Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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lipegfilgrastim, 6mg, solution for injection (Lonquex®) SMC No. (908/13)

Teva Pharma BV

04 October 2013 *(Issued March 2014)*

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

lipegfilgrastim (Lonquex®) is accepted for restricted use within NHS Scotland.

Indication under review: 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).

SMC restriction: where a long-acting granulocyte-colony-stimulating factor is appropriate.

In a randomised, double-blind study, in adults with breast cancer given myelosuppressive chemotherapy associated with a high risk of febrile neutropenia, lipegfilgrastim was compared with another long-acting granulocyte colony-stimulating factor when used as primary prophylaxis against febrile neutropenia. The study found lipegfilgrastim was non-inferior to the comparator preparation in terms of the mean duration of severe neutropenia in the first chemotherapy cycle.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

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Indication

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).

Dosing Information

For each chemotherapy cycle, approximately 24 hours after cytotoxic chemotherapy, 6mg of lipegfilgrastim is recommended to be injected subcutaneously into the abdomen, upper arm or thigh.

Treatment should be initiated and supervised by physicians experienced in oncology or haematology.

Self-administration of lipegfilgrastim should only be performed by patients who are well motivated, adequately trained and have access to expert advice. The first injection should be performed under direct medical supervision.

Product availability date

24 February 2014

Summary of evidence on comparative efficacy

Febrile neutropenia induced by chemotherapy is a serious, and potentially fatal, complication of cancer treatment which can result in infection and sepsis. Incidence is greater during the early cycles of myelosuppressive therapy. Febrile neutropenia may lead to delay or dose reduction in chemotherapy, the need for antibiotics and hospital admission, all factors associated with poorer outcome. Granulocyte colony-stimulating factor (G-CSF) is a glycoprotein that regulates the production and release of neutrophils from bone marrow. Lipegfilgrastim is a long-acting form of filgrastim, a human G-CSF.

The submitting company has requested that SMC considers the use of lipegfilgrastim when positioned for use only where a long-acting G-CSF is considered appropriate.

The pivotal study to support the use of lipegfilgrastim was a multi-national, multi-centre, randomised, double-blind, controlled phase III study.[1,2,3] It recruited adults (≥18 years) with breast cancer, American Joint Committee on Cancer stages II to IV, who were chemotherapy-naïve. Eligible patients had an absolute neutrophil count ≥1.5x10^9/L, platelet count ≥100x10^9/L and Eastern Co-operative Oncology Group (ECOG) performance status 0 to 2, who were scheduled to receive four cycles of doxorubicin (60mg/m^2) and docetaxel (75mg/m^2). Patients were randomised in a ratio 1:1 to receive lipegfilgrastim 6mg (n=101) or pegfilgrastim 6mg (n=101), administered subcutaneously on day two of each chemotherapy cycle.

The primary outcome was the duration of severe neutropenia in the first chemotherapy cycle, defined as the number of days with severe (grade IV) neutropenia (absolute neutrophil count $<0.5x10^9$/L). The primary analysis of non-inferiority was conducted in the per-protocol population (all randomised patients without major protocol violation). The mean duration of severe neutropenia was 0.7 days in the lipegfilgrastim group and 0.8 days in the pegfilgrastim group, corresponding to an estimated least squares mean treatment difference of -0.22 days (95% confidence interval [CI]: -0.50 to 0.06). Non-inferiority was considered to be demonstrated as the upper limit of the two-sided 95% CI of the treatment difference was less than the pre-specified margin of one day. This was supported with an analysis in the intention-to-treat population: least squares mean treatment difference of -0.19 days (95% CI: -0.46 to 0.09). The proportions of lipegfilgrastim and pegfilgrastim patients with severe neutropenia during the first cycle of chemotherapy were 44% (41/94) and 51% (48/94), respectively.

The incidence of febrile neutropenia during the study was low in both groups: lipegfilgrastim (1/101) and pegfilgrastim (3/101). Small proportions of patients in both treatment groups required a delay in their chemotherapy treatments (13 to 19% in cycles two and three, and 4 to 8% in cycle four). No patients in the lipegfilgrastim group required omission or reduction of chemotherapy, compared with four patients in cycle two and two patients in cycles three and four in the pegfilgrastim group.

Quality of life was assessed using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire – C30 (version 3). There was no significant difference between the treatments in the change in scores from baseline to the end-of-study visit.

A phase II, double-blind, randomised, controlled dose-finding study recruited a similar population of patients as the pivotal study: adults with breast cancer scheduled to receive four cycles of doxorubicin and docetaxel.[3] Patients were randomly assigned 1:1:1:1 to lipegfilgrastim 3mg (n=53), 4.5mg (n=51), 6mg (n=50) and pegfilgrastim 6mg (n=54) to be administered by subcutaneous injection on day two of each cycle. The primary outcome was the mean duration of severe neutropenia in the first chemotherapy cycle. This was 0.8 days (standard deviation, SD 1.10) in the 6mg lipegfilgrastim group and 0.9 days (SD 0.99) in the pegfilgrastim group.

Summary of evidence on comparative safety

Treatment emergent adverse events were reported in the majority of patients during the pivotal study (99% of lipegfilgrastim and 98% of pegfilgrastim patients). Treatment emergent adverse drug reactions (defined as all treatment emergent adverse events except those explicitly designated by the investigator as not related to study drug) occurred in 28% and 26% of patients, respectively. A small proportion of patients discontinued due to adverse events (3% and 2%, respectively).[2]

Treatment emergent adverse events that occurred in at least 10% of patients in the lipegfilgrastim and pegfilgrastim groups respectively included: alopecia (92% versus 85%), nausea (60% versus 52%), asthenia (28% versus 29%), neutropenia (26% versus 32%), bone pain (14% versus 9.9%), erythema (12% in both groups), leucopenia (12% versus 7.9%), and diarrhoea (9.9% versus 12%).[1]

The European Medicines Agency (EMA) assessment report concludes that the safety profile of lipegfilgrastim is acceptable. There is, however, some uncertainty regarding a potential effect of this product or even class of products on the progression of underlying malignancy (ies)[3].

Summary of clinical effectiveness issues

The pivotal study demonstrated that lipegfilgrastim was non-inferior to pegfilgrastim in terms of the duration of severe neutropenia during the first cycle of myelosuppressive chemotherapy. Duration of severe neutropenia is a surrogate marker for the risk of febrile neutropenia, a clinically significant complication of chemotherapy.

The chemotherapy regimen used in the study is considered to have a high risk of febrile neutropenia, greater than 20% without G-CSF prophylaxis.[3] During the study, there was a small number of episodes of febrile neutropenia.

All the evidence presented by the submitting company concerned the use of lipegfilgrastim for primary prophylaxis of febrile neutropenia. No data were presented for secondary prevention of febrile neutropenia. In addition, evidence for lipegfilgrastim that is relevant to Scottish practice is limited to studies of adults with breast cancer.

The Summary of Product Characteristics for lipegfilgrastim recommends that the first injection should be performed under direct medical supervision, which is not a requirement for administration of pegfilgrastim.

Summary of comparative health economic evidence

The submitting company presented a simple cost-minimisation analysis which compared lipegfilgrastim to pegfilgrastim for the reduction in the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy. The submitting company has requested that SMC considers the use of lipegfilgrastim when positioned for use only where a long-acting G-CSF is considered appropriate. Pegfilgrastim was confirmed by SMC experts to be the appropriate comparator as it is the only licensed long-acting G-CSF.

The economic analysis was based on a 12 week time horizon. This was based on the estimated duration of an average chemotherapy regimen. Clinical data to support comparable efficacy which underpins the cost-minimisation analysis were taken from the pivotal phase III study which demonstrated non-inferiority between lipegfilgrastim and pegfilgrastim.

Drug acquisition costs were included in the model. Administration costs, adverse event and neutropenic event costs associated with each treatment were included in the model but were assumed to be the same in both arms. The only cost difference between the two arms of the model was the drug acquisition costs. The submitting company estimated the total cost per patient over 5.2 cycles would be £3,390.71 for lipegfilgrastim and £3,569.18 for pegfilgrastim. This resulted in savings with lipegfilgrastim of £178.46 per patient treated and therefore lipegfilgrastim was estimated to be the preferred treatment on cost-minimisation grounds.

Key assumptions relating to the cost of pegfilgrastim, number of injections per cycle and proportion of injections administered by a nurse were tested in one-way sensitivity analysis. It was determined that the incremental cost associated with a 10% decrease in the daily cost of pegfilgrastim was not a primary concern as SMC requires analysis to be based on the current list price, and the other factors were likely to apply to both treatments equally. Therefore, the economic case was considered to be demonstrated.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

The National Institute for Health and Care Excellence (NICE) issued clinical guideline 151 "Neutropenic sepsis: prevention and management of neutropenic sepsis in cancer patients" in 2012.[4] The guideline recommended that in adults receiving chemotherapy, G-CSF should not be routinely offered as prophylaxis of neutropenic sepsis unless it is integral to their regimen or it is used to maintain the dose intensity of the regimen.

Guidance regarding the use of G-CSF to reduce the incidence of chemotherapy-induced febrile neutropenia prepared by the European Organisation for Research and Treatment of Cancer (EORTC) were updated in 2010.[5] The guideline supports the use of G-CSF in patients who have a risk of developing febrile neutropenia ≥20%. Risk assessment should incorporate the risk associated with the proposed chemotherapy regimen and an assessment of patient factors related to an increased risk, eg age ≥65 years, advanced stage of disease, and previous episodes of febrile neutropenia. The guideline also recommends the use of G-CSF as supportive treatment to maintain chemotherapy intensity and density, for regimens in which reductions of these are linked with a poorer prognosis. In patients with febrile neutropenia, treatment with G-CSF is recommended to be limited to only those who are not responding to antimicrobial management and who are developing life-threatening complications. No specific G-CSF formulation was favoured over the others for any of the indications recommended in the guideline.

Additional information: comparators

Several G-CSF preparations are available that are administered daily: lenograstim, filgrastim (various biosimilar preparations). Pegfilgrastim is a long-acting G-CSF administered once per chemotherapy cycle.

Cost of relevant comparators

Drug	Dose Regimen	Cost per cycle (£)
Lipegfilgrastim	6mg subcutaneous injection 24 hours after chemotherapy	652
Pegfilgrastim	6mg subcutaneous injection 24 hours after chemotherapy	686

Doses are for general comparison and do not imply therapeutic equivalence. Costs from www.mims.co.uk on 22 July 2013 except lipegfilgrastim (from company submission).

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 16 in year 1 and 95 in year 5, assuming that 32% of patients would receive a long acting G-CSF. The gross impact on the medicines budget was estimated to be £53k in year 1 and £320k in year 5. As other drugs were

assumed to be displaced, the net medicines budget impact is expected to achieve savings of £2.8k in year 1 and £16.8k in year 5.

Alternative scenario
The company also submitted a budget impact template showing another scenario in which the proportion of patients requiring long acting G-CSF was assumed to be 70%. The submitting company estimated that the number of patients eligible for treatment to be 35 patients in year 1 and 207 in year 5. The gross impact on the medicines budget was estimated to be £118k in year 1 and £702k in year 5. As other drugs were assumed to be displaced, the net medicines budget impact is expected to achieve savings of £6.2k in year 1 and £36.9k in year 5. SMC clinical experts suggest that patient numbers may be higher in practice.

References

The undernoted references were supplied with the submission. The reference shaded in grey is additional to those supplied with the submission.

1. BioGeneriX AG. Clinical Study Report XM22-03: Efficacy and safety of XM22 compared to pegfilgrastim in patients with breast cancer receiving chemotherapy. 21 October 2011
2. Bondarenko I, Gladkov OA, Elsaesser R et al. 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 (2013); 13: 386.
3. European Medicines Agency. Assessment report – Lonquex. EMEA/H/C/002556/0000. Available from www.ema.europa.eu [Accessed 23 September 2013]
4. National Institute for Health and Care Excellence. Clinical Guideline. Neutropenic sepsis: prevention and management of neutropenic sepsis in cancer patients. September 2012. Available from www.nice.org.uk [Accessed 22 July 2013]
5. Aapro MS, Bohlius J, Cameron DA et al. Position Paper: 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. Eur J Can 2011; 47: 8-32.

This assessment is based on data submitted by the applicant company up to and including 12 September 2013.

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.