5.03 LIPEGFILGRASTIM INJECTION, 0.6MG/0.6ML, LONQUEX®, TEVA PHARMA AUSTRALIA PTY LTD.

1 Purpose of Application

1.1 The submission requested a Section 100 (Highly Specialised Drugs Program), Authority Required, listing for lipegfilgrastim for reduction in the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy.

2 Requested listing

2.1 The abridged requested listing is shown below:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
LIPEGFILGRASTIM			$[redacted][a]	TEVA Pharma
6 mg/0.6mL, 1 x 0.6 mL syringe	1	11	$[redacted][b]	Lonquex® Australia Pty Ltd

Section 100 Highly Specialised Drug Program

[a]private hospital; [b]public hospital

2.2 Indications included breast cancer, acute myeloid leukaemia, B cell chronic lymphocytic leukaemia, Hodgkin disease, myeloma, germ cell tumours, squamous cell carcinoma, acute lymphoblastic leukaemia, non-Hodgkin lymphoma and sarcoma, with all requested restrictions being consistent with those for which pegfilgrastim is currently listed.

2.3 The requested basis for listing was a cost-minimisation analysis versus pegfilgrastim, with a [redacted]% price reduction on the current ex-manufacturer price [redacted].

2.4 Noting that the PBS indications for filgrastim and pegfilgrastim are not completely aligned, the ESC suggested that the PBAC clarify the specific indications it would be appropriate to recommend for PBS listing.

For more detail on PBAC's view, see section 7 "PBAC outcome"

3 Background

3.1 Lipegfilgrastim was TGA registered on 29 October 2015 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).

3.2 This was the first submission for lipegfilgrastim considered by the PBAC.

3.3 Pegfilgrastim was listed on the PBS on 1 February 2003 on a cost minimisation basis compared to filgrastim with 6 mg being considered equivalent to filgrastim injection 5ug/kg/day for 11.25 days. Since then the ex-manufacturer price of filgrastim has been reduced by approximately [redacted]%. The drug costs to treat a 73 kg patient with filgrastim injection 5 micrograms/kg/day for 11.25 days would be $[redacted]. 73 kg is the average weight of patients in the lipegfilgrastim trials, Studies 02 and 03.

For more detail on PBAC's view, see section 7 "PBAC outcome"

4 Clinical place for the proposed therapy

4.1 Lipegfilgrastim was proposed to be an alternative to pegfilgrastim. The PBAC agreed that it may also be an alternative to filgrastim and lenograstim.

For more detail on PBAC's view, see section 7 "PBAC outcome"

5 Comparator

5.1 The submission nominated pegfilgrastim as the main comparator. The ESC agreed that pegfilgrastim would be the agent most likely to be replaced, however, that there would also be some substitution for filgrastim, and although it may not be the main comparator, it could be considered a comparator.

5.2 The PBAC agreed with the ESC that filgrastim was also an appropriate comparator.

For more detail on PBAC's view, see section 7 "PBAC outcome"

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from a health professional (1) via the consumer comments facility on the PBS website. The comment described how lipegfilgrastim would be used to prevent neutropenia and lessen the risk of septic infection in patients receiving chemotherapy.

Clinical trials

6.3 The submission was based on two head-to-head trials comparing lipegfilgrastim to pegfilgrastim (n=410).

6.4 Details of the trials presented in the submission are provided in Table 1.

Table 1: Trials and associated reports presented in the submission

Trial	Protocol title/ Publication title	Publication citation
Direct randomised trials of lipegfilgrastim versus pegfilgrastim – pivotal trials		
Study 02 (XM22-02)	BioGeneriX XM22-02: Dose-finding of a fixed dose XM22 in patients with breast cancer receiving 4 cycles of chemotherapy versus 6 mg Neulasta®, TEVA.	Clinical Study Report
	Buchner A, Elsässer R, and Bias P. (2014). A randomized, double-blind, active control, multicenter, dose-finding study of lipegfilgrastim (XM22) in breast cancer patients receiving myelosuppressive therapy.	*Breast Cancer Res Treat*; 148:107-116
	Buchner A, Bias P and Kaufmann M. (2011). A randomized, double-blind, active control, multicenter, dose-finding study of XM22, glycopegfilgrastim, in patients with breast cancer receiving myelosuppressive therapy.	*Journal of Clinical Oncology,* 29 (15 SUPPL. 1)
	Buchner A, Bias P, Kaufmann M and Mueller U. (2012). A randomized, double-blind, active control, multicenter, dose finding study of lipegfilgrastim in breast cancer patients receiving myelosuppressive therapy.	*Supportive Care in Cancer,* 20: S240.
Study 03 (XM22-03)	BioGeneriX XM22-03: Efficacy and safety of XM22 compared to pegfilgrastim in patients with breast cancer receiving chemotherapy, TEVA.	Clinical Study Report
	Bondarenko I, Gladkov OA, Elsässer R, Buchner A and Bias P. (2013). Efficacy and safety of lipegfilgrastim versus pegfilgrastim: a randomized, multicenter, active-control phase 3 trial in patients with breast cancer receiving doxorubicin/docetaxel chemotherapy.	*BMC cancer,* 13: 386.
	Bondarenko I, Gladkov O, Elaesser R, Buchner A and Bias P. (2012). Efficacy and safety of lipegfilgrastim compared with pegfilgrastim in patients with breast cancer who are receiving chemotherapy.	*Journal of Clinical Oncology,* 30 (15 SUPPL. 1).
	Bondarenko I M, Gladkov OA, Elässer R, Buchner A, Bias P and Mueller U. (2012). Efficacy and safety of lipegfilgrastim compared with pegfilgrastim in patients with breast cancer who are receiving chemotherapy.	*Supportive Care in Cancer,* 20: S241-S242.
	Gladkov O, Buchner A, Bias P, Mueller U and Elsässer R. (2013). Chemotherapy-associated treatment burden in breast cancer patients receiving lipegfilgrastim or pegfilgrastim: Secondary efficacy data from a phase III study.	*Haematologica,* 98: 426.
	Gladkov OA, Bondarenko IM, Elsässer R, Buchner A and Bias P. (2012). Absolute neutrophil counts in a study of lipegfilgrastim compared with pegfilgrastim in patients with breast cancer who are receiving chemotherapy.	*Annals of Oncology,* 23: ix500.
	Udo M., Bondarenko I, Gladkov O, Elässer R, Buchner A and Bias P. (2012). Efficacy and safety of lipegfilgrastim compared with pegfilgrastim in patients with breast cancer who are receiving chemotherapy.	*Haematologica,* 97: 553.
	Bondarenko I, Bias P, Elsasser R, Buchner, A. (2013). Analysis of ANC recovery from a Phase III study of lipegfilgrastim versus pegfilgrastim in patients with breast cancer receiving doxorubicin/docetaxel chemotherapy	European Journal of Cancer, *49: S434-S435.*
	Gladkov OA, Buchner A, Bias P, Muller U, Elsasser R. (2016). Chemotherapy-associated treatment burden in breast cancer patients receiving lipegfilgrastim or pegfilgrastim: secondary efficacy data from a phase III study.	Supportive Care in Cancer, *24 (1): 395-400.*

Texts in italics are publications identified during the evaluation
Source: Table B.2-1, ppB-13-B-14 of the submission

6.5 The key features of the direct randomised trials are summarised in Table 2.

Table 2: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Primary outcome	Use in economic evaluation
Randomised controlled trials of lipegfilgrastim versus pegfilgrastim – pivotal evidence						
Study 02 (XM22-02)	208	R, MC, DB 12 weeks	Low	Patients with breast cancer treated with chemotherapy	Duration of severe	Yes

Study 03 (XM22-03)	202	R, MC, DB 12 weeks	Low	consisting of doxorubicin 60mg/m^2 and docetaxel 75mg/m^2 given every 3 weeks.	neutropenia[a] (DSN) in days in cycle 1	

DB=double blind; MC=multi-centre; R=randomised.

[a] defined as grade 4 neutropenia with an absolute neutrophil count (ANC) <0.5x10^9/L

[b] FN was defined to have occurred if at least one of the following conditions held true during a CTX cycle:
- Oral body temperature >38.5°C for at least 1 hour (2 consecutive measurements on the same day, at least 60 minutes apart) and an observed severe neutropenia (i.e. absolute neutrophil count (ANC) value <0.5x10^9/L) on the day before, on the same day or on the day after the elevated temperature readings.
- Documentation of neutropenic sepsis, i.e. a sepsis in combination with an ANC value <0.5x10^9/L.
- Documentation of serious or life-threatening neutropenic infection, i.e. a life-threatening infection in combination with an ANC value <0.5x10^9/L.

Source: compiled during the evaluation

6.6 Study 02 (XM22-02) was a phase II dose-ranging study comparing 3 mg, 4.5 mg and 6 mg lipegfilgrastim versus 6 mg pegfilgrastim. As only the 6 mg dose is TGA-approved, only details and results relating to this dose are reported. Study 03 (XM22-03) was a non-inferiority trial comparing 6 mg lipegfilgrastim versus 6 mg pegfilgrastim. All trials were randomised and double-blind and considered to be at a low risk of bias.

6.7 No evidence is presented comparing lipegfilgrastim with filgrastim.

Comparative effectiveness

6.8 Table 3 summarises the results for the primary outcome in the direct head-to-head randomised trials comparing lipegfilgrastim and pegfilgrastim.

Table 3: Results of the primary outcome of duration of severe neutropenia across the head-to-head randomised trials comparing lipegfilgrastim and pegfilgrastim

	Study 02 (XM22-02)		Study 03 (XM22-03)	
	Lipegfilgastrim	Pegfilgastrim	Lipegfilgastrim	Pegfilgastrim
ITT population				
N	50	54	101	101
Mean (SD)	0.76 (1.10)	0.87 (0.99)	0.7 (1.0)	0.9 (0.9)
LS Mean (95% CI)	- [redacted]		- [redacted]	
Meta-analysis	- [redacted]			
PP population				
N	48	54	94	94
Mean (SD)	[redacted]		0.7 (0.9)	0.8 (0.9)
LS Mean (95% CI)	- [redacted]		-0.218 (-0.496, 0.062)	
Meta-analysis	- [redacted]			

ITT=intention to treat; PP=per protocol, LS mean=least squares mean, CI=confidence interval

Source: Table B.6-2, pB-70 and Figure B.6-1, pB-69 of the submission

6.9 There was no statistically significant difference between lipegfilgrastim 6 mg and pegfilgrastim 6 mg for the primary outcome of duration of severe neutropenia in days for either the intention to treat (ITT) or the per protocol (PP) population in the individual trials and in the meta-analyses. The upper 95% limits of the meta-analyses were [redacted] and [redacted] for the ITT and PP populations, respectively, and the non-inferiority criterion that the duration of severe neutropenia difference was smaller than 1 day was met in both analyses.

6.10 In response to whether a non-inferiority criterion of less than one day for the duration of severe neutropenia was a reasonable threshold for establishing non-inferiority in terms of effectiveness, the PSCR (p.1) argued that the non-inferiority margin of one day was pre-specified in the pivotal phase 3 lipegfilgrastim non-inferiority study (Study 03).

6.11 The clinical evidence provided in the submission was limited to patients being treated with chemotherapy for breast cancer, whereas the requested listing was for multiple indications. The PBAC has previously stated that "… it would flow-on any future new PBS-eligible patient populations recommended for pegfilgrastim to filgrastim because continuing flexibility in treatment options for the prophylaxis of chemotherapy induced febrile neutropenia is an important objective" (Pegfilgrastim PSD, November 2008). It is not clear whether this consideration can be interpreted to mean that establishing comparative effectiveness and safety in a single population supports use in other indications, as suggested by the submission. However, if this is implied, consideration is required as to whether it should also extend to lipegfilgrastim.

6.12 The PSCR (p.1) argued that "recommendations for the use of G-CSFs in international guidelines are based on the prevalence of febrile neutropenia, rather than use with specific chemotherapy regimens and/or cancer types, thus the clinical trial evidence provided for lipegfilgrastim can validly be "flowed on" or generalised to other PBS indications in which the value of G-CSF therapy following myelosuppresive chemotherapy is recognised". The ESC considered that the efficacy of lipegfilgrastim is unlikely to be affected by the type of cancer/chemotherapy regimen and that there is no signal to suggest dissimilar efficacy to pegfilgrastim for other regimens. The ESC noted that the Pre-Sub-Committee Response (PSCR) (p.1) highlighted two ongoing studies investigating lipegfilgrastim efficacy when used in patient receiving other chemotherapy regimens.

Comparative harms

6.13 Table 4 summarises the incidence of adverse events in the trials.

Table 4: Incidence of adverse events in the trials

	Study 02; n (%)		Study 03, n (%)		Meta-analysis
	Lipeg; N=50	Peg; N=54	Lipeg; N=101	Peg, N=101	RR (95% CI)[a]
Treatment emergent adverse events (TEAE)					
Any TEAE	[redacted]	[redacted]	100 (99.0)	99 (98.0)	[redacted]
Serious TEAE	[redacted]	[redacted]	3 (3.0)	7 (6.9)	[redacted]
Severe TEAE	[redacted]	[redacted]	26 (25.7)	35 (34.7)	[redacted]
Discontinued due to TEAE	[redacted]	[redacted]	3 (3.0)	2 (2.0)	[redacted]
Death	[redacted]	[redacted]	1 (1.0)	0 (0)	[redacted]
Treatment-emergent adverse drug reactions (TEADR)					
Related TEAE=TEADR	[redacted]	[redacted]	28 (27.7)	26 (25.7)	[redacted]
Serious TEADR	[redacted]	[redacted]	1 (1.0)	1 (1.0)	[redacted]
Severe TEADR	[redacted]	[redacted]	1 (1.0)	2 (2.0)	[redacted]
Discontinued due to TEADR	[redacted]	[redacted]	0 (0)	1 (1.0)	[redacted]

Lipeg=lipegfilgrastim, Peg=pegfilgrastim, RR=relative risk, CI=confidence interval; TEAE=treatment emergent adverse event

[a] *estimated during the evaluation using StatsDirect*

Source: Table B.6-14, pB103 and Table B.6-15, pB-104 of the submission

Clinical claim

6.14 The submission describes lipegfilgrastim as non-inferior in terms of comparative effectiveness and non-inferior in terms of comparative safety over pegfilgrastim. This claim was adequately supported (if the PBAC accepts that a non-inferiority criterion of less than one day for the duration of severe neutropenia is reasonable and that the PBS population is not significantly heavier than those enrolled in the trials as there is uncertainty regarding the efficacy of lipegfilgrastim in those weighing >80kg, see below) from the evidence presented for patients being treated with chemotherapy for breast cancer. Consideration is required as to whether this claim would extend to other indications.

6.15 The ESC considered that the submission's clinical claim of non-inferior comparative effectiveness and non-inferior comparative safety over pegfilgrastim was reasonable.

6.16 The PBAC considered that the claim of non-inferior comparative effectiveness was reasonable.

6.17 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

Economic analysis

6.18 The equi-effective doses are estimated as lipegfilgrastim 6 mg once per chemotherapy cycle and pegfilgrastim 6 mg once per chemotherapy cycle. There is uncertainty regarding the efficacy of lipegfilgrastim in those weighing >80 kg: the TGA-approved PI for lipegfilgrastim indicates that "[a] statistically significant difference in lipegfilgrastim exposure was observed between the heaviest (>80 kg) and the lightest (<60 kg) subjects studied. Exposure in the heaviest patients was approximately 30% that of the exposure in the lightest subjects. A decrease in efficacy cannot be excluded in patients >80 kg from the currently available data". Should a decrease in efficacy be observed among heavier patients, the assumption that a single syringe of lipegfilgrastim would substitute for a single syringe of pegfilgrastim may not hold.

6.19 The PSCR (p.3) argued that there is no demonstrated clinical impact of patient weight on the clinical efficacy of lipegfilgrastim and that a review of the pharmacodynamic study data shows that lipegfilgrastim provides greater absolute neutrophil counts across all weight classes/groups and that an analysis of the primary outcome data by patient weight shows no statistically or clinically significant differences in duration of severe neutropenia between lipegfilgrastim and pegfilgrastim in any weight subgroups.

6.20 The submission offered a [redacted]% discount on the ex-manufacturer price [redacted]

6.21 The ESC noted that should the PBAC consider filgrastim a comparator, under the National Health Act (1953), the PBAC could only recommend lipegfilgrastim at a higher price than filgrastim if it was satisfied that lipegfilgrastim provides, for some patients, a significant improvement in efficacy and/or reduction of toxicity over the alternate therapy or therapies. The ESC further noted that pegfilgrastim was recommended for PBS listing on a cost-minimisation basis with filgrastim. The Pre-PBAC Response (p.1) argued that pegfilgrastim would be the therapy predominantly substituted and included comments from two clinicians that elaborated on the differences in clinical use between pegfilgrastim and filgrastim.

6.22 The PBAC noted the Pre-PBAC Response, however considered that filgrastim is a relevant comparator and that its price is informative for the consideration of lipegfilgrastim.

6.23 Based on dosing of 5 micrograms/kg per day for 11.25 days, with an average weight of 73 kg (based on the average weight of patients in the lipegfilgrastim trials, Studies 02 and 03), the current cost of filgrastim is $[redacted] (total dose of 4,106.25 micrograms filgrastim at $[redacted] per microgram). This compares with an ex-manufacturer price of $[redacted] for lipegfilgrastim. The Pre-PBAC Response (p.2) disputed the ESC's calculation of the current filgrastim cost, and proposed a method of calculation that resulted in a cost of $[redacted], and proposed that this price is not substantially different from the anticipated price at listing of $[redacted] per syringe, which includes the 5% 1 April 2016 price reduction from the submission's original proposed price.

6.24 The PBAC considered that the appropriate price should be calculated using the average cost of filgrastim across the patient population.

Drug cost/patient/course:

	Lipegfilgrastim – requested DPMQ	Pegfilgrastim – current DPMQ
Private	$[redacted] (assuming 4 cycles of treatment)	$7,887.72 (assuming 4 cycles of treatment)
Public	$[redacted] (assuming 4 cycles of treatment)	$7,700.00 (assuming 4 cycles of treatment)

6.25 Should the requested price for lipegfilgrastim flow-on to pegfilgrastim, the drug cost/patient/course for both would be as estimated for lipegfilgrastim.

Estimated PBS usage & financial implications

6.26 This submission was not considered by DUSC.

6.27 The submission utilised PBS usage data for filgrastim, lenograstim and pegfilgrastim from the 2000/2001 to 2014/2015 financial years. Based on this usage, three approaches were taken to extrapolate the likely growth of the G-CSF market over the forward projections:

1. A second-order polynomial (base case analysis);
2. Linear extrapolation (tested in sensitivity analysis); and
3. Assuming a 7% growth rate in the market in each year (tested in sensitivity analysis).

6.28 The submission assumed in the base case of the financial estimates that lipegfilgrastim would only substitute for pegfilgrastim (and not for filgrastim or lenograstim). The assumed market uptake rates are [redacted]% in year 1, [redacted]% in year 2 and [redacted]% in years 3-5. All of the cost savings estimated is attributable to the price reduction offered for lipegfilgrastim which is expected to flow-on to pegfilgrastim. The price reduction would affect all forecast scripts of pegfilgrastim in the forward estimates (not just the proportion assumed to be substituted for by lipegfilgrastim). The estimates also relied on one syringe of lipegfilgrastim substituting for one syringe of pegfilgrastim, such that subsequent substitution of pegfilgrastim with lipegfilgrastim would be cost neutral.

Table 5: Estimated use and financial implications

	2016/2017	2017/2018	2018/2019	2019/2020	2020/2021
Cost of listing lipegfilgrastim					
Number of G-CSF scripts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion pegfilgrastim	80%	80%	80%	80%	80%
Number pegfilgrastim scripts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Uptake rate for lipegfilgrastim	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Number lipegfilgrastim scripts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Private (43%)/ Public (57%)[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of lipegfilgrastim[b]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to PBS/RPBS[c]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Cost savings assumed from the reduced-price flow-on to pegfilgrastim					
Total number pegfilgrastim scripts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Private (43%) Public (57%)[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost pegfilgrastim (if Lipeg not listed)[d]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost pegfilgrastim (if Lipeg not listed)[c]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Lipeg listed and price reduction flows on to Peg[b]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost pegfilgrastim (if Lipeg listed)[c]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net savings to the PBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Lipeg=lipegfilgrastim, Peg=pegfilgrastim

[a] based on private/public use of pegfilgrastim

[b] assuming DPMQ of $[redacted] for private and $[redacted] for public hospitals

[c] co-payment based on proportional use of pegfilgrastim, PBS=$[redacted]; RPBS=$[redacted]

[d] assuming DPMQ of $[redacted] for private and $[redacted] for public hospitals

The redacted table shows that at year 5, the estimated number of scripts was 10,000-50,000 and the net cost saving to the PBS would be $10 - $20 million.

6.29 The estimated cost saving were dependent on the price reduction proposed for lipegfilgrastim to flow-on to pegfilgrastim and the magnitude of the savings were dependent on the growth of the market. Substitution of pegfilgrastim to use of lipegfilgrastim may also have an impact if the assumption that one syringe of lipegfilgrastim would substitute for one syringe of pegfilgrastim does not hold.

For more detail on PBAC's view, see section 7 "PBAC outcome"

7 PBAC Outcome

7.1 The PBAC recommended an Authority Required listing of lipegfilgrastim under Section 100 (Highly Specialised Drugs Program) for prophylaxis of chemotherapy induced neutropenia. The recommendation was made on a cost-minimisation basis with filgrastim where the equi-effective doses are lipegfilgrastim 6 mg once per chemotherapy cycle, pegfilgrastim 6 mg once per chemotherapy cycle and filgrastim injection 5 microgram/kg/day for 11.25 days.

7.2 The PBAC noted that the submission's nominated comparator, pegfilgrastim, would be the agent most likely to be substituted. However, the PBAC considered that there would also be some substitution for filgrastim, and that filgrastim is therefore also a relevant comparator. The PBAC recalled that pegfilgrastim was listed on a cost-minimisation basis with filgrastim.

7.3 In making the positive recommendation, the PBAC noted it could only recommend listing of lipegfilgrastim at a higher price than filgrastim if it was satisfied that lipegfilgrastim provides, for some patients, a significant improvement in efficacy or reduction of toxicity over the alternative therapy or therapies. The PBAC considered filgrastim to be an appropriate alternate therapy in this setting. The PBAC noted the absence of data demonstrating an advantage of lipegfilgrastim over filgrastim for the clinical endpoint of interest. The PBAC therefore considered a cost-minimisation recommendation against filgrastim to be appropriate.

7.4 The PBAC recommended that lipegfilgrastim is listed for the same indications as pegfilgrastim. The PBAC were of the view that evidence of comparative clinical efficacy in one chemotherapy-induced neutropenia scenario was sufficient to enable extrapolation to other chemotherapy-induced neutropenia scenarios where evidence of efficacy of long half-life G-CSFs have previously been accepted.

7.5 The PBAC noted ESC advice about uncertainty regarding the efficacy of lipegfilgrastim in those weighing over 80 kg, however the PBAC accepted the sponsor's argument that patient weight was unlikely to have an impact on the clinical efficacy of lipegfilgrastim, at least relative to the efficacy observed in current practice.

7.6 The submission presented two head-to-head randomised trials, Study 02 (XM22-02) and Study 03 (XM22-03), comparing lipegfilgrastim and pegfilgrastim. The PBAC considered that the clinical data provided robust support of equivalent efficacy between lipegfilgrastim and pegfilgrastim. The PBAC also considered that the pre-specified non-inferiority margin, of less than one day for the duration of severe neutropenia, was appropriate and noted that the criterion was met in meta-analyses for the intention to treat and per protocol populations.

7.7 The PBAC considered that the clinical claim of non-inferior comparative effectiveness and safety over pegfilgrastim was reasonable.

7.8 The PBAC considered that net cost savings to Government would depend on the difference in price between pegfilgrastim and lipegfilgrastim at the point of lipegfilgrastim PBS listing. Substitution of filgrastim by lipegfilgrastim would be expected to be cost-neutral.

7.9 The PBAC advised, under Section 101(3BA) of the *National Health Act 1953*, that lipegfilgrastim and pegfilgrastim should be treated as interchangeable on an individual patient basis.

7.10 The PBAC advised that lipegfilgrastim is not suitable for prescribing by nurse practitioners.

7.11 The PBAC recommended that the Early Supply Rule should not apply.

7.12 The PBAC noted that this submission is not eligible for an Independent Review.

Outcome:
Recommended

8 Recommended listing

8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer
LIPEGFILGRASTIM 6 mg/0.6mL, 1 x 0.6 mL syringe	1	11	Lonquex® TEVA Pharma Australia Pty Ltd

Section 100 Highly Specialised Drug Program

Restrictions same as pegfilgrastim.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

10 Sponsor's Comment

TEVA welcomed the PBAC recommendation and have worked with the department to progress the listing of Lonquex onto the PBS, in order to provide patients with an alternative GCSF.