Comments on Appraisal Consultation Document

Erythropoiesis-stimulating agents (epoetin and darbepoetin) for treating cancer-treatment induced anaemia (including review of TA142)

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Confidential information is highlighted and underlined; with mark-up of commercial and academic in confidence

Summary

Thank you for the opportunity to respond to the Appraisal Consultation Document (ACD) for *'Erythropoiesis-stimulating agents (epoetin and darbepoetin) for treating cancer-treatment induced anaemia (including review of TA142)'* issued by NICE (April 2014).

We welcome the Institute's preliminary recommendation for the use of erythropoiesis-stimulating agents (epoetin and darbepoetin) within their marketing authorisations, as options for the treatment of cancer-treatment induced anaemia.

Our comments on specific aspects of the ACD are provided in this document (sections 1 to 4). We have also listed some minor factual inaccuracies in the ACD for correction (section 5).

Section A – Decision problem

1. Has all of the relevant evidence been taken into account?

We believe all of the relevant evidence has been taken into account.

Section B – Clinical and cost-effectiveness

2. Are the summaries of clinical and cost-effectiveness reasonable interpretations of the evidence?

2.1 Clinical effectiveness of erythropoiesis-stimulating agents

Outcomes related to anaemia: subgroup analyses

The ACD states that '*there were statistically significant (p<0.05) differences between the types of ESA and between chemotherapy treatments.' (Section 4.1.7, page 11).* We recommend reconsidering the inclusion of this statement in the ACD, for the following reasons:

The Assessment Report includes a caution regarding interpretation of subgroup analyses highlighting the small number of studies per subgroup, and indicating that the statistical significance of results may appear overstated because the issues of multiple testing were not addressed. In our comments on the Assessment Report, we reiterated that given the large number of subgroup analyses conducted (10) and the number of endpoints evaluated (6), some false positive results were to be expected if tested at the 5% significance level. Furthermore, in the analysis of haematological response which reported the clinically relevant endpoint of Hb increase ≥2 g/dL, there was no difference seen between the two ESA treatment groups.

Comments were made at the Appraisal Committee meeting, and reflected in the ACD (Section 4.3.3, page 27) regarding the small number of studies in the subgroup analysis, and how this limits interpretation of the results of subgroup analyses. Furthermore, with regards to the consideration of the evidence, the Committee has noted in Section 4.3.7 (page 30) that it is reasonable to assume that all ESAs have the same effectiveness.

Given the acknowledged questionable statistical validity of the subgroup analyses (also stated on page 12), we would recommend the removal of the statement that '*there were statistically significant (p<0.05) differences between the types of ESA and between chemotherapy treatments'* to prevent potential misinterpretation by NHS stakeholders.

Section C – Implementation

3 *Are the provisional recommendations sound and a suitable basis for guidance to the NHS?*

3.1 Recommendation for selection of erythropoiesis-stimulating agents with the lowest acquisition cost

The ACD states *'The erythropoiesis-stimulating agent with the lowest acquisition cost for the course of treatment should be used.'* (Section 1.2, page 3). We recommend reconsidering this statement to support the provision of recommendations that are consistent with NHS procurement practice.

We support the decision for the use of procurement prices for ESAs to inform the recommendations in this appraisal given this reflects the relevant price to the NHS. We also agree that the inclusion of this recommendation that may ordinarily support NHS stakeholders with regards procurement locally given the potential variation in the cost of the technology under appraisal. However, as noted in our original response to the Assessment Report, we'd like to reiterate that the prices for ESAs are anticipated to be uniform, based on the regional tendering process.

Additionally, we would like to highlight that the NHS methodology for awarding tenders for ESAs includes both acquisition cost (accounting for c. 50% of the scoring) and qualitative criteria, such as clinical experience, safety and efficacy, dosing frequency and range of strengths available.

To support NHS implementation, we recommend the Institute reconsider the wording recommendation in Section 1.2 to provide applicability and consistency between technology appraisal guidance and the tendering methodology and decisions made by the NHS. This would be more applicable given the tendering decisions are undertaken in accordance with the UK Public Contracts Regulation[1] and typically based on other qualitative criteria instead of acquisition cost alone.

3.2 Biosimilar products

It is noteworthy that Section 1 of the ACD does not include the brand names or differentiate between the originator and biosimilar products considered in this review. Section 3 of the ACD is the first and only section that acknowledges that two of the six ESAs considered for this review are biosimilars: Binocrit and Retacrit (epoetin alfa and epoetin zeta biosimilars) and also includes brand names of biosimilar products for the first time.

Unlike generic drugs, biosimilars are by definition, "similar" but not identical to originator biologics.[2-5] Biologics are highly complex and it is technically impossible to develop an exact copy of a biologic agent, as the active substance is a collection of large protein isoforms and not a single molecular entity. In contrast, generic medicines contain the same ingredient as the reference medicine, the molecular structure of which can be readily defined by simple analytical methods.[2,5,6]

Biosimilars are therefore not the same as generic medicines and automatic substitution is not recommended.[7,8] Biosimilars have specific pharmacovigilance requirements and in order to meet those needs, health care professionals are required to maintain accurate records of prescribing and dispensing to aid the traceability of the medicines used. Each adverse drug reaction report must now include the brand name and batch number.[9] All recently marketed biological products have black triangle status.[3] Because of these considerations it is recognised that biologic or biosimilar

prescriptions should be written by brand name and not by International Non-proprietary Name (INN) and that automatic substitution is not recommended.

MHRA advice on:

Prescribing of biosimilars

All biosimilar products are prescription only medicines (POM). When prescribing biological products, it is good practice to use the brand name. This will ensure that automatic substitution of a biosimilar product does not occur when the medicine is dispensed by the pharmacist. Products (biosimilar and reference) that have the same international non-proprietary name (INN) are not to be presumed identical for the reasons given above.

Reporting suspected ADRs for biosimilars

In view of the subtle differences that are likely to exist between biosimilar products, even though the clinical effect of the products may be similar, and in view of the complexity of these molecules, it is very important that adverse drug reactions (ADRs) are properly assigned to the suspect product. Particular care needs to be taken when reporting ADRs associated with biosimilar products.

To ensure that any ADR that you report is assigned to the correct product, it is important that the product brand name rather than the substance name is used for reporting.[10]

Given substitutability and interchangeability cannot be assumed, we recommend that Section 1 include the brand names of the medicines and clearly state which of the appraised medicines are biosimilar medicines. This would ensure that the guidance issued by the Institute is in line with recommendations of the European Commission and MHRA, and All Wales Medicines Strategy Group and Scottish Medicines Consortium. This would also provide consistency with the Institute's HTA position paper (draft) on biosimilars as well as support NHS stakeholders in the appropriate implementation of guidance for biologics including biosimiliars.

4 Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

We do not believe that there are any particular equality related issues needing special consideration in this appraisal.

5. Factual inaccuracies

We would also like to take this opportunity to indicate some factual inaccuracies in the ACD (Table 1).

Table 1. Appraisal Consultation Document: Factual Inaccuracies

ACD Section	Current Text	Comments	Proposed Amendment (underlined)
Section 1.1, page 3	Erythropoiesis-stimulating agents (epoetin and darbepoetin) are recommended, within their marketing authorisations, as options for treating anaemia in people having cancer treatment.	This statement could be misunderstood as recommending ESAs for patients receiving radiotherapy alone for the treatment of cancer.	Erythropoiesis-stimulating agents (epoetin and darbepoetin) are recommended, within their marketing authorisations, as options for treating <u>patients with chemotherapy-induced anaemia.</u>
4.3.4, page 28	The committee noted that the 2012 Cochrane review by Tonia et al. showed that ESAs increased the risk of death compared with treatment without an ESA, but used a group of trials that <u>include higher haemoglobin concentrations, both at starting treatment</u> and target concentrations, than the trials chosen by the Assessment Group (Section 4.1.12)	This is incorrect, as Section 4.1.12, page 14, does not mention that Cochrane used a group of trials including higher haemoglobin concentrations, but instead states: The Assessment Group emphasised that its analysis only included studies complying with the licensed ESA starting dose, whereas the <u>Cochrane review did not restrict trials based on ESA dose.</u>	The committee noted that the 2012 Cochrane review by Tonia et al. showed that ESAs increased the risk of death compared with treatment without an ESA, but used a group of trials <u>that did not restrict trials based on ESA dose, unlike</u> the trials chosen by the Assessment Group (Section 4.1.12)

References:

1. The Public Contracts Regulation. 2006 Part 5, Section 30. Accessed 06/05/201 at http://www.legislation.gov.uk/uksi/2006/5/regulation/30/made).
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3. Niederwieser D, Schmitz S. Biosimilar agents in oncology/haematology: from approval to practice. European journal of haematology 2011;86:277-88.
4. Roger S, Mikhail A. Biosimilars: Opportunity or cause for concern? J Pharmaceut Sci 2007;10:405-10.
5. Guidelines on evaluation of similar biotherapeutic products (SBPs). WHO Expert Committee on Biological Standardization, Geneva, 2009. (Accessed 06/05/2014 at http://www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf.)
6. Rägo L. Biosimilar medicines and safety: New challenges for pharmacovigilance. Int J Risk Safety Med 2009;21:5-11.
7. Wadhwa M, Thorpe R. The challenges of immunogenicity in developing biosimilar products. Drugs 2009;12:440-4.
8. Liang BA, Mackey T. Emerging patient safety issues under health care reform: follow-on biologics and immunogenicity. Therapeutics and clinical risk management 2011;7:489-93.
9. Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use. 2010. (Accessed 06/05/2014, 2014, at http://ec.europa.eu/health/files/eudralex/vol-1/dir_2010_84/dir_2010_84_en.pdf)
10. Substitution of biosimilars. 2007. (Accessed 06/05/2014, 2014, at http://www.mhra.gov.uk/home/groups/es-policy/documents/websiteresources/con2030475.pdf)