All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

Final Appraisal Report
Filgrastim (Zarzio®▼)
Sandoz Limited
Advice No: 1310 – August 2010

Recommendation of AWMSG

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

- For the 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 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.

- 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 filgrastim 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 therapeutic options are inappropriate.

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

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

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This report should be cited as:
All Wales Medicines Strategy Group Final Appraisal Report
filgrastim (Zarzio ®) – August 2010

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

The recommendation of AWMSG is:

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

- For the 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 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.

- 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 filgrastim 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 therapeutic options are inappropriate.

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

Filgrastim (Zarzio®▼) 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	Zarzio®▼ 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 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[1]. Zarzio®▼ is indicated for the mobilisation of peripheral blood progenitor cells (PBPC)[1]. 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 Zarzio®▼ is indicated to increase neutrophil counts and to reduce the incidence and duration of infection-related events[1]. Zarzio®▼ is indicated 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 therapeutic options are inappropriate[1].
Dosing	Refer to summary of product characteristics (SPC) for dosing guidance according to indication[1].
Market authorisation date	6 February 2009[2]
UK Launch date	21 July 2009[3]

3.0 DECISION CONTEXT

3.1 Background

Chemotherapy-induced neutropenia is a major risk factor for infection related morbidity and mortality[4]. In addition, patients who develop severe (grade 3/4) or febrile neutropenia during chemotherapy frequently receive dose reductions and/or delays to their chemotherapy, which may also impact on the success of treatment[4]. The incidence of severe or febrile neutropenia can be reduced by prophylactic treatment with granulocyte-colony stimulating factor (G-CSF)[4].

There are three G-CSF products licensed in the UK: filgrastim, lenograstim and pegfilgrastim. All have identical modes of action; they stimulate the bone marrow to produce neutrophils, causing a marked increase in peripheral blood neutrophil counts within 24 hours[5].

Zarzio®▼ contains the active substance filgrastim, a non-glycosylated, methionylated form of human G-CSF produced in *E. coli* by recombinant DNA technology[1]. Zarzio®▼ has been developed as a similar biological medicinal product (biosimilar). Biosimilars are new biological products that have been developed to be similar to an existing biological product that has already been authorised by the licensing authorities, usually

termed the reference product[6]. Biosimilars should, however, not be considered identical to the reference product, as differences in efficacy or safety characteristics may exist[7,8]. Consequently, European Medicines Agency (EMA) guidelines require a biosimilar to demonstrate comparable quality, efficacy and safety to its reference product[7,9]; in this case the reference product is Neupogen® (filgrastim) manufactured by Amgen Ltd[10].

Zarzio®▼ is highlighted as a potential replacement for Neupogen® (filgrastim, Amgen) by the company in their submission. Assuming an uptake rate of 100%, the total number of patients receiving Zarzio®▼ in Wales is estimated to be between 193 and 322[2].

3.2 Comparators

- Filgrastim (Neupogen®, Ratiograstim®▼, and TevaGrastim®▼)

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[1,10-14].

- Neulasta® (pegfilgrastim).
- Granocyte® (lenograstim).

3.3 Guidance and related advice

European Organisation for Research and Treatment of Cancer (EORTC), American Society of Clinical Oncology (ASCO) and North Wales Cancer Network guidelines all support the use of GSFs when the risk of febrile neutropenia is 20% or greater[4,15,16]. No guidelines recommend one specific G-CSF product over another.

In November 2009 Ratiograstim®▼ was recommended by AWMSG as an option for use within NHS Wales in the treatment of neutropenia[17]. Additionally, in August 2008 AWMSG recommended Neulasta® as an option for restricted use within NHS Wales for 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[18].

4.0 SUMMARY OF EVIDENCE ON CLINICAL EFFICACY

The company submission is based on four Phase I, randomised, double-blind, crossover, single or multiple studies which compared the pharmacokinetic and pharmacodynamic properties of Zarzio®▼ and Neupogen® for intravenous and subcutaneous administration. The primary objective of these studies was to demonstrate equivalence between the two products. A Phase III trial (EP06-301) with the primary objective of evaluating the safety, tolerability and immunogenicity of Zarzio®▼ is also provided by the company as supportive evidence of efficacy[2].

The Phase I studies were conducted in a total of 146 healthy volunteers (81 males and 65 females; ranging from 21 to 54 years of age)[2]. Both the pharmacokinetic results and the pharmacodynamic response (ANC and CD34+ cell count) of these studies demonstrate the biosimilarity of Zarzio®▼ to Neupogen®[19]. Following a single IV infusion of 5 micrograms per kilogram of Zarzio®▼ or Neupogen®, the 90% confidence intervals for the area under the serum concentration-time curve from 0 hours to the last quantifiable concentration (AUC_{0-last}) and the maximum serum concentration (C_{max}) of filgrastim lie within the acceptance limits of 80–125% for all doses[2,19](see section 6.0).

The Phase III study was designed as an open, single-arm, multicentre study in 170 chemotherapy-naïve breast cancer patients receiving Zarzio®▼ as primary prophylaxis of severe neutropenia during doxorubicin and docetaxel chemotherapy. The main efficacy variables were incidence and duration of severe neutropenia in cycles one to four, the incidence of febrile neutropenia and the time to neutrophil recovery. The mean duration of severe neutropenia with Zarzio®▼ was 1.8 days during cycle one[19], compared with the historical expectation of up to seven days with no growth factor support[2]. The trial is considered by the Committee for Medicinal Products for Human Use (CHMP) to be of limited usefulness[19] (see 6.0).

5.0 SUMMARY OF EVIDENCE ON COMPARATIVE SAFETY

A comparison of the safety profile of Zarzio®▼ and Neupogen® was provided based on four studies in a total of 146 healthy volunteers. Adverse drug reactions were consistent with those typically seen with Neupogen®. There were no serious adverse events (AEs) or deaths and no evidence of immunogenicity[2,19]. In the Phase III trial (EP06-301) approximately half of the G-CSF associated AEs were thought to be related to Zarzio®▼ and half to chemotherapy. The severity of the AEs was mild in the majority of cases (89%) and moderate in a small number of cases (11%). In addition, the study did not adjust the dose according to body weight. The differing doses used however (75% received a dose of up to 8 micrograms per kilogram and 22% received a dose of between 4.5 and 5.5 micrograms per kilogram[19]) resulted in similar occurrence rates of AEs[2].

It is currently unclear whether long-term treatment of severe chronic neutropenia 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

- The comparability of the efficacy based on a pharmacodynamic study in healthy volunteers is considered acceptable by CHMP; the two most important surrogate markers are considered to be ANC and CD34+ cell count[19]. The standard acceptance range of 80 to 125% for ANC and CD34+ levels is recommended in EMA guidelines to show biosimilarity of G-CSFs[19-21].
- No direct comparison efficacy data has been provided other than Phase I studies in healthy volunteers designed to demonstrate the biosimilarity of Zarzio® and Neupogen®.
- CHMP highlight in their report that comparison of the supportive Phase III trial with historical data on Neupogen® is hampered by the type of patients included in the trial and differences in exposure[19]. This trial was therefore of limited usefulness for the assessment of the comparability of Zarzio®▼ and Neupogen® with regards to both efficacy and safety in the clinical setting[19].

- The submission considers only healthy volunteers or breast cancer patients, although the licensed indications for G-CSF products are wider than this. It is also assumed that all patients are currently treated with Neupogen®. Nonetheless, the extrapolation to all indications of the reference product is acceptable since the mechanism of action is the same[19-21].

7.0 SUMMARY OF EVIDENCE ON COST-EFFECTIVENESS

7.1 Cost effectiveness evidence

7.1.1 Context

The company submission describes a simple cost minimisation analysis of treatment with Zarzio®▼ compared with either Ratiograstim®▼ or Neupogen®[2]. An assumption of equivalence is made between these three filgrastim products, on the basis that Neupogen® has been the common reference product for designation of Zarzio®▼ and Ratiograstim®▼ as biosimilar products[2]. A base case scenario of 10 days of treatment per cycle, for five cycles, at a dose of 0.5 million units (MU) per kg per day (the recommended dose for the management of neutropenia in cancer patients[1,10,14]) in a 70kg adult patient has been modelled, based on list prices in the British National Formulary (BNF)[22].

Various sensitivity and scenario analyses have been presented, including a further analysis of Zarzio®▼ against pegfilgrastim (Neulasta®) in which nursing time is also considered due to the less frequent administration associated with the latter. The company submission states that it is unlikely that Zarzio®▼ will be used as a replacement for pegfilgrastim, and it is implicitly assumed that Zarzio®▼ and pegfilgrastim are equivalent in all dimensions of health outcomes. To reflect the different costs associated with the different frequencies of administration, it is assumed that administration requires 15 minutes of nursing time once per cycle for pegfilgrastim and a variable number of times per cycle for Zarzio®▼.

7.1.2 Results

Table 1 details the estimated costs for the three filgrastim products under the base case scenario. Based on BNF list prices[22], Zarzio®▼ is the least costly filgrastim product[2].

Table 1. Company estimates of costs for base-case scenario[2]

	Neupogen®	Ratiograstim®▼	Zarzio®▼
Total dose per treatment cycle	350	350	350
Cost per injection[22]	£65.74	£62.25	£59.00
Dose per injection (MU)	30	30	30
Injections needed	11.67	11.67	11.67
Cost per treatment cycle	£766.97	£726.25	£688.33
Number of cycles per course	5	5	5
Total cost per course	£3,834.83	£3,631.25	£3,441.67

One-way and two-way sensitivity analyses reflect changes in the assumptions of daily dose, patient weight, number of days of treatment, etc. As these parameters are varied equally for all comparators the results are as expected: treatment with Zarzio®▼ remains the least costly due to its lower list price.

A scenario analysis in which Zarzio®▼ is compared against pegfilgrastim indicates that Zarzio®▼ remains the least costly, despite greater administration costs, as long as the number of days of treatment per cycle is fewer than nine days. At nine days of treatment per cycle or greater, treatment with pegfilgrastim becomes the least costly of the two options due to lower administration costs[2].

7.1.3 WMP critique of the company's economic evidence

Strengths of the economic evidence include:

- A pragmatic approach to the base case analyses has been taken, and various sensitivity analyses have been conducted to represent different durations of use of G-CSF products that may be encountered due to the range of their licensed indications. Results are as would be expected given the lower list price for Zarzio®▼.
- The analyses appropriately use current list prices for costing the available filgrastim products.

Limitations of the economic evidence include:

- The approach used to estimate acquisition costs implicitly assumes no vial wastage, which may be inappropriate when filgrastim products are generally available as pre-filled syringes. Nonetheless each prefilled syringe delivers the same filgrastim dose across the biosimilar and reference products, and the actual list prices are lower for Zarzio®▼ than for the Neupogen® and Ratiograstim®▼[22].
- 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.
- It is unclear whether or not a cost minimisation analysis is appropriate to compare Zarzio®▼ against pegfilgrastim, as this approach fails to consider the potential for greater convenience of a once per cycle injection regimen with pegfilgrastim compared with the multiple daily injections required with other G-CSF products. The company submission states that it is unlikely that Zarzio®▼ will be used as a replacement for pegfilgrastim, AWMSG has recommended pegfilgrastim for restricted use in NHS Wales[18]. Refer to section 3.3 for further details.

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 Zarzio®▼.

8.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

8.1 Budget impact evidence

8.1.1 Context and Methods

Based on IMS sales data for Neupogen® and Ratiograstim®▼ in the UK, the assumption of 10 days of filgrastim treatment per cycle of chemotherapy, an average patient weight of 70kg, and the fact that the Welsh population accounts for around 4.9% of the UK population, the company estimates that there were a total of 1,068 treatment cycles of filgrastim (964 for Neupogen® and 104 for Ratiograstim®▼) in Wales during 2009. These figures are not considered to vary over the next five years. The company has simply estimated the cost savings should all cycles of treatment with Neupogen® or Ratiograstim®▼ be replaced with the Zarzio®▼ filgrastim product[2].

8.1.2 Results

The company estimated savings from the use of Zarzio®▼ instead of Neupogen® and/or Ratiograstim®▼ are summarised in Table 2.

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

	Cycles/year	Cost/year	Cost if 100% replacement with Zarzio®▼	Cost difference
Neupogen®	964	£739,356	£663,553	**-£75,803**
Ratiograstim®▼	104	£75,530	£71,587	**-£3,943**
Totals	1,068	£814,886	£735,140	**-£79,746**

8.1.3 WMP critique

The estimates of the number of cycles of treatment of filgrastim used each year are based on filgrastim sales data, which the company acknowledges may be underestimates. It appears to have been simply assumed that each cycle of treatment would involve 10 days of filgrastim treatment, which would appear to be subject to a degree of uncertainty. The company has appropriately used the current NHS list prices for costing purposes, but 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. Furthermore, the acquisition costs are effectively estimated on a cost per MU basis rather than a cost per pre-filled vial basis, which fails to account for vial wastage. A further biosimilar filgrastim product, TevaGrastim®▼, has recently been launched and is the subject of a concurrent appraisal by AWMSG. Due to the limitations of the current analysis, the extent to which the company-estimated cost savings from the use of Zarzio®▼ could be realised in practice, is uncertain.

8.2 Comparative unit costs

All filgrastim products are dosed on a per kg body weight basis. Table 3 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 60kg and an 80kg patient and using BNF listed costs[22].

Table 3. Example costs of filgrastim products in the management of neutropenia in cancer patients

Product	Dose unit required*	8-day cost[22,23†]
Zarzio®▼	60kg patient: 1 x 300 microgram syringe per day 80kg patient: 1 x 480 microgram syringe per day	£472 £752
Ratiograstim®▼	60kg patient: 1 x 300 microgram syringe per day 80kg patient: 1 x 480 microgram syringe per day	£498 £794.32
TevaGrastim®▼	60kg patient: 1 x 300 microgram syringe per day 80kg patient: 1 x 480 microgram syringe per day	£498 £794.32
Neupogen®	60kg patient: 1 x 300 microgram syringe per day 80kg 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 cytotoxic-induced neutropenia management. Assumes use of prefilled syringes, which necessitates wastage where the required dose cannot be delivered by whole syringe content. In many of the other indications the dose would be 10 micrograms per kilogram[1,10,12,14].

†Example of eight days of treatment based on that assumed in previous appraisal of Ratiograstim®▼[17] for consistency. The SPCs note that up to 14 days of treatment may be required[1,10,12,14].

9.0 ADDITIONAL INFORMATION

9.1 Shared care arrangements

Zarzio®▼ 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

The company have highlighted in their submission two ongoing safety studies (EP06-501 and EP06-103) which are likely to provide additional evidence within the next 6-12 months[2].

9.3 Pharmacovigilance

Since 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[9]. Automatic substitution should be avoided for biosimilars in order to maintain pharmacovigilance[8]. For this reason it is considered good practice to prescribe biological medicines by brand name[24].

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].

Glycosylation: The addition of carbohydrate groups to a protein[25].

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[26].

REFERENCES

1. Sandoz Ltd. Zarzio®▼. Summary of product characteristics. Oct 2009. Available at: www.medicines.org.uk/EMC/medicine/22310/SPC/Zarzio+Solution+for+Injection. Accessed Apr 2010.
2. Sandoz Ltd. Form B: Detailed appraisal information. Zarzio®▼. Mar 2010. Accessed Apr 2010.
3. Sandoz Ltd. Form A: Preliminary appraisal information. Zarzio®▼. Aug 2009. Accessed Apr 2010.
4. Aapro MS, Cameron DA, Pettengell R, et al. EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphomas and solid tumours. *European Journal of Cancer* 2006; 42: 2433-53.
5. London New Drugs Group. Colony-stimulating factors. APC/DTC briefing document. Sep 2007. Available at: www.nelm.nhs.uk/en/Download/?file=MDs1MTE1MjI7RXZpZGVuY2UvRHJ1ZyBTcGVjaWZpYyBSZXZpZXdzL0dyYXN0aW1zU2VwdDA3LnBkZg__.pdf. Acccessed Apr 2010.
6. European Medicines Agency. Questions and answers on biosimilar medicines (similar biological medicinal products). Oct 2008. Available at: www.ema.europa.eu/pdfs/human/pcwp/7456206en.pdf. Accessed Apr 2010.
7. European Medicines Agency. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues. Feb 2006. Available at: www.emea.europa.eu/pdfs/human/biosimilar/4934805en.pdf. Accessed Apr 2010.
8. Mellstedt H, Niederwieser D, Ludwig H. The challenge of biosimilars. *Annals of Oncology* 2008; 19: 411-9.
9. European Medicines Agency. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. Feb 2006. Available at: www.emea.europa.eu/pdfs/human/biosimilar/4283205en.pdf. Accessed Apr 2010.
10. Amgen Ltd. Neupogen®. Summary of product characteristics. Nov 2001. Available at: www.medicines.org.uk/EMC/medicine/7907/SPC/Neupogen+30MU+and+48MU+Vials+and+Singleject+Syringes. Accessed Apr 2010.
11. Amgen Ltd. Neulasta®. Summary of product characteristics. Mar 2003. Available at: www.medicines.org.uk/EMC/medicine/11783/SPC/NEULASTA. Accessed Apr 2010.
12. Teva UK Ltd. TevaGrastim®▼. Summary of Product Characteristics. Mar 2010. Available at: www.ema.europa.eu/humandocs/PDFs/EPAR/tevagrastim/emea-combined-h827en.pdf. Accessed Apr 2010.
13. Chugai Pharma UK Limited. Granocyte®. Summary of product characteristics. Jun 2009. Available at: www.medicines.org.uk/EMC/medicine/8347/SPC/Granocyte+13+million+IU%2c+and+34+million+IU. Accessed Apr 2010.
14. Ratiopharm UK Ltd. Ratiograstim®▼. Summary of product characteristics. Mar 2010. Available at: www.ema.europa.eu/humandocs/PDFs/EPAR/ratiograstim/emea-combined-h825en.pdf. Accessed Apr 2010.
15. American Society of Clinical Oncology. 2006 update of ASCO practice guideline recommendations for the use of white blood cell growth factors: Guideline summary. *Journal of Oncology Practice* 2006; 2 (4): 196-201.

16. North Wales Cancer Network. Guidelines for the use of colony stimulating factor (G-CSF) in adult patients with solid tumours. Sep 2007. Available at: www.wales.nhs.uk/sites3/docmetadata.cfm?orgid=456&id=87565. Accessed Apr 2010.
17. All Wales Medicines Strategy Group. Final appraisal report: Filgrastim (Ratiograstim®▼) for the treatment of neutropenia. Sep 2009. Available at: http://www.wales.nhs.uk/sites3/Documents/371/filgrastim%20%28ratiograstim%29%20FAR.pdf. Accessed Apr 2010.
18. All Wales Medicines Strategy Group. Final appraisal report: Pegfilgrastim (Neulasta®) for the reduction of neutropenia. Aug 2008. Available at: http://www.wales.nhs.uk/sites3/Documents/371/Pegfilgrastim%20%28Neulasta%29%20FAR.pdf. Accessed Apr 2010.
19. European Medicines Agency. European public assessment report: Zarzio®▼. Feb 2009. Available at: http://www.ema.europa.eu/humandocs/PDFs/EPAR/Zarzio/H-917-en6.pdf.
20. European Medicines Agency. Guideline on the investigation of bioequivalence. www.ema.europa.eu/pdfs/human/qwp/140198enrev1.pdf. Accessed Apr 2010.
21. European Medicines Agency. Annex to guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. Guidance on similar medicinal products containing recombinant granulocyte-colony stimulating factor. www.ema.europa.eu/pdfs/human/biosimilar/3132905en.pdf. Accessed Apr 2010.
22. British Medical Association, Royal Pharmaceutical Society of Great Britain. *British National Formulary No. 59*. Mar 2010.
23. MIMS online: TevaGrastim®▼ monograph. Available at: www.mims.co.uk/Drugs/cardiovascular-system/anaemia-neutropenia/tevagrastim/?DCMP=ILC-SEARCH. Accessed May 2010.
24. Medicines and Healthcare products Regulatory Agency, Commission on Human Medicines. Biosimilar products. *Drug Safety Update* 2008; 1 (7): 8.
25. National Library of Medicine. Medical Subject Headings database: Glycoproteins. May 2009. Available at: www.ncbi.nlm.nih.gov/mesh/68006023. Accessed May 2010.
26. National Library of Medicine. Medical Subject Headings database: Recombinant proteins. Sep 2009. Available at: www.ncbi.nlm.nih.gov/mesh/68011994. Accessed May 2010.