All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

Final Appraisal Report
Filgrastim (TevaGrastim®▼)
Teva UK Limited
Advice No: 1410 – August 2010

Recommendation of AWMSG

Filgrastim (TevaGrastim®▼) is recommended as an option for use within NHS Wales for the treatment of neutropenia:

- For reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with established cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes) and for the reduction in the duration of neutropenia in patients undergoing myeloablative therapy followed by bone marrow transplantation considered to be at increased risk of prolonged severe neutropenia. The safety and efficacy of filgrastim are similar in adults and children receiving cytotoxic chemotherapy.

- For the mobilisation of peripheral blood progenitor cells (PBPC).

- In children and adults, with severe congenital, cyclic, or idiopathic neutropenia with an absolute neutrophil count (ANC) of ≤ 0.5 x 10^9/l and a history of severe or recurrent infections, long term administration of TevaGrastim®▼ is indicated to increase neutrophil counts and to reduce the incidence and duration of infection-related events.

- For the treatment of persistent neutropenia (ANC ≤ 1.0 x 10^9/l) in patients with advanced HIV infection, in order to reduce the risk of bacterial infections when other options to manage neutropenia are inappropriate.

Filgrastim (TevaGrastim®▼) is not suitable for shared care within NHS Wales for the above indications.

Filgrastim (TevaGrastim®▼) should be prescribed by brand name to avoid automatic substitution and therefore help with pharmacovigilance.

This report should be cited as:

1.0 RECOMMENDATION OF AWMSG:

The AWMSG recommendation is based on: the Preliminary Appraisal Report, the Company Response to this, medical expert opinion, lay perspective and discussions at the AWMSG meeting.

Date: Wednesday 18th August 2010

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- For the mobilisation of peripheral blood progenitor cells (PBPC).

- In children and adults, with severe congenital, cyclic, or idiopathic neutropenia with an absolute neutrophil count (ANC) of ≤ 0.5 x 10^9/l and a history of severe or recurrent infections, long term administration of TevaGrastim®▼ is indicated to increase neutrophil counts and to reduce the incidence and duration of infection-related events.

- For the treatment of persistent neutropenia (ANC ≤ 1.0 x 10^9/l) in patients with advanced HIV infection, in order to reduce the risk of bacterial infections when other options to manage neutropenia are inappropriate.

Filgrastim (TevaGrastim®▼) is not suitable for shared care within NHS Wales for the above indications.

Filgrastim (TevaGrastim®▼) should be prescribed by brand name to avoid automatic substitution and therefore help with pharmacovigilance.

Additional note:

Due to the potential for small differences between biosimilars from different manufacturers and/or the reference product (Neupogen®) post-marketing pharmacovigilance is essential and will be facilitated by the Risk Management Plan.

2.0 PRODUCT DETAILS

Licensed indication	TevaGrastim®▼ is indicated for reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with established cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes) and for the reduction in the duration of neutropenia in patients undergoing myeloablative therapy followed by bone marrow transplantation considered to be at increased risk of prolonged severe neutropenia. The safety and efficacy of filgrastim are similar in adults and children receiving cytotoxic chemotherapy. TevaGrastim®▼ is indicated for the mobilisation of peripheral blood progenitor cells (PBPC). In patients, children or adults, with severe congenital, cyclic, or idiopathic neutropenia with an absolute neutrophil count (ANC) of ≤ 0.5 x 10^9/l and a history of severe or recurrent infections, long term administration of TevaGrastim®▼ is indicated to increase neutrophil counts and to reduce the incidence and duration of infection-related events. TevaGrastim®▼ is indicated for the treatment of persistent neutropenia (ANC less than or equal to 1.0 x 10^9/l) in patients with advanced HIV infection, in order to reduce the risk of bacterial infections when other options to manage neutropenia are inappropriate[1].
Dosing	Refer to summary of product characteristics (SPC) for dosing guidance according to indication[1].
Market authorisation date	15th September 2008[2].
UK Launch date	18th November 2009[2].

3.0 DECISION CONTEXT

3.1 Background

Neutropenia is a major side effect of chemotherapy and the primary cause of dose reduction[3, 4]. Neutropenia has traditionally limited chemotherapy to three to four week intervals, allowing time for the hematopoietic system to regenerate[3, 4]. The recovery of the neutrophil population can be facilitated by the glycoprotein granulocyte colony-stimulating factor (G-CSF), which promotes the production of neutrophils and enhances the effector function of mature neutrophils[5]. The company estimate that in 2010 there will be 713 breast cancer patients and 501 non-Hodgkin Lymphoma (NHL) patients in Wales eligible for G-CSF treatment during chemotherapy[2].

The active substance of TevaGrastim®▼ is filgrastim, a recombinant form of G-CSF produced by expression in *E. Coli*[5]. TevaGrastim®▼ has been developed as a similar biological medicinal product (biosimilar)[5]. The European Medicines Agency (EMA) defines a biosimilar as a biological medicine similar to an existing, authorised reference product, used in general to treat the same disease[6]. The reference product for TevaGrastim®▼ is Neupogen®, a form of G-CSF manufactured by Amgen Ltd[7]. Unlike generic small molecule drugs, biological medicines are in part defined by their manufacturing process; different expression systems can result in divergent isoforms or

post-translational modifications[8, 9]. Biosimilars therefore should not be considered identical to the reference product, as differences in efficacy or safety characteristics may exist[8, 9]. EMA guidelines require that a biosimilar be demonstrated to have comparable quality, efficacy and safety to its reference product[8, 10]. The extrapolation of data from one indication to another is permitted, allowing the use of a biosimilar in indications for which it may not have been formally studied.

3.2 Comparators

- Filgrastim (Neupogen®, Ratiograstim®▼, Zarzio®▼).

Ratiograstim®▼ contains a filgrastim molecule identical to TevaGrastim®▼. Both Ratiograstim®▼ and TevaGrastim®▼ are produced in the same facility using exactly the same manufacturing process[2].

The following G-CSF products are also available, although it should be noted that filgrastim is approved for a wider range of indications than lenograstim and pegfilgrastim[11-14].

- Lenograstim (Granocyte®).
- Pegfilgrastim (Neulasta®).

3.3 Guidance and related advice

European Organisation for Research and Treatment of Cancer (EORTC), American Society of Clinical Oncology and North Wales Cancer Network guidelines all support the use of G-CSFs when the risk of febrile neutropenia is ≥ 20%[15-17]. No guidelines recommend any particular G-CSF preparation over another.

In November 2009 Ratiograstim®▼ was recommended by AWMSG as an option for use within NHS Wales in the treatment of neutropenia[18]. Additionally, in August 2008 AWMSG recommended 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)[19].

4.0 SUMMARY OF EVIDENCE ON CLINICAL EFFICACY

The company submission is based on three Phase III, multi-centre, randomised, controlled trials. Study XM02-02-INT focussed on the equivalence of efficacy between TevaGrastim®▼ and Neupogen®[5, 20]. Two other studies, XM02-03-INT and XM02-04-INT, also investigated the efficacy of TevaGrastim®▼ in comparison with Neupogen®, but the primary objective of these studies was to demonstrate safety of TevaGrastim®▼(see section 5.0)[5, 21, 22].

Study XM02-02-INT was carried out in chemotherapy-naïve patients (n=348) with stage II to stage IV breast cancer. Chemotherapy consisted of doxorubicin (60 mg/m^2) and docataxel (75 mg/m^2) for up to four cycles. The study drug (5 micrograms per kilogram) was administered daily, beginning one day after completion of chemotherapy and continued for a minimum of five days and a maximum of 14 days. Patients were randomised to treatment with TevaGrastim®▼, Neupogen® or placebo in the first cycle; patients in the placebo group switched to TevaGrastim®▼ after the first cycle[2].

The primary endpoint was the duration of severe neutropenia (DSN) during the first cycle of chemotherapy and the main objective was to demonstrate the equivalence of TevaGrastim®▼ and Neupogen in reducing DSN during the first chemotherapy cycle. Equivalence was defined by a 95 % confidence interval for the difference in DSN within

the range -1 to 1 days. DSN was defined by the number of days with grade 4 neutropenia with ANC ≤ 0.5 x 10^9/l (ref 2).

For cycle one, the least square mean of DSN for the per protocol set was 1.119 days for TevaGrastim®▼ and 1.087 days for Neupogen®. The estimated difference between TevaGrastim®▼ and Neupogen® was 0.032 days (95% CI: -0.262 to 0.325). This was within the pre-specified range required to demonstrate equivalence. Results were comparable for the full analysis set[2].

Relevant secondary outcomes were DSN in cycles 2–4, time of ANC nadir, time to first and second ANC maximum, time to ANC recovery and incidence of febrile neutropenia. There were no significant differences between TevaGrastim®▼ and Neupogen® for any of these outcomes[5].

Study XM02-03-INT was a randomised controlled trial of 240 patients with squamous cell lung cancer or non-squamous cell lung cancer eligible for platinum-based myelosuppressive chemotherapy, who were chemotherapy naïve or had received no more than one previous chemotherapy regimen[22]. Study XM02-04-INT was a randomised controlled trial of 92 chemotherapy naïve patients with aggressive non-Hodgkin lymphoma eligible to receive a CHOP treatment regimen (see glossary)[21]. In both studies patients were randomised to receive Neupogen® or TevaGrastim®▼ (both 5 micrograms per kilogram per day) in cycle one; all patients received TevaGrastim®▼ in subsequent cycles. In both studies there were no clinically significant differences between mean DSN, ANC over time, depth of ANC nadir, time to ANC recovery or incidence of febrile neutropenia when comparing TevaGrastim®▼ and Neupogen®[5].

5.0 SUMMARY OF EVIDENCE ON COMPARATIVE SAFETY

In both safety studies (XM02-03-INT and XM02-04-INT), TevaGrastim®▼ was safe and well-tolerated at the stated dose[21, 22]. The most common drug-related treatment emergent adverse events (TEAEs) were all established effects of G-CSF treatment. In a pooled analysis of the two safety studies and the pivotal study (XM02-02-INT), the incidence of several TEAEs was significantly lower for the TevaGrastim®▼ group than the Neupogen® group. The CHMP are of the opinion that these differences are unlikely to be clinically significant[5].

It is currently unclear whether long-term treatment of severe chronic neutropenia patients with G-CSF will predispose patients to cytogenetic abnormalities, myelodysplastic syndromes or leukaemic transformation. It is therefore recommended in the SPC to perform morphologic and cytogenetic bone marrow examinations in patients approximately every 12 months[1]. Similarly, transient cytogenic modifications have been observed in normal donors following G-CSF use. The significance of these changes in terms of the development of haematological malignancy is unknown and risk of promotion of a malignant myeloid clone cannot be excluded. Long-term safety follow-up of donors is ongoing; it is recommended in the SPC that the aphaeresis centre perform a systematic record and tracking of the stem cell donors for at least ten years to ensure monitoring of long-term safety[1].

6.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES

- Equivalence between TevaGrastim®▼ and Neupogen® has been demonstrated only for prophylaxis of severe neutropenia after cytotoxic chemotherapy in a homogenous patient group. However, this is acceptable according to EMA guidance for biosimilars, which allows extrapolation to the other approved indications if the mechanism of action is the same[23].
- In the pivotal study, the primary objective was equivalence of TevaGrastim®▼ and Neupogen® in reducing DSN during the first cycle of chemotherapy. This is consistent with EMA guidelines, which state that the emphasis should be on the first cycle when testing equivalence of G-CSF biosimilars in this context[23].
- With regard to the mobilisation of peripheral blood progenitor cells (PBPCs), there is uncertainty over whether the efficacy of TevaGrastim®▼ in oncology can be extrapolated to this area of use. However, the CHMP are of the opinion that the proposed risk management plan adequately addresses this issue[5].
- In both safety studies patients were randomised to TevaGrastim®▼ or Neupogen® in cycle one only. In subsequent cycles all patients received TevaGrastim®▼. There was therefore no reference group (receiving Neupogen®) for later treatment cycles.
- Of 348 patients in the pivotal study, 346 (99 %) were female and 300 (86 %) were Caucasian. Across the three studies supporting efficacy and safety, 439 (65 %) were female and 606 (90 %) were caucasian[5]. Whilst this ethnic profile is representative of Wales, males are under-represented due to the large number of breast cancer patients enrolled. The extrapolation of data to males undergoing chemotherapy — for any of the wide range of malignancies for which TevaGrastim®▼ is indicated — is therefore subject to some uncertainty.
- The chemotherapy regimens in studies XM02-02-INT and XM02-04-INT are associated with a ≥ 20% risk of febrile neutropenia[16]. G-CSF therapy is therefore recommended according to EORTC guidelines[16]. For study XM02-03-INT the chemotherapy regimen(s) used are not specified; it is therefore not possible to comment on whether G-CSF therapy was appropriate.
- The detailed analysis of safety data relies on a pooled examination of cycle one from the two safety studies and one efficacy study. Overall long-term safety data are not yet available. The proposed pharmacovigilance programme fulfils EMA requirements[5].
- The completion rate for study XM02-03-INT was 52.5 %, compared with 95.7 % and 82.6 % for the other two studies. This relatively low completion rate can be attributed to the existing poor health status, and therefore high drop-out rate, of the patients in this study[5].

7.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

7.1 Cost effectiveness evidence

7.1.1 Context

No evidence of cost effectiveness has been provided in the company submission[2] on the basis that the TevaGrastim®▼ brand of filgrastim is identical to the Ratiograstim®▼ brand of filgrastim, and the latter has been recommended by AWMSG as a treatment option within its licensed indications in Wales[18]. Both products are supported by the same clinical trial data[2, 18], which demonstrated equivalence in terms of pharmacokinetic and pharmacodynamic characteristics, and no clinically significant differences relative to the reference product (Neupogen®) in the prophylaxis of severe neutropenia following cytotoxic chemotherapy in patients with breast cancer[2, 18]. The list prices for TevaGrastim®▼ and Ratiograstim®▼ are reportedly the same[2].

7.1.2 WMP critique of the company's economic evidence

Strengths of the economic evidence include:

- On the basis that TevaGrastim®▼ and Ratiograstim®▼ are identical products, and Ratiograstim®▼ has been recommended as a treatment option in Wales[18], the approach of the company would seem pragmatic.

Limitations of the economic evidence include:

- A further competitor biosimilar filgrastim product (Zarzio®▼) has been launched since the review of Ratiograstim®▼ and has not been considered in the TevaGrastim®▼ submission (see Table 2, section 8.4).
- In the absence of further supportive data since the Ratiograstim®▼ submissions, the limitations of the clinical and economic evidence presented in support of Ratiograstim®▼[18] would apply equally to the evidence for TevaGrastim®▼.
- It should be noted that actual acquisition costs of the available G-CSF products may differ in practice from those based on list prices due to contracting arrangements.

7.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by WMP have not identified any published evidence on the cost effectiveness of Tevagrastim®▼.

8.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

8.1 Budget impact evidence

8.1.1 Context and Methods

The company has adopted the same approach to the budget impact analysis for TevaGrastim®▼ as was used for Ratiograstim®▼[18]. The analysis considers only patients with breast cancer and NHL. To estimate the numbers of patients eligible for treatment with filgrastim, a range of Welsh cancer case statistics have been combined with English estimates of chemotherapy use.

Reportedly based on 2007 and 2008 market research data and the assumption of 32 days of filgrastim use, the company estimates that a total of 325 patients with breast cancer and NHL would receive G-CSF in Wales in year one[2]. It is assumed in the company submission that the number of cases of breast cancer will remain approximately static each year, whereas the number of cases of NHL will increase by around 1.5 % per year. It is also assumed that all chemotherapy units currently using Neupogen® will switch to TevaGrastim®▼ over the first two years, such that in years three, four and five all filgrastim will be provided as TevaGrastim®▼[2]. Other available G-GSF products are not considered in the analysis.

8.2 Results

The annual budget impact from the use of TevaGrastim®▼ instead of Neupogen® is summarised in Table 1. The company estimates that the use of TevaGrastim®▼ will result in cost savings compared with the assumed current use of Neupogen®[2].

Table 1. Company estimates of budget impact using list prices for filgrastim over five years[2]

	n (patients)	Cost (£)			
		Neupogen®	Tevagrastim®▼	Total	Net budget impact*
Current	325	1,092,650	0	1,092,650	
Year 1	325	796,631	270,890	1,067,521	- 25.129
Year 2	342	263,511	811,425	1,074,936	- 74,868
Year 3	353	0	1,086,657	1,086,657	- 100,129
Year 4	362	0	1,114,359	1,114,359	- 102,685
Year 5	368	0	1,133,935	1,133,935	- 103,281
*Cost difference vs. continued assumed use of Neupogen® for all patients					

8.3 Critique

The analysis considers only breast cancer and NHL patients, although the licensed indications for G-CSF products are wider than this. It is assumed that all patients are currently treated with Neupogen®; however, other G-CSF products are available and have been recommended as treatment options in Wales (e.g. Ratiograstim®▼ [Filgrastim], Neulasta® [Pegfilgrastim])[18, 19] (see section 3.3). A further biosimilar version of filgrastim (Zarzio®▼), which has a lower list price than Ratiograstim®▼ (see Table 2, section 8.4), has recently been launched and is the subject of a concurrent appraisal by AWMSG. The budget impact analysis presented by the company, therefore, may not consider all relevant comparator treatments. The estimates of eligible patient numbers are reportedly based on market research data from 2007 and 2008, before these other G-CSF products were recommended as options, and so may no longer be accurate. The company has appropriately used the current NHS list prices for costing purposes; however, it should be noted that actual acquisition costs of the available G-CSF products may differ in practice from those based on list prices, due to contracting arrangements. Due to the limitations of the analysis, the extent to which the company-estimated cost savings from the use of TevaGrastim®▼ will be realised in practice is uncertain.

8.4 Comparative unit costs

All filgrastim products are dosed on a per kg body weight basis. Table 2 presents example costs for their use in cancer patients for the prevention or management of neutropenia (dose of 5 micrograms per kilogram), based on eight days of use during one chemotherapy cycle for a 60 kg and an 80 kg patient and using BNF listed costs[24].

Table 2. Example costs of filgrastim products in the management of neutropenia in cancer patients

Product	Dose unit required*	8-day cost[24†]
TevaGrastim®▼	60 kg patient: 1 x 300 microgram syringe per day 80 kg patient: 1 x 480 microgram syringe per day	£498 £794.32
Zarzio®▼	60 kg patient: 1 x 300 microgram syringe per day 80 kg patient: 1 x 480 microgram syringe per day	£472 £752
Ratiograstim®▼	60 kg patient: 1 x 300 microgram syringe per day 80 kg patient: 1 x 480 microgram syringe per day	£498 £794.32
Neupogen®	60 kg patient: 1 x 300 microgram syringe per day 80 kg patient: 1 x 480 microgram syringe per day	£525.92 £838.80

This table presents example costs only and does not imply therapeutic equivalence between the agents contained herein.
*All products dosed at 5 micrograms per kilogram for neutropenia management. Assumes use of prefilled syringes, which necessitates wastage where the required dose cannot be delivered by whole syringe content. In other indications the dose would be 10 micrograms per kilogram[1, 7, 13, 14].
†Example of 8 days of treatment based on the mean total duration of filgrastim treatment of around 32 days across four chemotherapy cycles (as assumed in the budget impact analysis)[2]. The SPCs note that up to 14 days of treatment may be required[1, 7, 13, 14].

9.0 ADDITIONAL INFORMATION

9.1 Shared care arrangements

TevaGrastim®▼ would not be suitable for a shared care agreement. Filgrastim therapy should only be given in collaboration with an oncology centre, which has experience in G-CSF treatment and haematology and has the necessary diagnostic facilities[1].

9.2 Ongoing Studies

No ongoing studies were highlighted in the company submission.

9.3 Pharmacovigilance

As data from pre-authorisation studies are unlikely to identify all differences between a biosimilar and its reference product, clinical safety must be monitored closely during the post-approval phase[10]. Automatic substitution should be avoided for biosimilars in order to maintain pharmacovigilance[9]. For this reason it is considered good practice to prescribe biological medicines by brand name[25].

Patient organisation and medical expert opinion was sought.

GLOSSARY

Biosimilar: A biological medicine that is similar, but not identical to, an existing reference product. Biosimilars are of greater complexity than small-molecule drugs and differences can therefore arise during the manufacturing process[6].

CHOP: A chemotherapy regimen, comprising cyclophosphamide, hydroxydaunorubicin (doxorubicin), vincristine (Oncovin®) and prednisolone, used commonly for the treatment of NHL[26].

Duration of severe neutropenia (DSN): Number of days with grade 4 neutropenia with an absolute neutrophil count of ≤ 0.5 x 10^9/l (ref 2).

Glycoprotein: A protein which contains a carbohydrate molecule as part of its structure. The addition of carbohydrate groups to a protein is termed glycosylation, a form of post-translational modification[27].

Isoforms: Forms of the same protein that differ slightly in primary structure, sometimes leading to differences in function between different isoforms of the same protein[28].

Post-translational modification: The addition or subtraction of chemical groups from a protein after its initial synthesis. Post-translational modifications are crucial for the correct function of some proteins[29].

Recombinant protein: A protein produced by the insertion of DNA encoding the protein into a host organism, usually bacteria, and the stimulation of its production[30].

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