All Wales Therapeutics and Toxicology Centre
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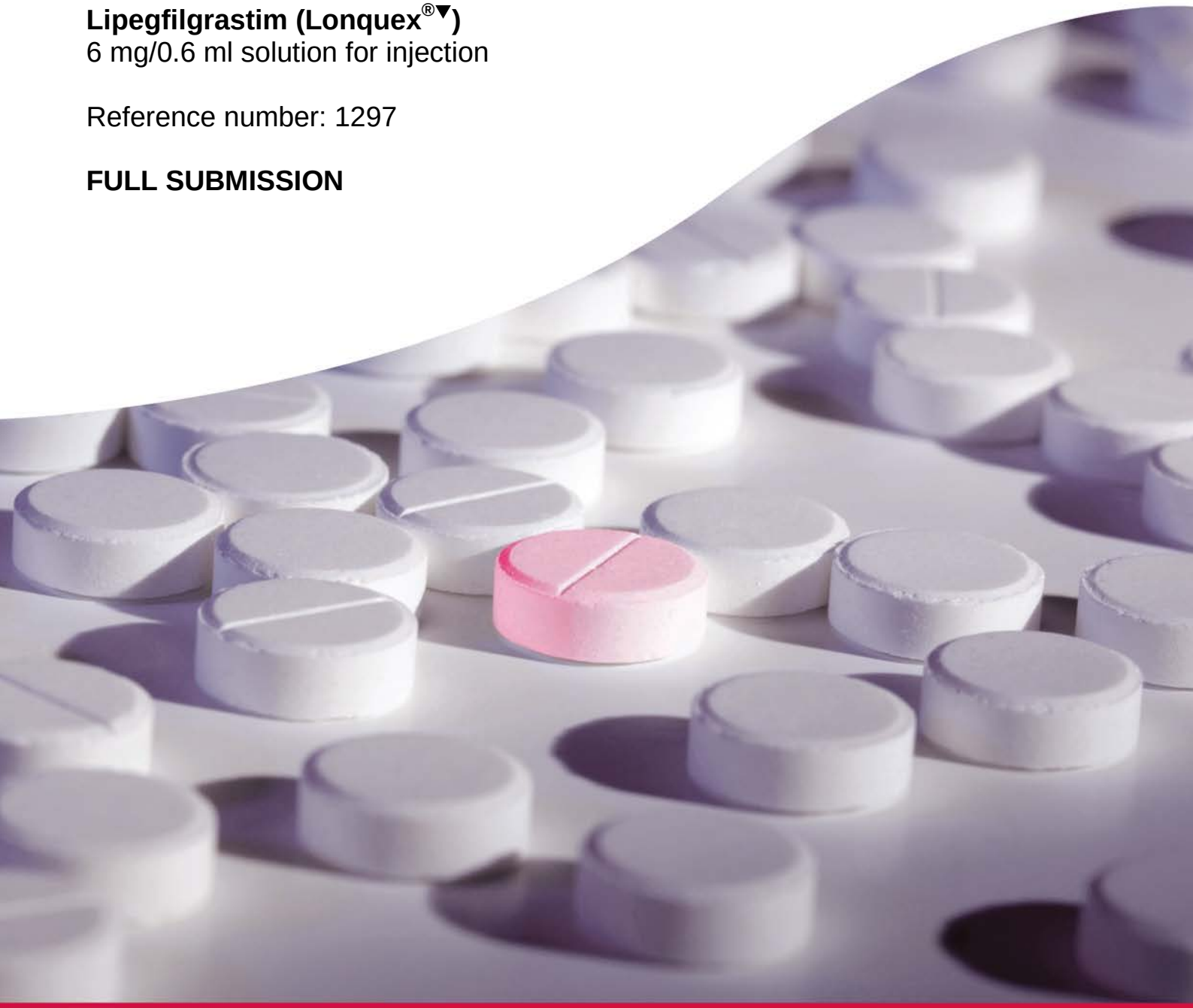
AWMSG SECRETARIAT ASSESSMENT REPORT

Lipegfilgrastim (Lonquex®▼)
6 mg/0.6 ml solution for injection

Reference number: 1297

FULL SUBMISSION



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AWMSG Secretariat Assessment Report
Lipegfilgrastim (Lonquex®▼) 6 mg/0.6 ml solution for injection

This assessment report is based on evidence submitted by TEVA UK Ltd. on 4 March 2014[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Lipegfilgrastim (Lonquex®▼) 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)[2].
Dosing	Treatment should be initiated and supervised by physicians experienced in oncology or haematology. One 6 mg dose of lipegfilgrastim (a single pre-filled syringe of Lonquex®▼) is recommended for each chemotherapy cycle, administered as a subcutaneous injection approximately 24 hours after cytotoxic chemotherapy[2]. Refer to the Summary of Product Characteristics for further information[2].
Marketing authorisation date	25 July 2013[3].
UK launch date	24 February 2014[1].

2.0 DECISION CONTEXT

2.1 Background

Chemotherapy-induced neutropenia (CIN) is a major risk factor for infection-related morbidity and mortality[4]. Patients who develop severe (grade 3/4) or febrile neutropenia (FN) during chemotherapy frequently receive dose reductions and/or delays to their chemotherapy, which may impact on the success of treatment[1,4,5]. The prophylactic use of recombinant granulocyte colony-stimulating factor (G-CSF) products reduces the incidence, severity and duration of CIN and FN[6] and is recommended when there is a ≥ 20% overall risk of FN[4,5,7]. Recombinant G-CSF is a glycoprotein which stimulates the production of neutrophils from bone marrow[8,9]. Long-acting G-CSFs require once per chemotherapy cycle administration, versus daily administration for short-acting formulations[10]. Currently, pegfilgrastim (Neulasta®) is the only long-acting G-CSF available in NHS Wales. Lipegfilgrastim does not have biosimilar status and was granted marketing authorisation on the basis that it was a new active substance[11]. The applicant company have highlighted lipegfilgrastim as an alternative to pegfilgrastim, positioned for use only where a long-acting G-CSF is considered appropriate (See Section 2.3 for guidance)[1]. The company estimate that 7,809 patients in Wales receive chemotherapy each year and approximately 150 patients would be eligible for lipegfilgrastim[1].

2.2 Comparators

The comparator included in the company submission was pegfilgrastim (Neulasta®).

2.3 Guidance and related advice

- National Institute of Health and Care Excellence (NICE). Clinical Guideline 151. Neutropenic sepsis: prevention and management of neutropenic sepsis in cancer patients (2012)[9].
- European Organisation for Research and Treatment of Cancer (EORTC). 2010 update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours (2011)[4].
- North Wales Cancer Network. Guidelines for the use of granulocyte colony stimulating factors in adult oncology and haematology patients (2009)[5].
- American Society of Clinical Oncology. ASCO 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline (2006)[7].

The All Wales Medicines Strategy Group (AWMSG) has previously recommended pegfilgrastim (Neulasta®) as an option for restricted use within NHS Wales for the 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). Its use should be restricted to patients where the risk of febrile neutropenia is high and where the risk of neutropenia from chemotherapy is likely to be prolonged (more than six days) or for patients with special circumstances e.g. geographical access, needle phobia (2008)[12].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission[1] includes details of one phase II dose-finding study (XM22-02) and two phase III studies (XM22-03, lipegfilgrastim versus pegfilgrastim; XM22-04, lipegfilgrastim versus placebo). Details of the most relevant studies are presented below.

3.1 Evidence on clinical efficacy

XM22-03 was a phase III, randomised, double-blind, parallel-group, multicentre study evaluating the efficacy and safety of lipegfilgrastim versus pegfilgrastim in chemotherapy-naive, female adults with high-risk (stage II-IV) breast cancer. Patients received routine myelosuppressive chemotherapy[1,11]; on day 1 of each chemotherapy cycle (three weeks per cycle, maximum of four cycles), all randomised patients (n = 202) received 60 mg/m^2 doxorubicin intravenous injection followed by 75 mg/m^2 docetaxel intravenous infusion. Approximately 24 hours after the start of chemotherapy, patients received 6 mg lipegfilgrastim (n = 101) or 6 mg pegfilgrastim (n = 101) by subcutaneous injection[1,11]. To begin full-dose chemotherapy on day 1 of each subsequent cycle, patients had to have recovered to an absolute neutrophil count (ANC) of ≥ 1.5 x 10^9/l and a platelet count of ≥ 100 x 10^9/l. A delay of the subsequent cycle for up to 14 days was permitted[1,11]. Seven patients in each treatment group had major protocol violations and were excluded from the according-to-protocol (ATP) population. The ATP population (n = 94 in each treatment group) was used for the efficacy analyses[1].

The primary endpoint was the duration of severe neutropenia (DSN) in days in cycle 1. Severe neutropenia was defined as grade 4 neutropenia with ANC < 0.5 x 10^9/l. Lipegfilgrastim demonstrated noninferiority compared to pegfilgrastim (lipegfilgrastim mean = 0.7 days; pegfilgrastim, mean = 0.8 days) with a treatment difference of −0.218 days (95% confidence interval [CI] −0.498 to 0.062)[1,11]. The incidence of severe neutropenia in the lipegfilgrastim group was comparable or lower than that in the pegfilgrastim group[1,11]. The highest incidences of severe neutropenia occurred in cycle 1 (lipegfilgrastim patients, 43.6%; pegfilgrastim patients, 51.1%)[1,11]. Only three patients

in the ATP population had investigator-assessed FN during the study; all three cases occurred in the pegfilgrastim group during cycle 1, with no FN cases in the lipegfilgrastim group. In the ITT population there was an additional case of investigator-assessed FN in the lipegfilgrastim group[11]. The time to ANC recovery (see Glossary) was shorter for lipegfilgrastim-treated patients than for pegfilgrastim-treated patients in cycles 1, 2 and 3, with $p < 0.05$ in each case (unadjusted p-values)[1]. In both treatment groups, the time to ANC recovery was longest in cycle 1[1]. The time to ANC recovery from nadir (see Glossary) was shorter for lipegfilgrastim-treated patients than for pegfilgrastim-treated patients, although $p < 0.05$ was only observed in cycle 3 (unadjusted p-value)[1]. Quality of life (QoL) was assessed using the EORTC QLQ-C30 (version 3) and the breast cancer specific module EORTC QLQ-BR23; no relevant differences between the treatment groups were observed[1,11]. The results generally indicated some deterioration in patients' QoL over the course of the study, which is not unexpected in cancer patients undergoing chemotherapy[1,11].

3.2 Comparative safety

The applicant company provided safety data from the pivotal study XM22-03 (in breast cancer patients) and study XM22-04, which was a randomised, double-blind, multicentre, placebo-controlled phase III study in patients with non-small cell lung cancer (NSCLC)[1]. In total, 349 patients were exposed to 6 mg lipegfilgrastim (XM22-03, n = 101; XM22-04, n = 248); 101 patients were exposed to 6 mg pegfilgrastim and 125 to placebo, in studies XM22-03 and XM22-04 respectively[1,11].

In study XM22-03, treatment-emergent adverse events (TEAEs) were experienced by 99.0% of patients in the lipegfilgrastim group and 98.0% of patients in the pegfilgrastim group[1]. However, CHMP noted that none of the system organ class differences between treatment groups were regarded as clinically relevant[11]. The frequency of some of the adverse events (AEs) known as class effects of G-CSF products, like bone pain, musculoskeletal pain and headache, were slightly higher in the lipegfilgrastim arm. Diarrhoea was reported less frequently in the lipegfilgrastim group[1,11].

In study XM22-04, despite the advanced disease status of enrolled patients, the difference in mortality between lipegfilgrastim and placebo early in the study was highlighted by CHMP as a concern (31 [12.5%] patients versus 9 [7.2%] patients respectively)[11]. However, this difference disappeared by the end of the year, with one-year mortality rates being comparable between the two arms (44% for lipegfilgrastim and 44.7% for placebo)[11]. In total, 89.1% in the lipegfilgrastim group and 92.0% of patients in the placebo group experienced TEAEs[1]. The most frequently associated TEAEs with deaths in this study were NSCLC and disease progression (11 events versus 1; lipegfilgrastim and placebo respectively)[11].

Based on all of the safety data submitted for licensing, CHMP concluded that the safety profile of lipegfilgrastim is acceptable. On the whole, the nature and frequency of TEAEs associated with lipegfilgrastim was in keeping with those encountered with use of a G-CSF product (e.g. bone pain, arthralgia, back pain and headache) and with those expected in patients with advanced malignancies treated with myelotoxic chemotherapy (e.g. alopecia, nausea, asthenia, diarrhoea, neutropenia and leucopenia)[11]. There is, however, some uncertainty regarding a potential effect of this product or even class of products on the progression of underlying malignancy(ies)[11]. Therefore, following CHMP advice, the company will be further evaluating the risk of deaths and tumour progression in a 3-arm post-authorisation safety study[1,11].

3.3 AWTTC critique

- Lipegfilgrastim is licensed for reduction in the duration of neutropenia and the incidence of FN in adult patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes)[2]. The applicant company has highlighted lipegfilgrastim as an alternative to pegfilgrastim, positioned for use only where a long-acting G-CSF is considered appropriate[1]. Data has not been provided to inform a comparison with short-acting G-CSFs licensed for the indication under consideration.
- The applicant company provided clinical effectiveness evidence from a study of female patients with breast cancer. No comparative evidence of lipegfilgrastim and pegfilgrastim has been provided in male patients, and there is evidence to suggest that breast cancer patients are less likely to develop neutropenia than patients with other types of cancer, e.g. blood cancers such as non-Hodgkin's lymphoma (NHL)[1,13]. However, CHMP state that as the expected FN incidence in a breast cancer population treated with doxorubicin and docetaxel is above 20%, supportive treatment with G-CSF is appropriate[11]. The company are in the process of launching a Phase IIIb study comparing lipegfilgrastim with pegfilgrastim in NHL patients, to further explore efficacy and safety[1].
- G-CSFs can be used as primary prophylaxis (administration in every chemotherapy cycle, beginning in cycle 1) or secondary prophylaxis (administration in all remaining chemotherapy cycles following FN)[5]. The company do not provide evidence concerning the use of lipegfilgrastim as secondary prevention of FN[1].
- All of the patients enrolled in XM22-03 were from outside of the European Union (EU), with 15 centres in Russia and 12 centres in the Ukraine[1,11]. It is unclear how applicable this is to patients in NHS Wales.
- The applicant company have largely provided data on chemotherapy-naive patients, excluding patients with prior malignancy within the previous five years (other than basal cell or squamous cell carcinomas or in situ carcinoma of the cervix). It is unclear how this relates to chemotherapy-experienced patients.
- The shelf-life for lipegfilgrastim is shorter than that of pegfilgrastim (two years versus three years, respectively)[2,14].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The applicant company submitted a cost minimisation analysis (CMA) comparing lipegfilgrastim to the only other long-acting formulation of G-CSF available in Wales, pegfilgrastim (Neulasta®). Based on the results of the pivotal trial, XM22-03 (see Section 3.0), the company have assumed that the efficacy and safety of lipegfilgrastim and pegfilgrastim are the same. The CMA adopts an NHS Wales and personal and social services perspective, and a time horizon equivalent to duration of a standard management course of chemotherapy (5.2 cycles). Medication costs for lipegfilgrastim and pegfilgrastim have been verified in the Monthly Index of Medical Specialities (MIMS)[15].

Costs of administration, neutropenic events (NE) and AEs are used in sensitivity analyses. NEs are classified as severe, very severe and FN. Patients with severe and very severe neutropenia receive a course of ciprofloxacin and Augmentin for an average of six days; 10% of severe and 20% of very severe also receive a prophylactic course of antibiotics. All cases of FN are managed as inpatients, with resource use taken from NHS Reference Costs[16]. The AEs considered are bone pain, myalgia, erythema, anthralgia and nausea. Paracetamol is used to manage bone pain, myalgia

and arthralgia. Erythema is managed with topical corticosteroids and nausea by domperidone. All costs are expressed in 2012 prices.

An Excel model was developed to measure the difference in costs between lipegfilgrastim and pegfilgrastim. In the base case, incidence of NEs and AEs is assumed equivalent to those reported in the pegfilgrastim arm of the study across the four cycles of chemotherapy.

The base case analysis applies the following calculations:

- Mean treatment cost per cycle = cost per injection × number of injections per cycle.
- Treatment costs per chemotherapy management course = mean treatment cost per cycle × number of cycles. The number of cycles is not evidenced within the company submission.
- Average drug administration cost per patient = number of injections per cycle × number of cycles × proportion of injections administered by a nurse × cost per hour of outpatient nurse time to administer an injection.
- Average NE cost per patient = sum of all management costs per NE × incidence of NE per 1,000 patients ÷ 1,000. Average AE cost per patient = sum of all management costs per AE × incidence of AE per 1,000 patients ÷ 1,000.

4.1.2 Results

The company's base case results are provided in Table 1. These compare total cost per patient over a chemotherapy management course, comprising 5.2 cycles. Treating a patient with lipegfilgrastim is reported to save £178 compared with pegfilgrastim, with all savings accruing from the lower drug acquisition cost of lipegfilgrastim compared with pegfilgrastim (£652 versus £686 per cycle).

Table 1. Results of base case cost per patient per chemotherapy management course

Event	Lipegfilgrastim (£)	Pegfilgrastim (£)	Difference (£)
Treatment	£3,391	£3,569	−£178
Administration	£317	£317	£0
NE	£216	£216	£0
TEAE	£2	£2	£0
Total cost	£3,926	£4,104	−£178

NE: neutropenic event; TEAE: treatment-emergent adverse event.

Sensitivity and scenario analyses

Table 2 presents the results from a range of one-way sensitivity analyses and scenario analyses. The CMA is sensitive to relative changes in prices or doses per cycle between the two medicines; changes to administration pathway do not change the magnitude of difference in costs. The CMA is not sensitive to changes in the number of cycles or number of days per cycle if the change is identical for each product.

Table 2. One-way and scenario sensitivity analyses

Inputs		Lipegfilgrastim minus pegfilgrastim	Change from base case	Plausibility
	Base case	−£178		Plausible
1	25% lower daily cost of injections (pegfilgrastim)	+£714	+£892	25% reduction in cost in both drugs plausible but not just one
2	25% lower daily cost of injections (lipegfilgrastim)	−£1,025	−£847	
3	1.1 days requiring injections per cycle (pegfilgrastim)	−£535	−£357	Plausible for certain tumour types for both drugs
4	1.1 days requiring injections per cycle (lipegfilgrastim)	+£161	+£339	
5	Number of treatment cycles 5.0 to 5.3	−£172 to −£182	+£6 to −£4	Plausible for certain tumour types for both drugs
6	50% of injections administered by a nurse (pegfilgrastim)	−£19	+£159	Plausible if service re-design enables patients to self-inject
7	50% of injections administered by a nurse (lipegfilgrastim)	−£337	−£159	
8	NEs for lipegfilgrastim from study rather than assuming equivalence with pegfilgrastim	−£393	−£215	Plausible
9	AEs for lipegfilgrastim from study rather than assuming equivalence with pegfilgrastim	−£178	0	Plausible
10	NEs and AEs rates reported in the study for each drug	−£393	−£215	Plausible

+ indicates an increase in relative cost of lipegfilgrastim
AE: adverse event; NE: neutropenic event.

Threshold analysis shows costs are equalised when the price of lipegfilgrastim is equal to that of pegfilgrastim.

The company note:

- The study had four chemotherapy cycles rather than 5.2 as modelled. This is likely to underestimate the number of NEs, AEs and dose modifications but the scale is judged not significant.
- The model excludes the benefit from a trend to fewer dose modifications with lipegfilgrastim which may, in turn, improve clinical outcomes and patient survival.
- Study results for patients with breast cancer are generalised to patients with other types of cancer. As mentioned previously, the company is undertaking a study in patients with NHL to explore efficacy in a population with a higher incidence of neutropenia.
- The model excludes the benefits for patients from a lower rate of severe neutropenia with lipegfilgrastim compared to pegfilgrastim (statistically significant difference in cycle 2).

4.1.3 AWTTC critique

The CMA presented by the company is only appropriate if the company has demonstrated lipegfilgrastim is therapeutically equivalent to pegfilgrastim with respect to all dimensions of health outcomes (benefits and harms) and any relevant issues concerning patient preference that may impinge on these outcomes. The company note key differences between lipegfilgrastim and pegfilgrastim, with the former:

- having a reduced incidence of severe neutropenia, particularly in cycle 2;
- having a statistically significantly higher ANC nadir in cycles 2 and 3;

- having a faster time to ANC recovery from ANC nadir in all cycles suggesting a faster time to immune recovery, although $p < 0.05$ was only observed in cycle 3;
- having a statistically significantly shorter time to ANC recovery in cycles 1, 2, and 3;
- having more patients reporting bone pain-related symptoms (23.8% lipegfilgrastim versus 16.8% pegfilgrastim) and slightly more treatment-emergent adverse drug reactions (TEADRs) (27.7% versus 25.7%, respectively; not statistically significant, but no p value provided);
- enabling patients to manage with no dose reductions or omitted chemotherapy treatments in cycles 2 to 4.

These results indicate a different clinical effect of lipegfilgrastim compared with pegfilgrastim and hence cost utility analysis (CUA) would be the more appropriate form of analysis.

Strengths of the economic evidence include:

- Sensitivity analyses modelled some selected, non-statistically significant differences in other outcomes such as NEs and AEs. These are associated with resource use and costs. This is not strictly appropriate for CMA (because of the assumption of equivalence) but the hybrid provides more information than simply the CMA.
- Resource use and unit costs were derived from valid sources for NE and administration costs.

Weaknesses of the economic evidence include:

- Given the differences in clinical and safety outcomes a CUA would be more appropriate. This would enable differences in QoL and life expectancy to be evaluated.
- Cost of AEs used in the model range from £5.04 for paracetamol to manage incidences of bone pain, myalgia and arthralgia to £15.19 to manage nausea. No costs to attend medical services such as GP, practice nurse, a day case or indeed requiring inpatient treatment are included. Given many of these events are classed as severe or very severe, health care resource use in clinical practice is likely to be materially higher than those modelled. This has been addressed through threshold analysis.
- Many key references, for example clinical data from the study and duration of chemotherapy cycles in clinical practice, cannot be verified. Original sources are not provided, as data are “on File” or from IMS market research data.
- As the company acknowledge, the model does not differentiate between different tumour types, with efficacy, safety and dose regimens for lipegfilgrastim and pegfilgrastim reported for patients with breast cancer assumed to apply to all types of tumour.
- Patients were recruited from outside of the EU and chemotherapy was for a maximum of four cycles. These differences may limit the extent to which data can be generalised, but this is not anticipated to be a major weakness.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches by AWTTC identified two CMAs comparing lipegfilgrastim to pegfilgrastim in the indication under consideration. Both are abstracts presented at a conference in 2013, and as such are limited in the details provided. The first abstract[17] describes a study set in Spain and reports that using lipegfilgrastim saves 650€ per patient treated, compared with pegfilgrastim. The second study is set in Scotland and estimates potential cost savings of £61,904 over five years, assuming lipegfilgrastim replaces pegfilgrastim in up to 30% (data not verified) of patients currently taking pegfilgrastim over that period[18]. The NHS in Scotland is similar to that in Wales, but the Spanish health care system is different and hence savings may not generalise.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

The company use the national incidence of malignant cancers, excluding non-melanoma skin cancer, of 592 patients per 100,000 individuals at risk[19] and assume 54% receive chemotherapy. Applying these rates to the population in Wales gives an estimate of 7,809 patients receiving chemotherapy. Of these, 6% are assumed to require G-CSF for FN, with 32% of these patients (1.9% of total) currently receiving pegfilgrastim. The company suggests that this group, numbering 150, could receive lipegfilgrastim[1].

Annual treatment cost per patient with lipegfilgrastim is £3,391 and £3,569 for pegfilgrastim, giving a saving of £178 per patient.

Table 3. Company-reported costs of lipegfilgrastim compared to pegfilgrastim for the treatment of patients with FN and receiving cytotoxic chemotherapy for malignancy

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of eligible patients for long-acting G-CSF	150	150	150	150	150
Uptake (%)	†	†	†	†	†
Treated patients* using lipegfilgrastim	†	†	†	†	†
Annual cost of lipegfilgrastim per patient	£3,391	£3,391	£3,391	£3,391	£3,391
Annual cost of pegfilgrastim per patient	£3,569	£3,569	£3,569	£3,569	£3,569
Net additional cost/cost saving per patient	–£178	–£178	–£178	–£178	–£178
Overall net cost per annum	†	†	†	†	†

* Note patients are rounded to the nearest whole number for display purposes but decimal places are used for calculations.
†Commercial in confidence data removed.

The company advises all sensitivity analyses demonstrate lipegfilgrastim is cost saving, having a lower cost per cycle than pegfilgrastim and no additional costs associated with it.

5.1.2 AWTTC critique

The estimated number of patients receiving chemotherapy and pegfilgrastim cannot be verified from the submission. Original sources are not provided, as data is “on File” or from IMS market research data.

5.2 Comparative unit costs

Table 4 provides unit costs for lipegfilgrastim and pegfilgrastim.

Table 4. Acquisition cost of lipegfilgrastim and pegfilgrastim, long-acting G-CSFs to manage neutropenia in adults treated with cytotoxic chemotherapy for malignancy

Regimens	Example doses	Cost per syringe*	Cost of 5.2 treatment cycles
Lipegfilgrastim 6 mg pre-filled syringe	One injection per chemotherapy cycle	£652.06	£3,391
Pegfilgrastim 6 mg pre-filled syringe	One injection per chemotherapy cycle	£686.38	£3,569
*Cost based on MIMS April 2014[15]			

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, lipegfilgrastim (Lonquex®▼) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

The company do not anticipate that lipegfilgrastim (Lonquex®▼) will be routinely supplied by a home healthcare provider. However, in certain circumstances where there is a clinical need, lipegfilgrastim may be supplied by a home healthcare provider commissioned by NHS Wales.

6.2 Ongoing studies

The company submission states that there are no ongoing studies from which additional evidence is likely to be available within the next 6–12 months.

6.3 AWMSG review

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

6.4 Evidence search

Date of evidence search: 7 March 2014.
Date range of evidence search: No date limits were applied to database searches.

GLOSSARY

Time to ANC recovery
The time in days from chemotherapy administration until the patient's ANC increased to ≥ 2.0 x 10^9/l after the expected nadir[11].

Time to ANC recovery from nadir
The difference in days between the day of the occurrence of ANC nadir to the first day after ANC nadir with ≥ 1.5 x 10^9/l ANC value[11].

REFERENCES

1 TEVA UK Ltd. Form B: Detailed appraisal submission. Lipegfilgrastim (Lonquex®▼). Mar 2014.
2 TEVA UK Ltd. Lonquex®▼. Summary of Product Characteristics. Sep 2013. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002556/WC500148380.pdf. Accessed Apr 2014.
3 European Medicines Agency. Authorisation details: Lonquex®▼. Sep 2013. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002556/human_med_001667.jsp&mid=WC0b01ac058001d124. Accessed May 2014.
4 Aapro MS, Bohlius J, Cameron DA et al. 2010 update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours. *European Journal of Cancer* 2011; 47 (1): 8-32.
5 North Wales Cancer Network. Guidelines for the use of granulocyte colony stimulating factors in adult oncology and haematology patients. Oct 2009. Available at: http://www.wales.nhs.uk/sites3/page.cfm?orgid=456&pid=57819. Accessed Apr 2014.
6 Lyman GH, Rolston KV. How we treat febrile neutropenia in patients receiving cancer chemotherapy. *Journal of Oncology Practice* 2010; 6 (3): 149-52.
7 Smith TJ, Khatcheressian J, Lyman GH et al. ASCO 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. *Journal of Clinical Oncology* 2006; 24 (19): 3187-205.
8 London New Drugs Group. Colony-stimulating factors. APC/DTC briefing document. Sep 2007. Available at: http://www.medicinesresources.nhs.uk/upload/documents/Evidence/Drug%20Specific%20Reviews/GrastimsSept07.pdf. Accessed Apr 2014.
9 National Institute for Health and Care Excellence. Clinical Guideline 151. Neutropenic sepsis: full guideline. Sep 2012. Available at: http://guidance.nice.org.uk/CG151. Accessed Apr 2014.
10 British Medical Association, Royal Pharmaceutical Society of Great Britain. British National Formulary. Apr 2014. Available at: http://www.bnf.org/bnf/index.htm. Accessed Apr 2014.
11 European Medicines Agency. CHMP assessment report: Lonquex®▼. Procedure No.:EMEA/H/C/002556/0000. Sep 2013. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002556/WC500148382.pdf. Accessed Apr 2014.
12 All Wales Medicines Strategy Group. Pegfilgrastim (Neulasta®) solution for injection. Reference No. 242. Appraisal information. Aug 2008. Available at: http://www.awmsg.org/awmsgonline/app/appraisalinfo/242. Accessed Apr 2014.
13 Pettengell R, Schwenkglenks M, Leonard R et al. Neutropenia occurrence and predictors of reduced chemotherapy delivery: results from the INC-EU prospective observational European neutropenia study. *Support Care Cancer* 2008; 16: 1299-309.
14 Amgen Ltd. Neulasta®. Summary of Product Characteristics. Dec 2013. Available at: http://www.medicines.org.uk/emc/medicine/11783/SPC/NEULASTA/. Accessed Apr 2014.
15 Haymarket Publications. Monthly Index of Medical Specialities (MIMS). Apr 2014. Available at: http://www.mims.co.uk/. Accessed Apr 2014.
16 Department of Health. NHS references costs 2012-2013. Nov 2013. Available at: https://www.gov.uk/government/publications/nhs-reference-costs-2012-to-2013. Accessed Apr 2014.

17 Sanchez-De La Rosa R, Garcia-Bujalance L. Economic impact model of lipegfilgrastim to prevent neutropenia in cancer patients in Spain. Presented at ISPOR 16th Annual European Congress. 2 Nov 2013.
18 Montouchet C, Ruff L, Cerchiari A et al. Budget impact of lipegfilgrastim for the management of chemotherapy-induced neutropenia. Presented at ISPOR 16th Annual European Congress. 2 Nov 2013.
19 Health in Wales. Cancer in Wales, 1995-2009. All cancers: a comprehensive report. 2009. Available at: http://www.wales.nhs.uk/sites3/Documents/242/11%20AllCancers.pdf. Accessed Apr 2014.