NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Erythropoiesis-stimulating agents (epoetin and darbepoetin) for treating anaemia in people with cancer having chemotherapy (including review of TA142)

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees

Consultee	Comment	Response
Amgen	**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).	Thank you for your comments.
	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.	Comment noted.
	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	Comment noted. Section 4.3.7 of the FAD states that the Committee understood that the subgroup analysis suggested that there may be a difference between epoetin and darbepoetin in effect on haemoglobin concentrations. However, it recognised that

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	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.	the analysis of darbepoetin contained few studies, that the confidence intervals of the estimates were wide, and that the Assessment Group did not adjust the analyses for multiple testing. The Committee concluded that it was likely that the erythropoiesis-stimulating agents (ESAs) did not differ in clinical effectiveness. In line with the NICE process, evidence that was part of the Committee's deliberations should be presented in the FAD. Therefore the evidence provided by the Assessment Group is summarised in sections 4.1 and 4.2 of the FAD, and does not represent the Committee's conclusions.
	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	Comment noted. The Committee understood that the current tendering process in the NHS for ESAs takes into account a number of factors related to the drugs, and noted that it had already considered these factors in its deliberations. The Committee noted that because it assumed that the ESAs were equally effective, using the ESA with the lowest acquisition cost for a course of treatment would best

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	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.	employ scarce NHS resources (see FAD section 4.3.13). Comment noted. Sections 3.3 to 3.17 of the FAD identify the originator and biosimilar products. Further discussions on biosimilars, including prescribing advice, have been included in sections 3.18 and 4.3.7 of the FAD.

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	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.	Comment noted.
	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	The committee noted that the 2012 Cochrane review	This is incorrect, as Section 4.1.12, page 14, does not	The committee noted that the 2012 Cochrane review by Tonia et al. showed

The recommendations in the FAD have been revised to include chemotherapy rather than cancer treatment, thereby reflecting the marketing authorisations of the ESAs.

Section 4.3.4 of the FAD has

Consultee	Comment				Response
	28	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 include higher haemoglobin concentrations, both at starting treatment and target concentrations, than the trials chosen by the Assessment Group (Section 4.1.12)	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 Cochrane review did not restrict trials based on ESA dose.	that ESAs increased the risk of death compared with treatment without an ESA, but used a group of trials that did not restrict trials based on ESA dose, unlike the trials chosen by the Assessment Group (Section 4.1.12)	been revised to reflect the meta-analyses conducted by the Assessment Group and Tonia et al. more accurately.

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).
2. Fox A. Biosimilar medicines--new challenges for a new class of medicine. Journal of biopharmaceutical statistics 2010;20:3-9.
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

Consultee	Comment	Response
	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)	
Janssen-Cilag	**Janssen's Response to the Appraisal Consultation Document** **Anaemia (cancer-treatment induced) erythropoiesis-stimulating agents [ID541]** Please find below Janssen's response to the Appraisal Consultation Document (ACD) for anaemia (cancer-treatment induced) erythropoiesis-stimulating agents [ID541] issued in April 2014. We are pleased to have an opportunity to provide our comments and are supportive of NICE's initial positive recommendation. We wish to highlight two key points in relation to the appraisal: **1. The Committee's conclusion that the wholesale prices were the most relevant prices to the NHS and therefore the appropriate prices on which to base its decision. (Section 4.3.10 of the ACD)** We do not support the use of wholesale prices in the NICE MTA process. We support the use of BNF list prices, as is usual practice within the NICE technology appraisal process. **2. The current absence of any pharmacovigilance requirements in the ACD** We wish to ensure that Section 1 of the guidance produced during this MTA contains appropriate wording in line with the recommendations made by the ABPI on brand named prescribing to support pharmacovigilance requirements and the use of other standardised wording for biosimilar medicines. The ABPI recommendation is as follows: When referencing the originator biological medicine and it's biosimilar medicines, it is appropriate to use the name of the active drug substance. However when any individual medicine is being referred to then	Thank you for your comments. The Guide to the methods of technology appraisal 2013 indicates a preference for using nationally available price reductions in the reference-case analysis to reflect the price relevant to the NHS. Therefore the Committee concluded that the contract prices were the most relevant prices to the NHS and therefore the appropriate prices on which to base its decision (see FAD section 4.3.11). Comment noted. The Committee was aware that some of the technologies in this appraisal are biosimilars, and understood that there are some specific considerations for prescribers relating to biopharmaceuticals and

Consultee	Comment	Response
	the brand name should be used because substitutability and interchangeability cannot be assumed. This is extremely important in order to support consistent implementation by the NHS of EU and MHRA requirements for pharmacovigilance and monitoring of biological medicines, including biosimilar medicines, as set out in the ABPI's position paper on biosimilar medicines. The brand names of all biological medicines, including biosimilar medicines should be used in all guidance and guidelines documents and evidence summaries issued by NICE.	biosimilars. Sections 3.18 and 4.3.7 of the FAD now include a summary of current prescribing advice for biosimilars and the corresponding Committee considerations respectively.
Sandoz	We would like to commend you for an excellent appraisal of the evidence and welcome your recommendations to support the use of ESAs for treating anaemia in people having cancer treatment. We have one comment only relating to the summary of adverse events as stated in section 3.4 in the ACD: 3.4 The summary of product characteristics for Eprex and Binocrit lists headache, nausea and pyrexia as very common adverse reactions and deep vein thrombosis, hypertension, pulmonary embolism, diarrhoea, vomiting, rash, arthralgia and influenza-like illness as common adverse reactions in patients with cancer. Stroke is also commonly seen with Binocrit. For full details of adverse reactions and contraindications, see the summary of product characteristics. The safety as well as the efficacy profile for biosimilars and their reference molecule are considered similar by the EMA. Please note that the information regarding "stroke" was included in the PI (SmPC+PIL) in course of the renewal procedure for Binocrit finalised in 2012 due to a general request for all Epoetins from the PhVWP in 2010 (kindly refer to the attached document). This request concerned all Epoetins and was due to the results from the TREAT study concerning Darbepoetin alfa. DE presented the assessment of the results of the recently published clinical TREAT study showing that diabetic patients with CRF (chronic renal failure) and moderate anaemia are at increased risk for stroke when treated with darbepoetin alfa targeting Hb levels of 13 g/dL. The findings of the TREAT study indicated that epoetins are not beneficial in diabetic patients with chronic renal disease suffering from moderate anaemia. It can be assumed that the effects are not limited to darbepoetin alfa. The findings from the TREAT study were considered as a class effect. Therefore, an amendment of the SmPCs (and PIL) for all epoetins was justified. Please note that moreover the following centrally authorized Epoetins have also included the requested	Thank you for your comments. The summary of adverse events in the FAD directly reflects those listed in the summaries of product characteristics for each technology at the time of the appraisal.

Consultee	Comment	Response
	wording from the PhVWP in their PIs (Aranesp, Mircera, Neorecormon, Retacrit and Silapo) and there is no Sandoz specific deviation in this respect. The reason why the EPREX UK SmPC and PIL has not been updated so far remains unclear to Sandoz. As EPREX is authorized via MRP there might be a delay in the SmPC update due to the different regulatory way of approval. Furthermore please note that the PRAC was not in place at the time of the recommendation from the PhVWP and this might also have influenced a delay in the local SmPC update.	

The Department of Health and the Royal College of Nursing confirmed that they had no comments to make regarding this consultation.

Comments received from clinical specialists and patient experts

No comments received

Comments received from commentators

No comments received

Comments received from members of the public

Role*	Section	Comment	Response
Health professional (NHS)	**Section 1** (Appraisal Committee's preliminary recommendations)	No comment these are very reasonable recommendations.	Thank you for your comments.

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Role*	Section	Comment	Response
	Section 2 (Clinical need and practice)	There have been no red cell shortages for over a decade, demand for red cells is falling as a result of patient blood management initiatives including the appropriate use of erythropoietin. Donor blood is precious and requires volunteer and NHS resources to maintain stocks but in the UK meeting demand remains achievable. Transmission of bacterial or viral infection by red blood cells is very rare. Whilst NHSBT supports the appropriate use of alternatives to transfusion it is important to maintain confidence in the blood supply by accurately expressing risk. NHSBT can provide references and figures if required.	The Committee understood that the supply of blood transfusions may be limited, and that transfusions may be associated with problems such as iron overload, immune injury and infections, although it noted this comment highlighting that there have been no shortages of red blood cells for some time, and that transfusions rarely transmit infections (see section 4.3.1 of the FAD).
	Section 3 (The technologies)	No comment this section is very clear and concise	Noted.
	Section 4 (Evidence and interpretation)	No comment. Excellently presented.	Noted.
	Section 5 (Implementation)	No comment to add	Noted.
	Section 6 (Related NICE guidance)	No comment	Noted.
	Section 7 (Proposed date for review of guidance)	No comment	Noted.