Ebihara S., Asada M., Kanda A., Sasaki H. and Yamaya M. *Granulocyte colony-stimulating factor promotes tumor angiogenesis via increasing circulating endothelial progenitor cells and Gr1+CD11b+ cells in cancer animal models.* International Immunology. 2005;18:1-9.

Reproductive toxicity

No fertility or postnatal development studies were conducted. Effects on embryofetal development were investigated in one species, rabbits. This is acceptable given the known toxicity profile of filgrastim and pegfilgrastim, the absence of effects on reproductive organs in repeat dose studies with lipegfilgrastim, clinical experience with the PEG moiety present in other drug substances, embryofetal findings in rabbits (consistent with filgrastim, see below) and the proposed use in cancer patients with chemotherapy.

Effects on embryofetal development were investigated in rabbits at 10 to 200 µg/kg administered SC every other day during organogenesis, gestation Day 8-19. Every other day dosing in rabbits resulted in continuous exposure to the drug although anti-drug antibodies were raised after repeated dosing, leading to lower exposure after the last dose than after the first dose (see Table 5 below). Exposures to lipegfilgrastim based on C_{max} were up to 6 times the clinical exposure, while exposures based on AUC after a single dose were around 2.5 times the clinical exposure.

Table 5: Relative exposure in the embryofetal development study

Species	Study	Dose (µg/kg)	C_{max} (ng/mL)		AUC_{0-t} (ng·h/mL)		Exposure ratio#			
							C_{max}		AUC	
			GD8	GD21	GD8	GD21	GD8	GD21	GD8	GD21
Rabbit	Embryofetal development	10	10.2	3.29	236	108	0.06	0.02	0.02	0.01
		50	93.2	12.0	2,758	255	0.6	0.07	0.2	0.02
		200	981	203	32,218	5,760	5.8	1.2	2.4	0.4
Human healthy volunteers	steady state	6 mg (cycle 1)	168		13,500		–		–	

animal: human C_{max}, or animal AUC: human AUC; * Estimated AUC_{0-t} 13500 ng.h/mL and C_{max} 168 ng/mL after a single dose of 6 mg (100 µg/kg) from sponsor's *Summary of Clinical Pharmacology Studies* .

Increased leucocyte counts were observed in all dose groups, indicating lipegfilgrastim is pharmacologically active in rabbits. Administration of 200 µg/kg lipegfilgrastim to pregnant rabbits during organogenesis caused abortions and increased resorptions (post-implantation loss). The fetal mortality rate (including deaths over a 6 h 'incubator stay') and the number of runts were increased at 50 and 200 µg/kg, and fetal weights decreased in all dose groups. The observed maternal body weights and placenta weights at 200 µg/kg were significantly lower than the control group. Lipegfilgrastim was not teratogenic in rabbits. The incidences of visceral (pale and small kidney) and skeletal variations (enlarged fontanelle, unossified or incomplete ossification of skull and talus) were increased at 200 µg/kg and the incidence of incomplete ossification of skull was also increased at 50 µg/kg.

Pregnancy classification

The sponsor has proposed Pregnancy Category B3.[4] This is considered appropriate and consistent with experimental animal data showing an increased incidence of post-

[4] Pregnancy Category B3: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.
Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

implantation loss, abortion and fetal variations, and the Pregnancy Category for filgrastim and pegfilgrastim.

Local tolerance

A local tolerance study in rabbits revealed no macroscopic or microscopic changes at the intra-arterial (IA), intra-muscular (IM), IV, paravenous (PV) or SC administration sites indicating lipegfilgrastim was compatible for the intended clinical route of administration.

Nonclinical summary and conclusions

- In vitro studies confirmed the expected potency and activity of lipegfilgrastim as a G-CSF. The affinity of lipegfilgrastim for the recombinant human G-CSF receptor was lower than the unconjugated moiety (XM21) but similar to pegfilgrastim [Neulasta] (respective KD values: 481, 121 and 516 nM). In vivo studies in rats and monkeys showed dose dependent increases in neutrophils and prolonged activity than the non-pegylated intermediate, XM21.
- Secondary pharmacodynamic study showed that lipegfilgrastim (and comparators, filgrastim [Neupogen] and pegfilgrastim [Neulasta]) had little/no effect on the proliferation/viability of human cancer cell lines that do not express G-CSF receptor.
- Safety pharmacology studies found no effects on CNS (rats) or cardiovascular (dogs) functions.
- Pharmacokinetic studies in rats and monkeys showed prolonged elimination t1/2 and delayed absorption than the non-pegylated moiety. The pharmacokinetic profile of lipegfilgrastim was similar to the profile of Neulasta. Pharmacokinetics in rats and monkeys was non-linear at the dose range of 100 to 1500 µg/kg; indicative of saturable elimination. The volume of distribution in rats was close to rat plasma volume, suggesting distribution within the intravascular space.
- Repeat-dose toxicity studies were all GLP compliant. Lipegfilgrastim was well tolerated with SC administration of 100 to 1500 µg/kg/week for up to 26 weeks in rats and 13 weeks in monkeys. ADA developed after repeated dosing in monkeys and rabbits and reduced both exposure and pharmacodynamic responses. The development of ADA limited the usefulness of monkeys for studying long term effects beyond 13 weeks. Immunogenicity was low in rats. Therefore, long term studies were conducted only in rats, which are considered adequate.
- All toxicity findings were class effects of G-CSFs. Findings included increased leukocytes, primarily of neutrophils, decreases in red cell count, haematocrit and haemoglobin (and a corresponding increase in reticulocytes), myeloid hyperplasia in bone marrow, spleen, liver and lymph nodes (consisting primarily of neutrophilic granulocytes), extramedullary haematopoiesis in spleen (and enlarged spleen), and increased myeloid/erythroid ratio of bone marrow. In addition, marked, dose-dependent increases in plasma ALP and slight increases in GGT occurred in rats, probably secondary to the effects on bone (atrophy of trabecular bone) and increased leukocytes. There was a trend of decreased plasma cholesterol in both species. All changes except the bone were completely reversible after a recovery period of 4 to 8 weeks. Atrophy of trabecular bone in rats was partially reversible.
- No genotoxicity and/or carcinogenicity studies were submitted. The lack of genotoxicity and carcinogenicity studies is acceptable. It is noted that G-CSF has been reported to stimulate tumour growth and intra-tumoural vessel density in animal tumour models.

- An embryofetal development study in rabbits showed increased post-implantation loss and abortions at 200 µg/kg, runts and fetal deaths at SC doses of 50 to 200 µg/kg every other day, and decreased fetal weights at all doses (10 to 200 µg/kg). The incidences of visceral and skeletal variations (pale, small kidney, enlarged fontanelle, unossified or incomplete ossification of skull and talus) were increased at 200 µg/kg. The incidence of incomplete ossification of skull was also increased at 50 µg/kg. Lipegfilgrastim was not teratogenic. These findings are consistent with results from G-CSF and pegylated G-CSF.
- No fertility or postnatal development studies were conducted. This is acceptable given the known toxicity profile of filgrastim and pegfilgrastim, the absence of effects on reproductive organs in repeat dose studies with lipegfilgrastim, clinical experience with the PEG moiety present in other drug substances, embryofetal findings in rabbits (consistent with filgrastim and pegylated filgrastim) and proposed use in cancer patients with chemotherapy.
- Local tolerance study in rabbits revealed no macroscopic or microscopic changes.

Nonclinical conclusions and recommendation

- Primary pharmacology studies in vitro and in animal species confirmed the expected potency and pharmacological activity of lipegfilgrastim.
- Secondary pharmacodynamic and safety pharmacology studies raised no safety concerns.
- Toxicity profile of lipegfilgrastim is consistent with those of G-CSF and pegylated G-CSF. Findings were related to the pharmacological activities of G-CSF and were completely or partially reversible.
- Embryofetal toxicity was observed in rabbits, similar to the effects of other G-CSFs. Pregnancy Category B3 is appropriate.
- There are no nonclinical objections to registration.
- Amendments to the draft PI were recommended to the Delegate but these are beyond the scope of this AusPAR.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical Rationale

Human G-CSF is a glycoprotein that regulates the production and release of functional neutrophils from the bone marrow. Stimulating the G-CSF receptor can raise neutrophil count in some conditions and has been used in cancer to reduce neutropenia, a risk factor for infection and for increasing delay in the next chemotherapy cycle. Filgrastim is an un-glycosylated recombinant methionyl human G-CSF which binds to the G-CSF receptor, promoting the proliferation and differentiation of progenitor cells within the bone marrow and the release of mature neutrophils into the peripheral blood. Pegfilgrastim (INN Neulasta®) is filgrastim conjugated to PEG which increases its pharmacodynamic effect offering the option of a single injection per chemotherapy cycle.

XM22 is a covalent conjugate of a 19 000 Da E. coli produced r-metHuG-CSF (company code: XM21, equivalent to filgrastim) and a single, 20 000 Da PEG molecule. XM22 is the company code used in the sponsor submission for drug substance and drug product. The INN for XM22 is lipegfilgrastim.

XM22 differs from pegfilgrastim, in that its PEGylation occurs enzymatically through a glycolinker to the amino acid Thr134 rather than chemically to the terminal methionine, referred to as 'glycoPEGylation'. Lipegfilgrastim is thus a structurally distinct molecule to pegfilgrastim, however it binds to human the G-CSF receptor like filgrastim and pegfilgrastim.

Guidance

The relevant European Union (EU) Guideline which has been adopted by the TGA is the Committee for Medicinal Products for Human Use (CHMP) *Guideline on Clinical Trials with haematopoietic growth factors for the prophylaxis of infection following myelosupressive or myeloablative therapy*; London, 22 March 2007Doc. Ref. EMEA/CPMP/555/95 Rev. 1

Specifically referred to in evaluation and interpretation of the clinical trial data was Section 7 from this guideline;

> *Pegylated products should be evaluated using, double blind, randomised, controlled trials in the patient population and compare weight based and/or fixed doses of pegylated versus non-pegylated products. These should demonstrate non-inferiority with the comparator. Trial design should also take into account the incidence of febrile neutropenia. An appropriate primary endpoint .. would include duration of severe neutropenia.*

The guidance from Compliance with Good Clinical Practices as described in International Conference on Harmonization (ICH) E6 (1996), under the principles of the Declaration of Helsinki, and in accordance with any regional regulations was referred to for the two Phase III studies.

Contents of the clinical dossier

Scope of the clinical dossier

The data provided in this submission is identical to the updated and approved EU dossier. The only differences being minor amendments made following a pre-submission meeting with the TGA. These issues include concerns over Good Manufacturing Sites (GMP) sites, pre-submission final meeting minutes and patient narratives for deaths which have now been provided.

The submission contained the following clinical information:

- Literature references which varied from topics of 'back and neck pain' in children with cancer, to G-CSF given in patients with sickle cell disease, and were used as supporting evidence in the submission.
- Bioanalytic data, human pharmacokinetic studies (XM22-01,05, 06) in healthy patients and efficacy and safety studies in patients (XM22-02,03,04), population PK/PD for XM22 in healthy and oncology subjects, statistical tables, an integrated summary for safety, efficacy and Risk Management Plan (RMP) and two 6 month Periodic Safety Update Reports (PSURs) from July 2013 to June 2014.

The following studies were evaluated:

Phase I studies of PK, PD and safety

- XM22-01-CH. Dose escalation study in healthy subjects

- XM-22-05-CH. Single dose parallel group study in healthy subjects
- XM22-06. Open label three-way crossover study in healthy subjects

Phase II study of efficacy, PK, PD and safety, dose-finding study

- XM22-02-INT. Randomised double-blind parallel group active-controlled dose-finding study in patients with Stage II, III or IV breast cancer receiving doxorubicin/docetaxel for 4 cycles.

Phase III studies of efficacy, PK, PD and safety

- XM22-03. Non-inferiority study: randomised double-blind parallel-group active controlled study in patients with high risk Stage II, III or IV breast cancer scheduled to receive IV doxorubicin/docetaxel as routine chemotherapy for 4 cycles. Comparison of 6 mg Lonquex versus 6 mg pegfilgrastim on Day 2 of each cycle.
- XM22-04. Superiority study: randomised double-blind parallel-group placebo-controlled study in Patients with Stage IIIb/IV non-small cell lung cancer scheduled to receive IV cisplatin/etoposide cyclophosphamide (CTX) for 4 cycles. Comparison of single injection of 6mg Lonquex versus placebo on Day 4 of each cycle.

Paediatric data

The submission included no paediatric pharmacokinetic, pharmacodynamic, efficacy or safety data. In the application form to the '*are there are paediatric formulations for this product or have paediatric data been submitted?*' question the 'no' box is ticked. Yet to the following question '*If there are no paediatric formulations for this product or paediatric data have not been submitted, is there a formal justification as to why the product is not appropriate for use in children* ' there is no selection.

In the RMP it is stated that studies with the use of lipegfilgrastim in children have been agreed and described in the Paediatric Investigation Plan (PIP); these studies are Study XM22-07 and XM22-08 (agreed in September 2011, this first of which was started in September 2012). The planned date for submission of final data is March 2018 although the first date of submission of a report conducted as part of the PIP is Nov 2014.

There is no paediatric plan submitted to the USA and no data has been submitted to the FDA.

Comment: The sponsor is requested to provide the PIP data from November 2014 provided to the EMA.

Good clinical practice

GMP certification has been provided and the study reports for the new submitted clinical trial included assurances that it was conducted in accordance with the International Conference on Harmonization (ICH) Good Clinical Practices (GCP) guidelines and any regulations applicable in the countries where the trials were conducted. Independent ethics committees reviewed all documentation.

Pharmacokinetics

Studies providing pharmacokinetic data

A summary of the pharmacokinetic study is presented in Table 6 and under *Pharmacokinetics* in Attachment 2.

There were three Phase I studies in healthy volunteers examining pharmacokinetics; XM22-01, XM22-05 and XM22-06. In brief, after a single SC injection of 6 mg at three different sites (upper arm, abdomen and thigh) in healthy volunteers with lipegfilgrastim, the maximum blood concentration was reached after a median of 30 to 36 hours and the average terminal $t_{1/2}$ ranged from approximately 32 to 62 hours. The C_{max} and AUC were lower after SC injection in the thigh compared to SC injection in the abdomen and in the upper arm.

In the limited Study XM22-06, concentrations of lipegfilgrastim and observed differences among the injection sites were higher in males compared to female subjects however the pharmacodynamics were similar, independent of gender and injection site.

There was one Phase II study in cancer which also had pharmacokinetic data. This was XM22-02 in which breast cancer patients received lipegfilgrastim and concurrent docetaxel or doxorubicin. 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 SC injection of 6 mg lipegfilgrastim during the first cycle of chemotherapy. After a single SC 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 $t_{1/2}$ in the fourth cycle was longer than in Cycle 1, approximately 39 and 42 hours.

There was a Phase III study (XM22-04) with some pharmacokinetic data in patients with non-small cell lung cancer receiving chemotherapy consisting of cisplatin and etoposide. Here the mean maximum blood concentration of 317 ng/ml was reached after a median T_{max} of 24 hours and the mean terminal $t_{1/2}$ was approximately 28 hours after a single SC injection of 6 mg lipegfilgrastim during the first cycle of chemotherapy. After a single SC 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 $t_{1/2}$ was approximately 34 hours.

Table 6: Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID	*
PK in healthy adults	General PK - Single dose	XM22-01	
		XM22-05	
		XM22-06	
PK in special populations	Target population - breast cancer	XM22-02 and XM22-03	
	Non-small cell lung cancer	XM22-04	
Population PK analyses	Healthy subjects		
	Target population	PKPD analysis of XM22 undertaken	

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

Evaluator's conclusions on pharmacokinetics

Overall, there are concerns about the paucity of pharmacokinetic evidence to guide choice of dose for future studies, the translatability of the data from healthy subjects to cancer patients (and the variability within those populations such as breast versus lung cancer patients). There is no pharmacokinetic knowledge to guide treatment in clinical trial populations such as the elderly, the obese and the undernourished. The population pharmacokinetic data is helpful but several groups with altered pharmacokinetics were not documented, such as more than mild liver disease or comorbidity. The lack of individual data between body size and concentration, or of concentration and effect on absolute neutrophil count (ANC) makes extrapolation to other cancers, to the ANCs and people of different ethnicity, gender and age difficult.

Data in particular looking at patients over 75 years (where cancer is more common statistically for most cancers), the obese and those with organ impairment, with both PK and linked PK/PD information in particular would be very helpful. For example, it is difficult to see how a dose of 6 mg in an elderly woman weighing 50 kg with breast cancer should result in the same effect on ANC as a younger male weighing 90 kg having a mildly myelotoxic regimen (with different drugs) another cancer. Similarly there is a paucity of pharmacokinetic data for patients of non-Caucasian descent.

Pharmacodynamics

Studies providing pharmacodynamic data

There were three Phase I studies (XM22-01-CH: dose escalation study in healthy subjects; XM-22-05-CH: single dose parallel group study in healthy subjects; XM22-06: open label three-way crossover study in healthy subjects) and one Phase II study of efficacy, PK, PD and safety, dose-finding (XM22-02-INT: randomised double-blind parallel group active-controlled dose-finding study in patients with Stage II, III or IV breast cancer receiving doxorubicin/docetaxel for 4 cycles), providing new pharmacodynamic data in this application.

There were also two Phase III studies which had PD data.

Table 7 shows the studies relating to each pharmacodynamic topic and the location of each study summary.

Table 7: Submitted pharmacodynamic studies.

PD Topic	Subtopic	Study ID
Primary Pharmacology	ANC and duration of severe neutropenia (DSN)	XM22-01-CH
	ANC and AOBEC of XM22 and Neulasta given as fixed single 6 mg SC administrations to healthy subjects.	XM-22-05-CH
	PKs of XM22 after single SC dosing at three different administration sites in healthy subjects.	XM22-06
	Identification of the optimal fixed dose of XM22 compared to 6 mg Neulasta in patients with breast cancer receiving CTX.	XM22-02-INT

PD Topic	Subtopic	Study ID
	DSN, defined as Grade 4 neutropenia with an ANC <0.5 x 109/L.	XM22-03
	Incidence of FN in the first cycle.	XM22-04
Secondary Pharmacology	Effect on PK and immunogenicity, tolerability and safety	XM22-01-CH
	Evaluation of efficacy, safety, PKs, CD34+ cell mobilisation, and immunogenicity of XM22 in patients with breast cancer under CTX.	XM22-02INT
	Comparison of the respective PDs and PKs among body weight strata and evaluation of immunogenicity, tolerability and safety data of XM22 and Neulasta.	XM-22-05-CH
	Comparison of the PDs (ANC, CD34+ cell count), PKs in male vs. female subjects and evaluation of immunogenicity, tolerability and safety data of the three single doses of 6 mg XM22.	XM22-06
	Efficacy, safety, tolerability, PKs, CD34+ cell mobilisation, and immunogenicity of XM22 in patients with breast cancer under CTX.	XM22-03
	Evaluation of efficacy, safety, tolerability, PKs, CD34+ cell mobilisation, and immunogenicity of XM22 in patients with non-small cell lung cancer under CTX.	XM22-04
Gender other genetic and Age-Related Differences in PD Response	Effect of gender	XM22-06, XM22-04
	Effect of ethnicity	Population model (numbers too small in PD studies)
	Effect of age	XM22-04
PD Interactions		Population model
Population PD and PK-PD analyses	Healthy subjects	Population model
	Target population	Population model

There were no other pharmacodynamic studies submitted in this application.

Evaluator's conclusions on pharmacodynamics

Overall, the PD parameters were difficult to comments on because of small numbers in each of the groups (females, age over 65, obese, for example). Formal studies on patients and PK and on PK and PD outcomes were seemingly not undertaken. This would have

been very helpful as the sponsor proposes to move from a weight-based dosing regimen to a fixed dose (0.6 mg) regimen for all patients.

There was a high rate of withdrawal in several studies which are sources of bias, for example in Study XM22-04, 250 patients completed and 128 patients discontinued. In XM22-03, 2 patients stopped after the first dose because of pain.

The sponsor is requested to provide information on the patients who developed hyperleucocytosis, and withdrawal (see *Clinical questions* below). The patient narratives are noted but specifically extra information such as the body size and concentrations of XM22 at the time of the PD effects would be helpful to understand if there is a correlation of factors with PD outcomes. This is especially pertinent as the proposed dose of lipegfilgrastim is not weight (total, lean) or other PK factor based.

Dosage selection for the pivotal studies

Dose selection for the pivotal studies was undertaken in Studies XM22-01 and XM22-02, with PK simulation with data from healthy subjects used for sensitivity analyses. It was acknowledged that PK and PD data in response to G-CSF is different in a population receiving myeloablative therapy to healthy subjects.

XM22-01 was a single-blind, single centre, randomized Phase I study in 3 (planned 4) parallel groups which was preceded by a pilot cohort (25 µg/kg XM22). The primary objective was to compare the PDs of 3 different ascending doses of XM22 (50, 100 and 200 µg/kg) and 100 µg/kg Neulasta given as single SC doses to healthy subjects. A total of 53 healthy male and female Caucasian subjects were included in the treatment groups, 45 subjects were allocated to Group 1 (n = 15; 50 µg/kg XM22), Group 2 (n = 15; 100 µg/kg XM22) and Group 4 (n = 15, control group; 100 µg/kg Neulasta, divided in 3 cohorts of 5 subjects). Subjects entered into Group 3 received only Neulasta. Figure 3 shows the synoptic plots of G-CSF serum concentrations following single SC injection of the 3 dose levels of XM22 and Neulasta, respectively, to healthy subjects.

Figure 3: G-CSF serum concentrations after single SC administration of 3 doses XM22 and 1 dose Neulasta to healthy subjects.

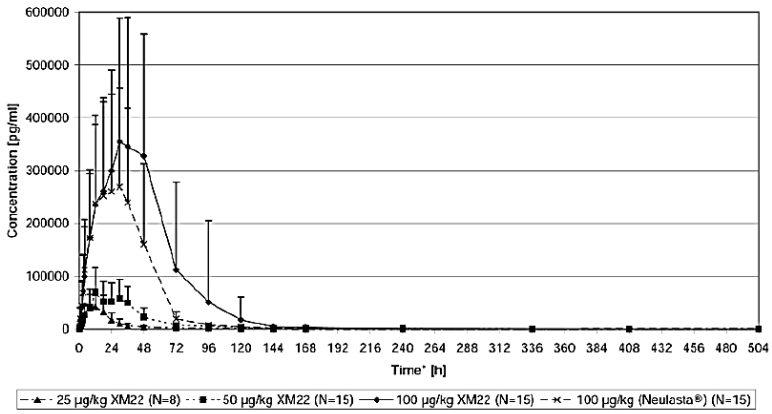
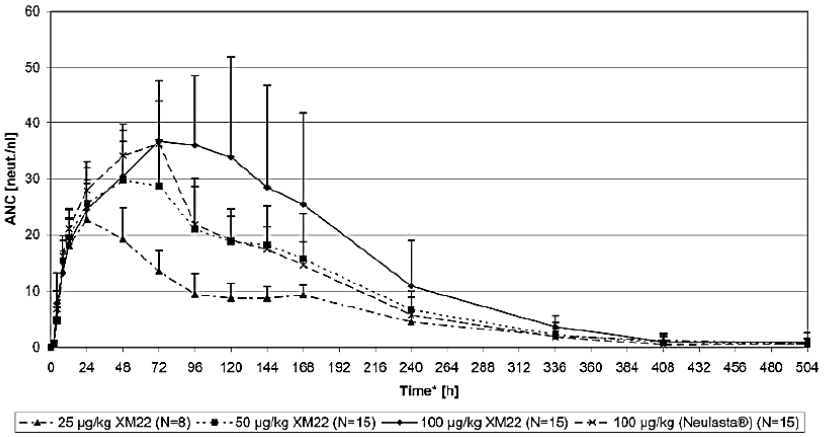


Figure 4 shows the synoptic a plot of the ANC count following single SC injection of the 3 dose levels of XM22 and Neulasta, respectively, to healthy subjects. It can be seen that the 50 µg/kg group has a similar ANC to Neulasta, and reached the same peak concentration at 100 µg/kg.

Figure 4: ANC plot following SC injection at three dose levels of XM22 and Neulasta



XM22-02 was a multinational, multicentre, randomised, double-blind, controlled study on the efficacy and safety of a fixed dose of three fixed dose levels of XM22 (3 mg, 4.5 mg and 6 mg) on the duration of severe neutropenia (DSN) to 6 mg Neulasta in patients with breast cancer receiving 4 cycles of chemotherapy with doxorubicin 60 mg/m^2 and docetaxel 75 mg/m^2. The primary objective was to identify the optimal fixed dose of XM22 compared to 6 mg Neulasta in patients with breast cancer receiving CTX for future clinical trials. Overall, the mean DSN was highest in the 3 mg XM22 group (1.1±1.1), followed by 6 mg Neulasta (0.9±1.0), 4.5 mg XM22 (0.8±1.1) and 6 mg XM22 (0.8±1.1). Mean and median DSN were very similar across all treatment groups and greatly reduced from that expected in non-G-CSF treated patients.

Figure 5: G-CSF serum concentrations after single SC administration of 3 doses XM22 or 1 dose Neulasta in Cycle 1. PK population.

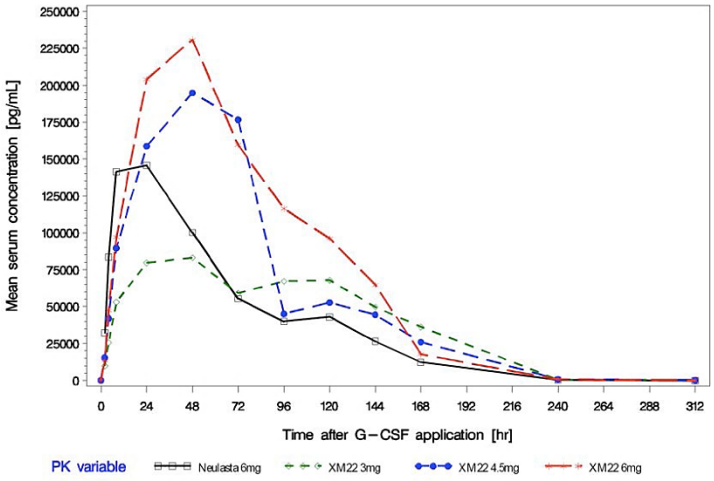
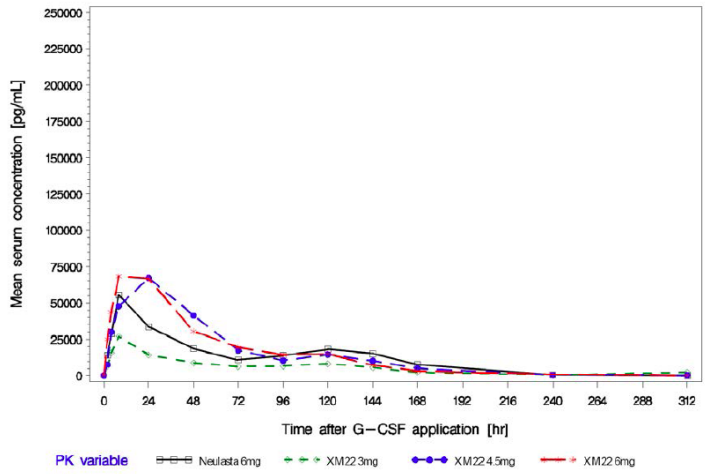


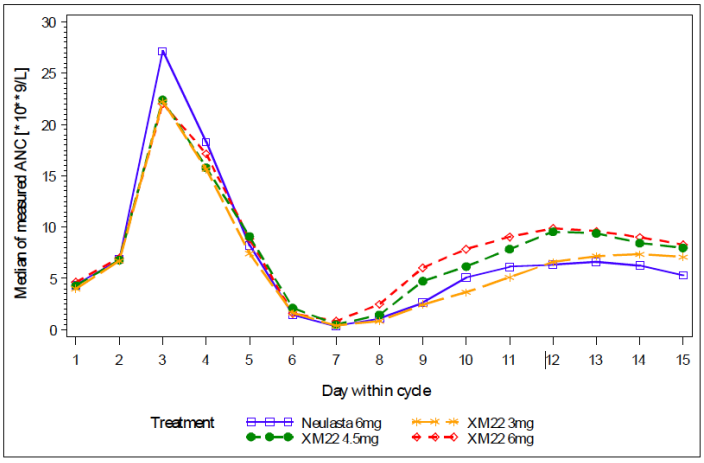
Figure 6: G-CSF serum concentrations after single SC administration of 3 doses XM22 or 1 dose Neulasta in Cycle 4. PK population.



Pharmacodynamic results.

The primary objective of this study was the rate of DSN in Cycle 1 in a fixed dose of XM22 compared to 6 mg Neulasta in patients with breast cancer receiving CTX defined as Grade 4 neutropenia (ANC <0.5 x 10^9/L). Figure 7 shows the synoptic plots of ANC following single SC injections of 3 mg, 4.5 mg or 6 mg XM22 or 6 mg Neulasta in patients with breast cancer receiving CTX in Cycle 1and shows that the ANC is higher with the 6 mg lipegfilgrastim than with the same dose of Neulasta.

Figure 7: Time course of measured ANC. ITT population.



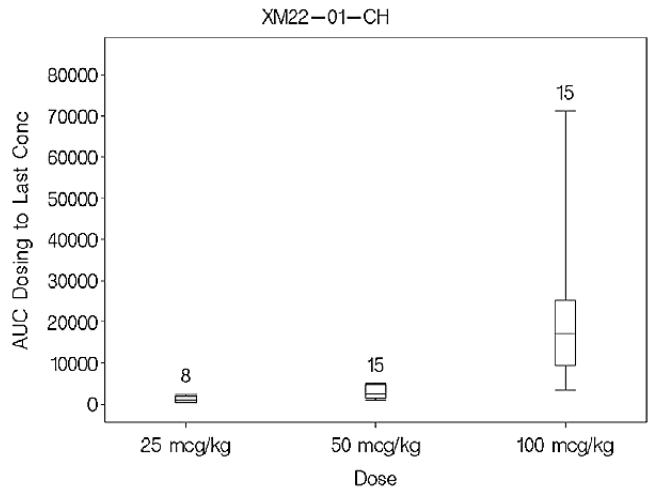
It can be seen that mean and median ANC were very similar across all treatment groups in this cancer population.

Comment: The benefit of 6 mg over 3 mg or 4 mg lipegfilgrastim on ANC is not clearly defined.

Population pharmacokinetic model

Here the proportionality of XM22 over the range of 25 through 100 µg/kg was evaluated using data from healthy subjects. The results in this population suggest that systemic exposure increases in a greater than proportional manner over this range.

Figure 8: Dose Normalized Observed AUC0-inf for XM22 Following Single Doses of 25, 50, or 100 µg/kg.



Boxes are 25th, 50th, and 75th percentiles; whiskers are 5th to 95th percentiles.
Asterisks show data points outside this range. The number of subjects is above each box.

Further modeling was not done on the dose choice as the 1 therapeutic dose (a fixed 6 mg dose) had already been selected for further development.

Pharmacokinetic data obtained in the initial studies demonstrated that overall exposure (as assessed by AUC from time 0 to infinity ($AUC_{0-\infty}$)) was about 60% higher and peak exposure (C_{max}) about 30% higher following administration of 100 µg/kg or 6 mg dose of XM22 as compared to that following the 6mg dose of Neulasta (Study XM22-01-CH and XM22-02- INT). The decline of serum concentrations from peak longer for XM22 resulting in longer mean residence time (approximately 58 hours). The pharmacodynamic data from these studies demonstrated that, at these doses, XM22 had a greater effect on ANC apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like (AOBEC) (approximately 30% higher) and CD34+ AOBEC (approximately 80% higher) than with Neulasta.

Comment: In XM22-02, the average DSN was highest in the 3 mg XM22 group (1.1±1.1), followed by 6 mg Neulasta (0.9±1.0), 4.5 mg XM22 (0.8±1.1) and 6 mg XM22 (0.8±1.1). Mean and median DSN were very similar across all treatment groups and greatly reduced from that expected in non-G-CSF treated patients. The difference from the 3 mg group to the 6 mg groups is 0.3 of a day. The clinical significance of this is not stated but is unlikely to be clinically relevant.

Ideally the modeling would have occurred on the XM22-01 and XM22-02 data to choose the dose, to drive the Phase III lipegfilgrastim versus placebo study rather than model doing that retrospectively. Based on the efficacy data; the clinical data suggests that 3 mg would be an effective dose for the study. The increase in AUC with the 6 mg lipfilgrastim compared to 6mg Neulasta is correlated with a 30% higher ANC.

Efficacy

Studies providing efficacy data Overview of clinical studies

The two studies to be discussed are the Phase III studies. Other clinical studies have been discussed above.

Evaluator's conclusions on efficacy for treatment of cancer patients following chemotherapy to decrease DSN and FN

In the pivotal studies (XM22-03 and XM22-04) DSN and febrile neutropenia (FN) data were collected. This is important as the indication refers to both reduced FN *and* a shortened DSN. In XM22-03, non-inferiority of 6 mg Lonquex® to 6 mg pegfilgrastim for the primary endpoint, (DSN) in the first cycle of chemotherapy was seen. There was a 2% less incidence in FN but the statistical and clinical interpretation of this is not clear.

In XM22-04, XM22 6 mg was seen to be no more effective than placebo in reducing FN at the end of Cycle 1, the primary endpoint.

In XM22-04, XM22 appeared superior in achievement of some of the secondary endpoints. However the clinical relevance of these was unclear. Neutropenia per se is important if it affects the next course of treatment or causes FN. FN was not affected but there was a statistically significant reduction in number of CTX treatments that were delayed with XM22 in Cycles 2-4 but not in dose reduction or omission. *Duration of severe neutropenia* was significantly different between the two groups (1 to 2 days extra DSN) and the *Incidence of severe neutropenia*, defined as Grade 4 (ANC $<0.5 \times 10^9$/L). This was statistically significantly different between the two groups.

Comment: Overall, the relevant endpoints clinically need to be clarified, as does the relationship between these and the indication. Overall FN appears to be one of the two most significant endpoints as this is associated with morbidity and mortality, as well as neutropenia that cause a delay in next chemotherapy cycle. These are in fact both noted in the indication. Thus the trials need to show that both DSN and FN are reduced.

In terms of DSN, XM22-03 has shown non inferiority to Neulasta. XM22-04 showed a statistically significant difference when analysed as a secondary endpoint. The clinical relevance of the 1 to 2 days was not discussed however.

In terms of the FN, there was a numerical difference in XM22-03 but numbers were small and it was also a secondary endpoint. In the Intent-to-Treat (ITT) population, 2 patients in the Neulasta® group and 1 patient in the XM22 group were hospitalised due to FN or infection. All 3 patients were hospitalised during Cycle 1 (the XM22 patient for 1 day in the intensive care unit (ICU)) and received antibiotics; the XM22 patient also received antipyretics. The incidence of very severe neutropenia over all cycles was low and non-statistically different in both groups (11.7% Neulasta® patients, 6.4% XM22 patients; p=0.2066). There was no difference in FN in Study XM22-04 in the first or the following cycles.

Overall it appears then that lipegfilgrastim 6 mg is non-inferior to pegfilgrastim 6 mg in breast cancer in terms of DSN. Also that lipegfilgrastim is not superior to placebo for reducing febrile neutropenia in non-small cell lung cancer (NSCLC), nor has the superiority of XM22 over Neulasta in FN been demonstrated in XM22-03, although it does have a statistically significant effect at reducing the ANC nadir (lowest point) and time to recovery.

These facts suggest the data does not support the indication.

Safety

Studies providing safety data Studies providing evaluable safety data

Detailed descriptions of the safety analysis of individual studies are provided in the respective study reports of which there are six. The evaluation of safety will focus on the findings from the 2 completed Phase III studies in cancer patients (XM22-03, XM22-04)

and the 1 completed dose-finding Phase II study in cancer patients (XM22-02-INT). Supportive data from the Phase I studies in healthy subjects (XM22-01-CH, XM22-05-CH, XM22-06) will be presented as relevant.

Pivotal efficacy studies

XM22-03 and XM22-04.

Pivotal studies that assessed safety as a primary outcome

Nil.

Dose-response and non-pivotal efficacy studies

There were three Phase I and one Phase II dose-response and non-pivotal efficacy studies providing safety data.

Patient exposure

Table 8: Cumulative exposure to lipegfilgrastim in clinical studies.

Study No.	Phase	Subject/ Patient type	XM22	Comparator	Treatment duration	No. treated
XM22-01-CH	I	Healthy	25, 50, or 100 µg/kg	Neulasta 100 µg/kg	Single dose	53
XM22-05-CH	I	Healthy	6 mg	Neulasta 6 mg	Single dose	36
XM22-06	I	Healthy	6 mg	–	Single dose in each study period	20
XM22-02-INT	II	Breast cancer	3, 4.5, or 6 mg	Neulasta 6 mg	12 weeks	208
XM22-03	III	Breast cancer	6 mg	Neulasta 6 mg	12 weeks	202
XM22-04	III	NSCLC	6 mg	Placebo	12 weeks	373

In all clinical studies, XM22 was administered as an SC injection. In the Phase II and III studies in cancer patients, XM22 was administered as a fixed dose once per CTX cycle, approximately 24 hours after CTX infusion. In the Phase I clinical studies in healthy subjects, XM22 was administered as a single weight-based dose in Study XM22-01-CH, as a single fixed dose in Study XM22-05-CH, and as a single fixed dose per treatment period in Study XM22-06 (up to 3 doses in total per subject).

Safety issues with the potential for major regulatory impact

Cardiovascular safety

No signal apart from the comments above with respect to the ECG.

Unwanted immunological events

Immnunogenicity is a long standing issue with these agents and there is an immunogenicity database collecting any new information. There were no significant issues within the submitted studies however.

Postmarketing data

Two PSURS reporting up to the middle of 2014 were provided and there were no new concerns raised.

First round benefit-risk assessment

First round assessment of benefits

The benefits of lipegfilgrastim in the proposed usage are:

1. Less doses of G-CSF therapy
2. Non-inferior to pegfilgrastim in DSN in breast cancer treatment
3. May reduce delays in CTX
4. May reduce neutropenia severity and time to recover from the nadir (although the clinical relevance was not clear).

Overall it appears then that lipegfilgrastim 6 mg is non-inferior to pegfilgrastim 6 mg in breast cancer and that lipegfilgrastim is not superior to placebo for reducing febrile neutropenia in NSCLC, although it does have a statistically significant effect at reducing the ANC nadir and time to recovery. The drug does not meet efficacy criteria for reduction of both DSN and FN.

First round assessment of risks

1. May worsen survival in NSCLC
2. May increase disease progression in NSCLC
3. Equivalent to placebo in FN prevention in NSCLC
4. May cause hyperleucocytosis
5. Causes a number of side effects, including bone pain and elevations in ALP, GGT and lactate dehydrogenase (LDH).

First round assessment of benefit-risk balance

This drug appears to be non-inferior to one already registered (Neulasta) for which there are several years of pharmacovigilance data on DSN in breast cancer patients. The drug may not be any better than placebo at preventing FN in lung cancer and may worsen survival and worsen disease free progression in this disease. It also has side effects which are not insignificant. The benefits in the secondary outcomes are around ANC, much of which has not yet been shown to translate into a clinical benefit (as opposed to a change in the ANC number).

The data from the release of Phase IV study in the UK and the paediatric data would be helpful.

First Round Recommendation Regarding Authorisation

The proposed indication is not justified from the data presented; authorisation is not recommended.

Evaluation of the data in Phase IV studies in the EU and the paediatric data is needed to satisfy concerns over the effect this drug has on cancer progression and survival.

Clinical Questions

Pharmacokinetics

1. The sponsor was requested to provide any additional data it holds regarding pharmacodynamic effect(s) according to gender, age (dichotomised at 65 years), body weight and body mass.
2. The sponsor was requested to perform an analysis of PK and PD parameters, comparing: (i) patients that withdrew from treatment versus patients that continued treatment, and (ii) patients that survived following treatment versus patients that died on study.
3. How did the sponsor decide on the drug dose for the study? Concentration data indicate that the 3 mg looks similarly effective.
4. The sponsor should justify why a weight based dosing regimen recommendation has not been made bearing in mind there was pharmacokinetic data submitted which used at least a weight based dosing regimen and the large (and increasing) number of cancer patients that are overweight, obese or are cachectic or underweight (such as patients with lung cancer and underlying airways disease).

Efficacy

1. The sponsor is requested to provide the comments of Swiss Medic which resulted in withdrawal of the submission to that regulator.
2. The sponsor is requested to provide the PIP data from November 2014 submitted to the EMA.
3. The sponsor is requested to provide an explanation regarding the lack difference in both dose reductions and omitted treatments seen in Study XM22-04 given these are considered clinically relevant end-points.
4. Although the upper limit for number of injections is not stated this should be indicated based on the current efficacy or safety data?
5. The sponsor is requested to provide a summary of the reasons as to why patients withdrew from XM-22-04.
6. What does the sponsor consider to be the clinical benefit of a DSN reduction of 1.6 days as seen in XM22-04?
7. The sponsor was requested to provides the statistical and clarify the clinical significance of the efficacy data presented in the clinical study report (CSR) for Study XM22-04?
8. The sponsor should be requested to provide references to support the assumptions of the incidence rate of FN under treatment with placebo and the incidence under treatment with XM22 as the actual incidence was much lower.
9. The sponsor was requested to explain proposed benefit of lipegfilgrastim for patients with NSCLC from, given they were observed to have worsened survival, disease progression and similar incidence of febrile neutropenia as compared to those exposed to placebo.

Safety

1. What was the percentage of women compared to men who developed hyperleukocytosis and was this associated with elevated plasma concentration of lipegfilgrastim?

2. What was the cause of 'pain' in the two patients that withdrew from Study XM22-03?
3. Given that Study XM22-04 failed to meet the primary efficacy end-point of reduction in incidence of febrile neutropenia, does the sponsor have evidence of safety and efficacy to demonstrate a benefit to continued administration of Lonquex in an individual patient once febrile neutropaenia has occurred?
4. The sponsor should identify if the patients who developed ECG abnormalities were concomitantly receiving doxorubicin.
5. The sponsor was requested to provide the data and the study investigator's stated reasons for the purported relationship to Lonquex for all patients who died.

Second Round Evaluation of clinical data submitted in response to questions

The details of the sponsor's responses to the Clinical questions and the evaluator's comments on these responses are detailed in Attachment 2.

Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of lipegfilgrastim in the proposed usage are unchanged from the first round clinical evaluation.

Second round assessment of risks

After consideration of the responses to clinical questions, the risks of lipegfilgrastim in the proposed usage are:

- The apparent risk of worsening survival for patients in Study XM22-04 may be plausibly accounted for due to an imbalance in baseline disease characteristics rather than exposure to lipegfilgrastim.
- Injection site pain sufficient to lead to treatment withdrawal was identified in a small number of patients

Second round assessment of benefit-risk balance

The benefit-risk balance of lipegfilgrastim is unfavourable given the proposed usage, but would become favourable if the changes recommended in the clinical evaluation are adopted.

Second round recommendation regarding authorisation

The evaluator recommends to the Delegate that lipegfilgrastim is approvable, providing the changes to the PI are implemented. The evaluator considers that the indication should be worded as per that approved in the EU.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (EU-RMP version 7.1 dated 10 April 2014 (data lock point 31 December 2013) and an Australian Specific Annex (ASA; dated 15 October 2014) which was reviewed by the RMP evaluator.

Safety specification

The sponsor provided a summary of Ongoing safety concerns which are shown at Table 9.

Table 9: Sponsor's summary of Ongoing safety concerns

Important identified risks	Musculoskeletal pain-related symptoms
	Allergic type reactions
	Pulmonary adverse effects (pulmonary interstitial lung disease, ARDS)
	Thrombocytopenia
	Leukocytosis
Important potential risks	Immunogenicity which manifest as lack of effect.
	Sweet's syndrome
	Sickle cells crisis in patients with Sickle cell disease
	Cutaneous vasculitis
	Splenomegaly, splenic rupture
	Risk in off label use
	Overdose
	Reduced pharmacodynamic effect in overweight patients >95 kg weight
	Progression of underlying malignancy
	Capillary leak syndrome
Important missing information	Risk in children <18 years of age
	Risk in patients ≥65 years of age
	Risk in pregnant and lactating women
	Risk in patients with renal or hepatic impairment

Pharmacovigilance plan

The following table summarises the pharmacovigilance activities presented in the EU-RMP and the ASA:

Table 10: Summary of pharmacovigilance presented by the sponsor

Identified risks	Pharmacovigilance activities
Musculoskeletal pain-related symptoms	Routine pharmacovigilance;
Allergic type reactions	Routine pharmacovigilance;
Pulmonary adverse effects (including interstitial lung disease, ARDS)	Routine pharmacovigilance;
Thrombocytopenia	Routine pharmacovigilance;
Leucocytosis	Routine pharmacovigilance;
Important potential risks	
Immunogenicity which may manifest as lack of effect	Routine pharmacovigilance; Additional pharmacovigilance activity: study XM22-07 and study XM22-08;
Sweet's syndrome	Routine pharmacovigilance;
Sickle cell crisis in patients with sickle cell disease	Routine pharmacovigilance;
Cutaneous vasculitis	Routine pharmacovigilance;
Splenomegaly, splenic rupture	Routine pharmacovigilance;
Risks in off-label use	Routine pharmacovigilance including a follow-up questionnaire; Additional pharmacovigilance activity: a drug utilisation study;
Overdose	Routine pharmacovigilance including a follow-up questionnaire;
Reduced pharmacodynamics effect in patients > 95kg body weight	Routine pharmacovigilance including a follow-up questionnaire;
Progression of underlying malignancy	Routine pharmacovigilance; Additional pharmacovigilance activity: a PASS to evaluate the risk of disease progression;
Capillary leak syndrome	Routine pharmacovigilance;
Important missing information	
Risks in children < 18 years of age	Routine pharmacovigilance; Additional pharmacovigilance activity: study XM22-07 and study XM22-08;
Risks in patients ≥ 65 years of age	Routine pharmacovigilance;

Risks in pregnant and lactating women	Routine pharmacovigilance;
Risks in patients with hepatic or renal impairment	Routine pharmacovigilance.

Risk minimisation activities

Routine risk minimisation through the Australian PI and Consumer Medicine Information (CMI) documents is proposed for all the safety concerns. No additional risk minimisation activities have been proposed by the sponsor.

Reconciliation of issues outlined in the RMP report

Table 11 summarises the first round evaluation of the RMP, the sponsor's responses to issues raised by the RMP evaluator and the evaluation of the sponsor's responses.

Table 11: Reconciliation of issues outlined in the RMP Evaluation Report (Round 1)

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
1. Safety considerations may be raised by the non-clinical and clinical evaluators through the TGA's consolidated request for further information and/or the Nonclinical and Clinical Evaluation Reports respectively. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the Risk Management Plan, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.	*The applicant acknowledges the evaluators request to consider and address aspects of the clinical and non-clinical responses that may impact the Risk Management Plan.*	The sponsor's response is satisfactory.

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
2. The sponsor should clarify whether it considers 'progression of underlying malignancy' includes 'worsening of underlying malignancy'. It should be noted that disease progression is a natural course for malignancies while worsening of underlying condition does not have to be.	*The applicant acknowledges that it might be desirable to differentiate between natural courses of malignancies and other courses. However, MedDRA does not offer such kind of differentiated wording to characterise those cases.* *MedDRA does include the following Preferred Terms (PTs) (which are laid down in section SVII.3 of the RMP to define the Potential Risk: 'Progression of underlying malignancy'):* • *Concomitant disease progression* • *Disease progression* • *Neoplasm progression* *However MedDRA does not include terms like 'worsening of underlying malignancy' or 'worsening of* neoplasm', neither as PTs nor as Lowest Level Terms (LLTs) or on any other level. *Therefore in practice all case reports for worsening of underlying malignancy will be coded with either 'Concomitant disease progression', 'Disease progression' or 'Neoplasm progression' in the safety database of the applicant.* *In periodic reports evaluating the Risk: 'Progression of underlying malignancy'(RMP wording) therefore all cases will be available, irrespectively of natural or other course and will be used to monitor the risk.*	The sponsor's response is acceptable. It is noted that in post-authorisation spontaneous adverse event reporting, it could be difficult to determine whether progression of malignancy is due to lipegfilgrastim or the disease trajectory.
3. The following is a list of risks associated with the use of other filgrastim (rbe) products. The sponsor should provide justification to why these are not relevant to lipegfilgrastim (rbe). In particular, why it does not expect these adverse events to occur given the pharmacological similarity between filgrastim (rbe) and lipegfilgrastim (rbe). Otherwise, they should be added to the list of safety concerns in the ASA: Immune system disorders: acute and chronic Graft versus Host Disease (GvHD) including transformation to leukaemia or MDS; Haematological malignancy;	*a. The applicant acknowledges that immune system disorders can be regarded as a risk in recipients of allogeneic peripheral blood progenitor stem cells (PBPC) mobilised with filgrastim. Current data indicate that immunological interactions between the allogeneic PBPC graft and the recipient may be associated with an increased risk of acute and chronic Graft versus Host Disease (GvHD) when compared with bone marrow transplantation* *This is relevant for Filgrastim (rbe) since it is indicated for the mobilisation of peripheral blood progenitor cells, in normal volunteers, for use in allogeneic peripheral blood progenitor cell transplantation.* *However, the applicant does not seek*	The sponsor's response is acceptable. If future application to extend the indication is sought, risks relevant to the indications should be included in the RMP.

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
Carcinogenicity; Exacerbation of rheumatoid arthritis; and Osteoporosis in severe chronic neutropenia patients.	*approval for lipegfilgrastim in this indication. 'Risks in off-label use' are included in the Lonquex RMP as an important potential risk. However, as per current guidelines the RMP should not explicitly list individual risks that can be connected with off-label use.* *b. As far as the applicant aware this risk is only applicable in connection with use in severe chronic neutropenia patients or in in normal donors. This is reflected in the following safety concern wordings:* *• 'Malignant cell growth (haematological malignancy and myelodysplastic syndrome) in patients with severe chronic neutropenia.' (AusPAR Filgrastim/Nivestim, January 2011, page 55)* *• ' Haematological and lymphoid malignancy in normal donors' (AusPAR Filgrastim/Zarzio, October 2013, page 24)* *This is relevant for filgrastim (rbe) since it´s approved indication includes - the mobilisation of peripheral blood progenitor cells, in normal volunteers, for use in allogeneic peripheral blood progenitor cell transplantation.* *- chronic administration to increase neutrophil counts and to reduce the incidence and duration of infections in patients with severe chronic neutropenia.* *However, the applicant does not seek approval for lipegfilgrastim in these indications. 'Risks in off-label use' are included in the Lonquex RMP as an important potential risk. However, as per current guidelines the RMP should not explicitly list individual risks that can be connected with off-label use.* *c. The applicant is not aware of carcinogenicity as being as safety concern of any G-CSF. Carcinogenicity studies with lipegfilgrastim were not performed as there is no evidence for a genotoxic effect of these cytokines. There is no indication for a potential carcinogenicity of lipegfilgrastim from chronic toxicity studies.* *d. Exacerbation of rheumatoid*	

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
	arthritis was not observed in lipegfilgrastim studies. In clinical Studies XM22-02, XM22-03 and XM22-04 no cases of MedDRA PT 'rheumatoid arthritis' (includes, amongst others, the LLTs 'progression of rheumatoid arthritis', 'rheumatoid arthritis aggravated') or MedDRA PT 'juvenile idiopathic arthritis' (includes, amongst others, the LLTs 'juvenile arthritis aggravated', 'juvenile idiopathic arthritis aggravated') have been seen. Exacerbation of rheumatoid arthritis does not appear in the Neulasta (Pegfilgrastim) European SmPC. *The reports concerning cases of exacerbation of rheumatoid arthritis following G-CSF therapy refer to filgrastim, given to rheumatoid arthritis patients for stem cell mobilisation as a preparation for autologous haemopoietic stem cell transplantation.*[5] *The population in this report (non-cancer patients) is different than that of lipegfilgrastim, as is the indication (stem cell mobilisation) which is not labelled for lipegfilgrastim. Therefore, the applicant regards that risk as non-relevant to lipegfilgrastim, and do not see it necessary to include it within its list of safety concerns.* *e. Cases of decreased bone density and osteoporosis have been reported commonly in children with Severe Chronic Neutropenia (SCN) receiving chronic treatment with filgrastim. Decreased bone mineral density has been attributed primarily to the underlying disease. However, chronic filgrastim treatment may further accelerate bone loss. This is relevant for filgrastim (rbe) since it is indicated for chronic administration to increase neutrophil counts and to reduce the incidence and duration of infections in patients with SCN. However, the applicant does not seek approval for lipegfilgrastim in this indication. 'Risks in off-label use' are included in the Lonquex RMP as an important potential risk. However,*	

[5] Snowden et al, (1998) *Bone Marrow Transplantation* 22 (11): 1035-41

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
	as per current guidelines the RMP should not explicitly list individual risks that can be connected with off-label use.	
4. Study XM22-07 is an open-label study to assess the pharmacokinetics, pharmacodynamics, efficacy, safety, tolerability and immunogenicity of lipegfilgrastim (rbe) in children with Ewing Family of Tumour or rhabdomyosarcoma. Final data was scheduled to be submitted in October 2014. The sponsor should provide a brief update on significant safety findings from this study.	*The EU paediatric investigation plan consists of two studies in paediatric cancer patients with CTX-induced neutropenia. The first Study XM22-07 (Phase I study, investigating the pharmacokinetics of a single dose of XM22) is completed (except for follow-up data) and the study report for the treatment period was submitted to EMA in December 2014. The report for Study XM22-07 is included with this response.* *Follow-up data for the study, including results of immunogenicity testing, survival status, and G-CSF therapy will be summarised in a separate addendum report.* *21 paediatric patients (aged 2 to 16 years) were treated with a single dose of XM22 in this study. The doses were weight-adjusted for each patient (100 µg/kg body weight).* *Brief summary of results:* *The primary objective of evaluating pharmacokinetic endpoints was met and the results raised no concerns regarding the pharmacokinetic, efficacy, or safety profile of XM22. The evaluations indicated a safety profile consistent with that seen in adult trials of XM22.* *This summary is included in section III.3 of the latest EU RMP Version 8.2 (sign off date 30 April 2015).* *A synopsis of the study is available in Annex 9 of the EU RMP Version 8.2.* *Whilst the sponsor acknowledges that a separate application will be required in Australia in order to have these data reported in the Product Information, for the TGA's reference the sponsor detailed the SmPC revisions recently agreed with the EMA following their evaluation of the XM22-07 Phase I findings*	The sponsor's response is satisfactory.

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
5. Benefit-risk assessment is beyond the scope of the RMP evaluation. As a post-authorisation safety study (PASS) has been planned to monitor the risk of 'progression of underlying malignancy', the sponsor's pharmacovigilance plan is considered adequate. The sponsor should undertake to report any significant safety findings from the PASS to the TGA.	*TEVA confim that the sponsor will report any significant safety findings from the PASS study to the TGA.*	The sponsor's response is satisfactory.
6. In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft PI be revised as follows: Use in paediatric patients: the sponsor states: 'The safety and efficacy of Lonquex® in children and adolescents aged up to 17 years have not yet been established. No data are available.' It is recommended that the Delegate considers adding a statement 'treatment in this patient group is not recommended'. Myeloid leukaemia and Myelodysplastic syndrome: the sponsor has advised in the Australian PI that patients with these conditions should not use lipegfilgrastim. This advice is provided under 'Precaution' in the middle of a long paragraph. In comparison, the same advice is included under 'indication' in the approved SmPC. It is recommended that this advice is included under 'indication' in the PI to ensure healthcare professionals' awareness.	*The recommendations of the RMP Evaluator in relation to the draft PI are noted. The sponsor commits to working with the Delegate to ensure that the PI effectively communicates important safety information.*	The sponsor's response is satisfactory. It is noted that the TGA's Advisory Committee on Safety of Medicines (ACSOM) advice supports the recommendations. The recommendations on PI remain for consideration by the Delegate.
7. In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the incorrect reference to Neulasta in the draft consumer medicine information (CMI) document be revised.	*The recommendations of the RMP Evaluator in relation to the Consumer Medicine Information (CMI) document are noted. The sponsor has revised the CMI to remove references to Neulasta as requested. The updated CMI (clean and tracked copies) are presented with this response.*	The sponsor's response is satisfactory.

Summary of recommendations

It is considered that the sponsor's response to the TGA has adequately addressed most of the issues identified in the RMP evaluation report. Outstanding issues are discussed below.

Outstanding issues

Issues in relation to the RMP

Details on the sponsor's response to the RMP evaluation report are in Table 11, Reconciliation of issues outlined in the RMP Evaluation Report.

Additional recommendations

- ACSOM Recommendation 4: (see below)
- Study XM22-04 should be included in the Product Information (PI) as a Precaution to notify clinicians of a biologically plausible mortality signal that is being investigated via further study.
- Nonclinical evaluator's recommendations.

Results and conclusions drawn from the nonclinical program for lipegfilgrastim detailed in the sponsor's draft Risk Management Plan are in general concordance with those of the nonclinical evaluator. Minor differences should be corrected:

1. Decreased red blood cells (RBC) (and haematocrit (Hct) and/or haemoglobin (Hb)) was observed throughout the 26-week study in rats. Thus 'a transient decrease in red blood cells' described by the sponsor is not correct. However, the decreases in RBC and related parameters were reversible after cessation of dosing.
2. Atrophy of trabecular bone in rats was seen in both the 13 week and 26 week studies.'

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

ACSOM Recommendation 1: The committee advised that the safety concern list provided by the sponsor could not be considered adequate until it incorporated safety issues that have been identified for filgrastim: immune system disorders (acute and chronic Graft versus Host Disease including transformation to leukaemia or myelodysplastic syndrome); haematological malignancy; carcinogenicity; exacerbation of rheumatoid arthritis; and osteoporosis in severe chronic neutropenia patients.

RMP evaluator comment: The sponsor has provided justification to why some risks related to filgrastim are not included in the current RMP (see sponsor's response to Recommendation 3 in Table 11). This is acceptable. If future application to extend the indication is sought, risks relevant to the indications should be included in the RMP.

ACSOM Recommendation 2: The committee advised that routine pharmacovigilance was appropriate for the remaining issues. However, it was noted that as the proposed indications in Australia are wider than the indications approved by the EMA, the Australian Annex to the RMP and its pharmacovigilance plans needs to address these additional indications (chronic myeloid leukaemia and myelodysplastic syndromes) and include a drug utilisation study relevant to the wider Australian indications.

RMP evaluator comment: In the updated ASA submitted with the sponsor's response, the sponsor states:

> *In contrast to the indication for Lonquex® in the EU, the proposed indication for Lonquex® in Australia does not specifically exclude chronic myeloid leukaemia and myelodysplastic syndromes. However, the proposed product Prescribing Information (PI) (PRECAUTIONS) states that 'the safety and efficacy of Lonquex® administration in patients with myelodysplasia or chronic myeloid leukaemia have not been established'. This is consistent with the Australian prescribing information for other PEGylated recombinant human N-methionyl granulocyte-colony stimulating factors (G-CSFs) including* pegfilgrastim *(Neulasta®, marketed by Amgen Australia Pty Ltd).*

This is acceptable in the context of risk minimisation.

ACSOM Recommendation 3: Noting that lipegfilgrastim is not distributed beyond the lymphatic/vascular system, there was no a priori evidence that different doses should be needed based on body weight. Investigation of a potential reduced pharmacodynamics effect in patients > 95 kg body weight via routine pharmacovigilance including a follow up questionnaire, as prescribed in the EU RMP, was sufficient.

ACSOM Recommendation 4:

a. In the absence of paediatric data, use in the paediatric population was not appropriate. Data from XM22-07 should be considered before any use in children (< 18 years) could be acceptable.

b. It would also be prudent if 'use only in adults' (or non-use in children) was specified in the approved Indications, to assist side-by-side comparisons with the use of other G-CSF molecules.

c. It would also be useful if, like in the European Union (EU), the exclusion of patients with chronic myeloid leukemia and myelodysplastic syndromes was addressed explicitly in the approved indications as well as in the Precautions.

d. Study XM22-04 should be included in the Product Information (PI) as a Precaution to notify clinicians of a biologically plausible mortality signal that is being investigated via further study.

RMP evaluator comment: As requested, the sponsor has provided an update on findings from Study XM22-07 (see sponsor's response to Recommendation 4 in Table 11).

In addition, the sponsor states in the updated ASA:

> *Whilst the proposed indication for Lonquex® in Australia is not specifically limited to adult patients, the section on Paediatric Use in the proposed Pl (PRECAUTIONS) does preclude use in paediatric patients since the safety and efficacy of Lonquex® in children and adolescents up to 17 years have not yet been established. As noted in the Clinical Overview, paediatric studies (Studies XM22-07 and XM22-08) are initiated as part of the XM22 Paediatric Investigation Plan (PIP), approved by the EU Paediatric Committee on the 6th May 2011. It is therefore expected that following submission of the paediatric studies to the TGA, the Australian Pl will be updated in due to course*.

The recommendations on PI appear to support the recommendations made by the RMP evaluator for consideration by the Delegate (see Recommendation 6 in Table 11).

Key changes to the updated RMP

In their response to the TGA the sponsor provided updated EU-RMP version 8.2 dated 30 April 2015 (data lock point 25 January 2015) with the Australian Specific Annex dated 26 June 2015. Key changes from the version evaluated in the first round evaluation are summarised below.

Table 12: Key changes to the EU-RMP and ASA

	Key change
Safety specification	Capillary leak syndrome has been upgraded from 'important potential risk' to 'important identified risk'; Cytokine release syndrome and extra-medullary haematopoiesis have been added as 'important potential risks'.
Pharmacovigilance activities	Targeted follow-up questionnaires have been added to monitor the following: Important identified risk: capillary leak syndrome Important potential risk: immunogenicity which may manifest as lack of effect, cytokine release syndrome and extra-medullary haematopoiesis.

RMP evaluator's comments: The evaluator has no objection to the above changes and recommends to the Delegate that the updated version is implemented (see below).

Suggested wording for conditions of registration

RMP

Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.

The suggested wording is:

> *Implement EU-RMP version 8.2 dated 30 April 2015 (data lock point 25 January 2015), Australian Specific Annex dated 26 June 2015 and any future updates as a condition of registration.*

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There was outstanding GMP clearance for three of the four manufacturing sites at the time of the second round chemistry evaluation (24 July 2015). There were no other objections to registration.

Nonclinical

The nonclinical evaluator did not object to registration; the PI changes recommended at in the first round evaluation report were satisfactorily resolved.

Clinical

The sponsor states that the dossier presented to the TGA is identical to that presented to the EMA on 20 November 2011, with the exception of updates, addressing issues during

the EU evaluation and the pre-submission meeting with the TGA. Overview of submitted clinical studies of lipegfilgrastim and post-marketing reports

Table 13: Details of clinical studies and post-marketing reports submitted

Study No.	Type of study	Design	Dosage regimen
XM22-01	PK, PD and safety, Healthy subjects	Phase I, single-centre, single-blind, randomised dose escalation study	Pilot cohort: single SC dose of 25 µg/kg Lonquex Main study: single SC dose of 50 or 100 µg/kg Lonquex or 100 µg/kg pegfilgrastim
XM22-05	PK, PD and safety, Healthy subjects	Phase I, single-centre, single-blind, randomised, parallel-group study	Single SC dose of 6 mg Lonquex or 6 mg pegfilgrastim
XM22-06	PK, PD and safety, Healthy subjects, Three different injection sites tested	Phase I, single-centre, open-label, randomised, three-way crossover study	Single SC dose of 6 mg Lonquex at 3 different injection sites (upper arm, abdomen, thigh), separated by 3-week washout
XM22-02-INT	Efficacy, PK, PD and safety, Breast cancer patients, Dose finding study	Phase II, multinational, multicentre, randomised, double-blind, parallel-group, active-controlled, dose finding study	Single SC injection of 3 mg, 4.5 mg or 6 mg Lonquex or 6 mg pegfilgrastim on day 2 of each chemotherapy cycle
XM22-03	Efficacy, PK, PD and safety, Breast cancer patients, Active-controlled study	Phase III, multinational, multicentre, randomised, double-blind, parallel-group study	Single SC injection of 6 mg Lonquex or 6 mg pegfilgrastim on day 2 of each chemotherapy cycle
XM22-04	Efficacy, PK, PD and safety, NSCLC patients, Placebo-controlled study	Phase III, multinational, multicentre, randomised, double-blind, parallel-group study	Single SC injection of 6 mg Lonquex or placebo on day 4 of each chemotherapy cycle

PSUR	Pertains to use between
PSUR-765-02-14	25 July 2013- 25 January 2014
PSUR-765-08-14	26 January 2014-25 July 2014

Pharmacology

Three Phase I studies of PK in healthy subjects were presented in the CER (Attachment 2).

Absorption

A single formulation of lipegfilgrastim is presented for SC use only.

In healthy volunteers, maximal serum concentration after a single dose was observed at approximately35 hours after administration. By contrast, after repeat dosing of 4 cycles maximal concentration in healthy subjects was achieved between 8 and 24 hours.

In the Phase II Study XM22-02, 3 mg, 4.5 mg and 6 mg Lonquex or 6 mg Neulasta was SC administered to patients with breast cancer receiving cancer chemotherapy. In Cycle 1, lipegfilgrastim or pegfilgrastim serum concentrations rose to a transient maximum and returned to pre-dose values by 240 h. In the Lonquex groups, the peak serum concentrations occurred around 46 to 48 h after dosing and were elevated with increasing Lonquex dose in a roughly dose-dependent manner. In Cycle 4, lipegfilgrastim and pegfilgrastim serum concentrations reached a maximum between 8 to 16 h after dosing, and returned to pre-dose values by 240 h. Overall, mean serum concentrations were markedly lower in Cycle 4 than in Cycle 1 for all treatment groups.

In the both the Phase III studies in patients with breast cancer (XM22-03) and lung carcinoma study (XM22-04), in Cycle 1, mean serum concentrations of Lonquex and reached a maximum between 24 and 48 h after dosing and returned to approximately pre-dose values by 240 h.

Bioavailability

Absolute bioavailability was not assessed given that the SC route of administration is the only one proposed.

Relative bioavailability between SC injections in upper arm, abdomen and thigh was assessed in Study XM-22-06. The evaluator states '*no clinically relevant differences in PD parameters were observed between dosing at the three different administration sites*'.

Distribution

Lonquex has a volume of distribution of 70mL/kg, approximating to the lymphatic and blood volume.

No data was presented on plasma protein binding, erythrocyte distribution or tissue distribution.

Effect of body weight: for categories of body weight dichotomised as < 60kg or > 80kg, there was a decrease in exposure of approximately 30% from the lowest to highest weight groups. There was no difference in pharmacodynamic effect for patients did not show a difference across patients according to weight <60, 60 to80 or >80 kg.

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. This pathway is dependent upon the absolute neutrophil count and is saturable during the nadir of ANC count associated with cytotoxic chemotherapy.

Extracellular protein degradation pathway is likely due to by neutrophil elastase and other plasma proteases, which is linear.

Longer terminal half-lives and mean residence times were seen for lipegfilgrastim than pegfilgrastim, indicating that metabolism and clearance were significantly slower for lipegfilgrastim.

Excretion

Excretion is via the mechanisms of metabolism described above.

Special populations

Paediatric population: the sponsor's response to TGA's request for further information contained the clinical study report for a Phase I PK study in 21 children, with secondary end-points of safety and efficacy. This study represents only part of the paediatric development program and does not provide sufficient evidence to satisfactorily demonstrate the safety and efficacy of lipegfilgrastim in such patients. The restriction of

use to adults should remain until the sponsor submits a full application for use in this population.

No separate studies in hepatic impairment were submitted. The effect of hepatic impairment in cancer patients has not been studied and this is documented in the PI.

No separate studies in renal impairment were submitted.

The effect of renal impairment was reported in the population PK modelling, with 31 patients with normal renal function, 20 patients having mild renal impairment and 2 having moderate renal impairment. The PI appropriately states (page 6) that: '*There was no meaningful effect of mild renal impairment (CrCl: 62-87 mL/min; n=20) on the pharmacokinetics of lipegfilgrastim in cancer patients*.'

The PI states that the impact of moderate or severe renal impairment has not been studied.

Patient data was only available for those aged <75 years. The lack of data available for patients that are ≥75 years of age is documented in the PI.

Very limited data was available for non-Caucasian patients, which precludes any specific dosing advice.

Pharmacodynamics

The studies providing pharmacodynamic data are summarised in the CER (Attachment 2).

The primary pharmacodynamic effect was maximum ANC count

Choice of drug dose

Weight based dosing of lipegfilgrastim and pegfilgrastim was compared in XM-22-01; doses of 100 µg/kg of each yielded comparable concentration-time profiles.

Study XM-22-02 compared three fixed-doses doses of lipegfilgrastim (3 mg, 4.5 mg and 6 mg) in patients with breast cancer receiving 4 cycles of chemotherapy. Although a difference in concentration-time profile was observed between 6 mg pegfilgrastim and 6 mg lipegfilgrastim, with C_{max} being approximately 30% higher for lipegfilgrastim, the observed pharmacodynamic effect on time-course of ANC count was similar.

Efficacy

The clinical evaluator did not recommend registration in the first round evaluation, but did so following the second round evaluation.

One dose-finding and two randomised controlled studies of efficacy were presented for evaluation.

Study XM22-03 was a Phase III non-inferiority Study XM22-03 with active control in 202 patients with Stage II to 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.

On an intention to treat analysis, this study showed non-inferiority of 6 mg Lonquex® to 6 mg pegfilgrastim for the primary endpoint, duration of severe neutropenia (DSN) in the first cycle of chemotherapy.

The depth of ANC nadir was comparable for Cycle 1 but higher for the lipegfilgrastim arm in subsequent cycles.

The incidence of very severe neutropaenia was not different between the treatment arms (11.4% pegfilgrastim versus 6.4% lipegfilgrastim, p=0.21).

The incidence of febrile neutropaenia was low in both treatment arms.

Study XM-22-04 was a placebo-controlled superiority study in 375 non-small cell lung cancer patients receiving up to 4 cycles of chemotherapy consisting of cisplatin and etoposide.

This combination of chemotherapy is associated with a low risk of requiring G-CSF administration. The primary end point of the ability of this study (to assess superiority of lipegfilgrastim over placebo) was predicated upon an assumed background incidence of febrile neutropaenia of 7 to 10% in the placebo arm.

Patients were randomised 2:1 to receive either 6 mg Lonquex® or placebo. The primary end point was the incidence of febrile neutropaenia. Randomisation yielded comparable baseline demographic characteristics, stage of disease and median duration since first diagnosis. More than 85% of both arms had the Eastern Cooperative Oncology Group (ECOG) status 0 or 1.[6] There was, however, an imbalance in the proportion of patients across tumour histological type:

Table 14: Baseline disease characteristics

Variable	Placebo (N=125)	XM22 6 mg (N=250)
	n (%)	n (%)
Stage (at enrolment in study)		
Stage IIIB	49 (39.2)	97 (38.8)
Stage IV	76 (60.8)	152 (60.8)
Not known	0 (–)	1 (0.4)
Histology		
Squamous carcinoma	72 (57.6)	168 (67.2)
Adenocarcinoma	40 (32.0)	56 (22.4)
Large cell carcinoma	4 (3.2)	7 (2.8)
Other	3 (2.4)	8 (3.2)
Not known	6 (4.8)	11 (4.4)
ECOG performance status		
0	19 (15.2)	28 (11.2)
1	96 (76.8)	194 (77.6)
2	10 (8.0)	28 (11.2)
Months since first diagnosis		
Mean ± SD (Median) Range	3.4 ± 9.1 (1.0) 0.0 to 58.0	2.4 ± 6.2 (1.0) 0.0 to 52.0

This study did not meet its primary end point; the incidence of febrile neutropaenia was not different between the placebo and lipegfilgrastim arms (odds ratio 0.39, 95% CI 0.121, 1.260, p=0.115). The incidence of febrile neutropaenia was not different between the treatment arms for Cycles 2 to 4.

However, the secondary outcomes of the study (incidence and duration of severe neutropaenia) both favoured the lipegfilgrastim arm.

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

*Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group.

6 *Am J Clin Oncol.* 1982;5:649-655.

Despite the lack of difference in incidence of febrile neutropaenia in this study, the incidence of hospitalisation due to febrile neutropaenia was significantly better in the lipegfilgrastim arm.

The secondary end points of chemotherapy dose reduction or omission was not different between the two treatment arms for Cycles 2 to 4. However there was a significant reduction in chemotherapy dose delays in the lipegfilgrastim arm for Cycles 2 to 4.

Safety

In Study XM22-03, the incidence of adverse events was comparable between the patients exposed to lipegfilgrastim and pegfilgrastim, with the listing of preferred terms being comparable between agents (see Table 15 below).

Table 15: Incidence of adverse events listed by MedDRA* Preferred Term

MedDRA Preferred Term	pegfilgrastim 6 mg (N=101)		Lonquex® 6 mg (N=101)	
	n	%	n	%
Alopecia	86	85.1	93	92.1
Nausea	52	51.5	61	60.4
Asthenia	29	28.7	28	27.7
Neutropenia	32	31.7	26	25.7
Bone pain	10	9.9	14	13.9
Erythema	12	11.9	12	11.9
Leukopenia	8	7.9	12	11.9
Diarrhoea	12	11.9	10	9.9
Vomiting	4	4.0	10	9.9
Anaemia	9	8.9	9	8.9
Myalgia	6	5.9	9	8.9
Headache	5	5.0	9	8.9
Decreased appetite	9	8.9	7	6.9
Dizziness	2	2.0	6	5.9
Fatigue	7	6.9	5	5.0
Stomatitis	7	6.9	5	5.0
Arthralgia	2	2.0	5	5.0
Dysgeusia	5	5.0	3	3.0

*MedDRA or Medical Dictionary for Regulatory Activities is a clinically validated international medical terminology dictionary (and thesaurus) used by regulatory authorities in the pharmaceutical industry during the regulatory process, from pre-marketing to post-marketing activities, and for data entry, retrieval, evaluation, and presentation. In addition, it is the adverse event classification dictionary endorsed by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

In the placebo-controlled Study XM22-04, treatment-emergent AEs of alopecia, anaemia, hypokalaemia, fatigue and pain were reported in the lipegfilgrastim arm.

Table 16: Study XM22-04, treatment-emergent AEs

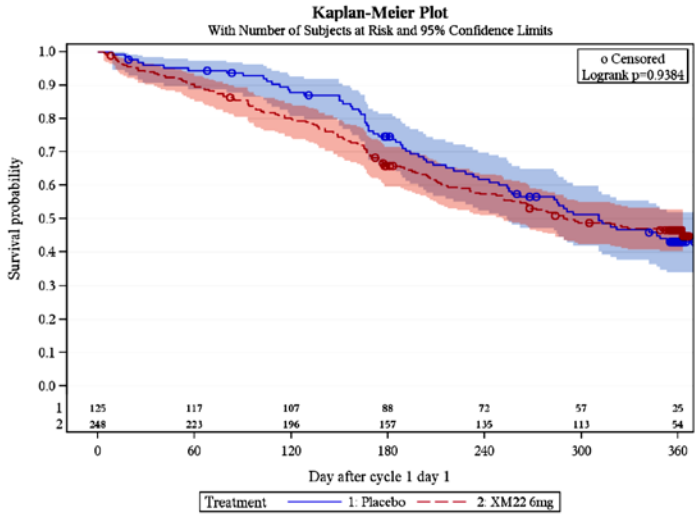
MedDRA Preferred Term	Placebo (N=125)		Lonquex® 6 mg (N=248)	
	n	%	n	%
Alopecia	42	33.6	101	40.7
Anaemia	30	24.0	63	25.4
Nausea	27	21.6	59	23.8
Neutropenia	44	35.2	51	20.6
Thrombocytopenia	10	8.0	32	12.9
Asthenia	23	18.4	28	11.3
Vomiting	15	12.0	28	11.3
Decreased appetite	12	9.6	23	9.3
Hypokalaemia	3	2.4	20	8.1
Leukopenia	14	11.2	16	6.5
Fatigue	6	4.8	16	6.5
Disease progression	5	4.0	16	6.5
Non-small cell lung cancer	4	3.2	16	6.5
Chest pain	8	6.4	14	5.6
Pyrexia	6	4.8	12	4.8
Hypophosphataemia	2	1.6	12	4.8
Weight decreased	2	1.6	12	4.8
Febrile neutropenia	10	8.0	11	4.4
Dyspnoea	9	7.2	11	4.4
Dizziness	4	3.2	9	3.6
Headache	4	3.2	9	3.6
Arthralgia	2	1.6	9	3.6
Haemoptysis	5	4.0	7	2.8
Diarrhoea	4	3.2	7	2.8
Back pain	2	1.6	6	2.4
Cough	3	2.4	5	2.0
Tachycardia	2	1.6	5	2.0
Abdominal pain upper	1	0.8	5	2.0
Blood phosphorus decreased	1	0.8	5	2.0
Bone pain	1	0.8	5	2.0
Hyperkalaemia	1	0.8	5	2.0
Pain	1	0.8	5	2.0
Pneumonia	4	3.2	4	1.6
Atrial fibrillation	5	4.0	3	1.2
Lung neoplasm malignant	3	2.4	3	1.2
Pain in extremity	3	2.4	3	1.2
Insomnia	3	2.4	2	0.8
Wheezing	3	2.4	2	0.8

Deaths

In XM22-04, there was an imbalance in mortality during the treatment-emergent phase of the study, however as discussed above, there was an imbalance at baseline in tumour histology type between the treatment arms, with neither survival nor disease progression being assessed a priori. The sponsors responses demonstrated that no deaths in this study were assessed as being 'likely' to be related to study medication, but were due to either the underlying disease or associated morbidity.

Mortality was not statistically significantly worse for the lipegfilgrastim arm during the period of administration, as demonstrated in the explorative survival analysis, with one year follow-up. The 95% confidence intervals of hazard of death for each treatment arm do not separate (Figure 9).

Figure 9: Kaplan-Meier plot of survival probability versus day after Cycle 1 Day 1



Furthermore, data requested at the pre-submission meeting of hazard of survival split at treatment cycle demonstrates that the 95% CI of the hazard ratios for each treatment arm do not separate across each of the four cycles. This additional analysis is supportive of registration.

One death occurred in Study XM22-03 as a result of enterocolitis but was considered not related to lipegfilgrastim exposure.

Discontinuations

Among the patients in XM22-03, there was a comparable, low incidence of premature discontinuation for patients exposed to lipegfilgrastim and placebo.

In Study XM22-04, the proportion of patients discontinuing due to adverse events were comparable between placebo and lipegfilgrastim.

With respect to laboratory tests, there were no reported significant changes in liver or renal function across the studies.

Immunogenicity

The evaluator states that '*there were no significant issues within the studies*'. The PI reports a risk of 'skin reactions', 'rash' and 'injection site reactions', which are consistent with the class of medicine.

Leukocytosis

Three patients were identified as experiencing the MedDRA term leucocytosis; two patients had Grade II and one Grade I and all events resolved.

The reported incidence of leucocytosis >100x10^9/L from pegfilgrastim exposure (as per the currently approved PI) is <0.5%. No patients experienced a white cell count >100x10^9/L with lipegfilgrastim exposure.

Ten patients were identified as experiencing a white cell count >50x10^9/L, an incidence of 10/785 (1.3%): nine were exposed to lipegfilgrastim and one to placebo.

No subjects were reported as experiencing leukostasis syndrome.

ECG changes

In Study XM22-03, the incidence of ST-T wave changes and increases in QTcF duration[7] were seen in similar proportions of the lipegfilgrastim and pegfilgrastim arms.

Risk management plan

The second round RMP evaluation was supportive of registration. The evaluator suggested PI amendments to the Delegate:

1. Regarding use in children, it is recommended that the Delegate considers adding a statement 'treatment in this patient group is not recommended.' The Delegate agrees with this advice.
2. The indication should reflect that of the SmPC, in that patients with Myeloid leukaemia or myelodysplastic syndrome should not be treated, and reflected in the indication. The Delegate agrees with this advice (see below).

Risk-benefit analysis

Delegate's considerations

In Australia, the currently approved products filgrastim and pegfilgrastim are the standard of care for patients requiring treatment for the myelosuppressive effects of cytotoxic chemotherapy. Given the clinical experience of use of filgrastim and pegfilgrastim, with the benefit of the safety and efficacy of lipegfilgrastim has to be measured against these currently approved therapies.

Efficacy

The totality of evidence presented favours the registration of lipegfilgrastim.

The observed incidence of febrile neutropaenia in Study XM22-04 was lower (1%) than was anticipated in the statistical analysis plan (7 to 10%), precluding the study from being able to satisfactorily assess a difference in incidence of febrile neutropaenia. However, the secondary end-points of this study were supportive of the efficacy benefit of lipegfilgrastim. Study XM22-03 demonstrated non-inferiority of lipegfilgrastim to pegfilgrastim.

The sponsor confirms in their response to clinical Question 4 that no efficacy data exists for the use of lipegfilgrastim when used in more than four consecutive cycles of cytotoxic chemotherapy.

The reports of post-marketing efficacy experience of lipegfilgrastim in the EU did not yield any new concerns for efficacy.

Safety

In regard to the imbalance in mortality during the placebo controlled period of the randomised controlled Study XM22-04, the sponsor sates in their response to clinical Question 9 that despite randomisation '*unfavourable prognostic factors, risk factors and baseline covariate were not necessarily equally distributed between the two treatment groups*'. This study neither assessed survival nor disease progression as a primary

[7]In cardiology, the QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. The QT interval represents electrical depolarisation and repolarisation of the ventricles. A lengthened QT interval is a marker for the potential of ventricular tachyarrhythmias like torsades de pointes and a risk factor for sudden death. The QT interval is dependent on the heart rate (the faster the heart rate the shorter the R-R Interval and QT interval) and may be adjusted (QTcF) to improve the detection of patients at increased risk of ventricular arrhythmia.

outcome measure and thus any observed differences are not necessarily due solely to the difference in effect of lipegfilgrastim and placebo.

Lipegfilgrastim and pegfilgrastim both contain the parent molecule filgrastim. According to their respective product information documents, for patients who develop hypersensitivity to either filgrastim or pegfilgrastim, cessation of the drug is mandated; these patients with hypersensitivity cannot be subsequently treated with lipegfilgrastim (as per the proposed PI) and as such this product does not offer a new therapeutic option to them.

The sponsor confirms in their response to clinical Question 4 that no safety data exists for the use of lipegfilgrastim when used in more than four consecutive cycles of cytotoxic chemotherapy. The safety data presented in the two Periodic Safety Update Reports (PSURs) were supportive of registration.

Indication

The proposed indication is *dissimilar* to that is approved in all other jurisdictions.

The TGA's Pharmaceutical Subcommittee (PSC) advised that (in the event of registration) the wording of the proposed Australian indication should include the exception of use in patients with CML and myelodysplastic syndromes as included in the EU indication.

The Delegate considers the appropriate indication to be:

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

Deficiencies of the data

The safety and efficacy of lipegfilgrastim in patients treated in the studies presented for evaluation were for a maximum of four cycles (that is, four doses of study drug). In the sponsor's response to clinical Question 4, the sponsor states that '*no data are available for higher number of injections*'.

The data as presented in clinical trials section of the PI contains biologically implausible values for the duration of severe neutropaenia. The data for duration of severe neutropaenia in Tables 1 and 2 [of PI] reports the mean ± SD for data which is non-normally distributed, leading to a negative 95% confidence interval. The appropriate measure of spread of data should be used.

The effect of moderate and severe renal impairment on PK of lipegfilgrastim has not been studied.

The effect of hepatic impairment on PK of lipegfilgrastim has not been studied.

No studies of pharmacokinetic interactions were submitted.

The effect on the PK of lipegfilgrastim in patients > 95kg compared to those below this weight has not yet been established.

Summary of Issues

The Delegate disagrees with wording of the sponsors' proposed indication.

The maximum dosage of Lonquex that can be safely administered has not been established (4 cycles are the maximum studied)

The effects of moderate or severe renal impairment or any degree of liver impairment have not been studied

Proposed regulatory action

The Delegate considers that given the data presented in the dossier and in response to the TGA's questions, there is sufficient evidence that the safety and efficacy of lipegfilgrastim has been satisfactorily established for registration to proceed.

Therefore, the Delegate had no reason to say, at this time, that the application for the product should not be approved for registration.

Conditions of Registration

Consistent with the action of the sponsor in agreeing to provide the results of PASS studies to the EMA and Israeli regulator, these studies should be submitted for evaluation to the TGA when available.

Request for ACPM advice

The committee is requested to provide advice on any issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

The main part of the sponsor's Pre-Advisory Committee on prescription Medicines (ACPM) response dealt with the TGA's comments on the PI documentation.

Indications

The clinical evaluator does not support the wording of the proposed indication. The clinical evaluator recommends to the Delegate that the wording of the EU indication is appropriate.

Sponsor's response (17 August 2015):

The applicant has amended the indication as follows:

> *Lonquex® is indicated 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)*

This is identical to the wording used in the current EU SmPC (16 June 2015) with one exception: the indication in the EU SmPC specifies 'adult patients' whereas this limitation is addressed under 'Precautions, Paediatric use' in the proposed Australian PI. In the sponsor's response to the RMP Evaluation Report, the evaluator acknowledged that paediatric studies (Studies XM22-07 and XM22-08) are initiated as part of the XM22 Paediatric Investigation Plan (PIP), approved by the EU Paediatric Committee on the 6 May 2011. Furthermore the results of Study XM22-07 were included with the sponsor's response (except for follow-up data) along with the revisions to the EU SmPC agreed with the EMA to include the paediatric population following their evaluation of this study. The applicant acknowledges that a separate post-approval variation application will be required in Australia in order to have these data reported in the PI. However, the applicant considers that the proposed text in the proposed PI explicitly excludes paediatric use and adequately minimises the potential for off-label use in this population.

Sponsor's response (9 September 2015):

Further to the response provided with our submission on the 17 August, the sponsor agrees to adopt identical wording of the EU indication (that is, restricted to 'adult' patients, should this be the Delegate's preferred approach to identifying the data limitations in children). The indication has been amended as follows:

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

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM resolved to recommend to the TGA Delegate of the Minister and Secretary that:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, considered Lonquex solution for injection containing 6 mg/0.6 mL of lipegfilgrastim to have an overall positive benefit–risk profile for the amended indication;

> *Lonquex is indicated for the reduction in the duration of neutropenia in adult patients with malignancy (except chronic myeloid leukaemia and myelodysplastic syndromes) treated with cytotoxic chemotherapy regimens determined to be of significant risk of prolonged neutropenia and infection or when individual patient risk factors justify its use.*

In making this recommendation the ACPM;

- Was of the view that the indication should not include 'reduction of febrile neutropenia' reflecting the results of Study XM-22-04, where the primary endpoint, incidence of febrile neutropenia, was not met.
- Advised that limiting the indication to adults was appropriate as there were limited data for use in the paediatric population.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACPM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI) and specifically advised on the inclusion of the following:

- Under Pharmacokinetics: *Absorption*, clarify whether the repeated administration (Cycle 4) information relates to healthy subjects or patients.
- Review the placement of Figure 1, as it comes under the title of *'Patients with renal or hepatic impairment'* which is confusing.
- In the CMI:
  - Under 'What is Lonquex used for' change '….and this will reduce your chance of developing infections' to '…and this *may* reduce your chance of developing infections'.
  - Under 'When you must not use it' remove 'any other substances, such as foods, preservatives or dyes' after the wording 'If you have *an allergies* to…'

Specific Advice

The ACPM advised the following in response to the Delegate's specific questions on this submission:

1. The committee is requested to provide advice on any issues that it thinks may be relevant to a decision on whether or not to approve this application.

The ACPM had some concerns regarding the pharmacokinetic data and the dose selected and queried whether the 6 mg dose was the most appropriate dose for lipegfilgrastim.

The ACPM was concerned that the efficacy data did not strictly support the indication. The ACPM noted that the primary endpoint of Study XM-22-04, the incidence of febrile neutropenia, was not met. However, the secondary outcomes, the incidence and duration of severe neutropenia, were met. The ACPM also noted that the chemotherapy used in this study did not normally require the administration of G-CSF. Study XM-22-03, where the primary endpoint, duration of severe neutropenia, lipegfilgrastim demonstrated non-inferiority to pegfilgrastim. The ACPM advised that the indication should be modified to better reflect the results of the clinical trials and suggested removal of *'...incidence of febrile neutropenia'*.

The ACPM was of the view that use of lipegfilgrastim should be limited to use in adults as insufficient data were presented for use in the paediatric population.

The ACPM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Lonquex solution for injection, prefilled syringe containing lipegfilgrastim rbe 6 mg/0.6 mL, indicated for:

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

Specific conditions of registration applying to these goods

1. The Lonquex EU-RMP version 8.2 dated 30 April 2015 (data lock point 25 January 2015), Australian Specific Annex dated 26 June 2015, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
2. It is a condition of registration that, as a minimum, the first five independent batches of Lonquex lipegfilgrastim (rbe) 6 mg/0.6 mL solution for injection, prefilled syringe imported into Australia are not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Office of Laboratories and Scientific Services (OLSS).

Attachment 1. Product Information

The PI approved for Longquex at the time this AusPAR was published is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

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