Comments on Assessment Report

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 Assessment Report (AR) for '*Erythropoiesis-stimulating agents (epoetin and darbepoetin) for treating cancer-treatment induced anaemia (including review of TA142)*' produced by Peninsula Technology Assessment Group (PenTAG).

We broadly agree with the approach adopted by PenTAG, recognising the limited clinical evidence that is fully aligned with the erythropoiesis-stimulating agent (ESA) class labels and also the assumption of equivalence of efficacy for all ESAs (in line with TA142 and as recommended by the Institute).

In the absence of robust data to support the mechanistic modelling of exact haemoglobin (Hb) levels over time as previously conducted in TA142, we are supportive of the empirical approach taken by PenTAG, which has allowed for robust estimates of necessary parameters and the use of many of the outcomes from the systematic review.

In particular with regards to the cost-effectiveness analysis, we are strongly supportive of the approach taken by PenTAG and recommend the use of NHS procurement prices for ESAs to inform any subsequent recommendations since this best reflects the relevant price to the NHS.

1. Acquisition costs of ESAs

Within the UK, ESA acquisition costs have declined rapidly over the last 5 years and are now uniformly available with substantial price reductions. They are expected to remain stable at these levels in the future, due to recent changes in the tendering process.

As noted on page 300 of the AR: *''Due to different purchasing decisions by hospitals (due in part to different patient population sizes) the same drug will be acquired at a range of prices. Ideally in an economic evaluation one would wish to use the average acquisition cost for each drug in the base case, but such information is generally kept confidential''*.

We therefore wish to provide additional supportive information relating to the subject of ESA procurement in the UK and the existing and future tender environment as raised by PenTAG in the AR.

Current UK tendering environment:
In the UK, procurement of branded medicines is conducted via competitive tenders which results in substantial price reductions being realised by the NHS. The NHS Commercial Medicines Unit (CMU) now facilitates most of these tenders that historically were done at a local area or NHS Trust level. The resulting contracts are usually for a period of 2 years with a possible extension of 2 further years by the NHS, ensuring longer term price stability.

Over the past 5 years, the procurement of ESAs in the UK has moved away from therapeutic class tendering towards simple product based discount contracts. At the same time, contracting NHS Trusts have merged to create greater buying power through the ability to negotiate for larger volume oriented contracts. This tendering activity, which asks competing manufacturers to offer their lowest price in a blind tender process, has resulted in substantial price reductions as manufacturers are required to compete to secure tender awards. For example, in Wales, the procurement of ESAs is conducted at a regional level via a single tender covering the whole of the country.

New UK tendering arrangements for ESAs:
Whilst substantial price reductions are already realised, NHS England have indicated that they would like to achieve consistent pricing across England for greater simplicity and transparency. To achieve this, new arrangements for ESA tendering were announced in 2013 confirming that ESAs will be commissioned centrally by NHS England. These arrangements will merge the 14 sub-regional contracts (present in 2013) into four large regions by 2015, one for each new NHS England region. This has given the NHS substantially increased purchasing power and consequentially, lower procurement prices than attained previously. As the competition in the market place remains strong (six manufacturers actively competing for market share), it is expected that ESA procurement prices across England will be similar to those observed in London.

Two regional England contracts (NHS London and NHS Midlands and East of England) have already been tendered and awarded in 2013; the remaining two England tenders (NHS North of England and NHS South of England) are being prepared to initiate new contracts in 2015. Furthermore, with minimum contractual periods of at least 2 years for each tender, procurement prices for ESAs will be stable for the foreseeable future. Similarly, in Wales, a single tender for ESAs is expected to occur in 2014 for a minimum 2 year contract (with an option for 2 year extension).

Whilst there may be some variation in prices for the same medicine in different regions of England and Wales (mainly due to different price–volume methodology applied), the level of price reduction realised by the NHS has been consistently above [redacted] for darbepoetin alfa over the past 3 years. This is summarised in Table 1 below which aims to highlight that at present, approximately 45% of the total population of England have agreed procurement of darbepoetin alfa at a price reduction of [redacted] which is secure, at minimum, for the next 2 years. It would be reasonable to assume that similar price reductions would be achieved in the two remaining tenders given NHS England's objective of achieving consistent pricing across the four regions.

Table 1 Overview of darbepoetin alfa NHS procurement prices across England and Wales

Region	Average price reduction from NHS list price	England and Wales population*	Contract start date	Contract end date	Darbepoetin alfa contract market share
NHS London	[redacted]	15%	1/1/2014	1/1/2016 with an option to extend for 2 additional years	[redacted]
NHS Midlands and East of England	[redacted]	29%	1/3/2014	1/3/2016 with an option to extend for 2 additional years	[redacted]
NHS North of England	To be conducted	X%	1/3/2015	1/3/2017 with an option to extend for 2 additional years	N/A
NHS South of England	To be conducted	X%	1/9/2015	1/9/2017 with an option to extend for 2 additional years	N/A
Wales	[redacted]†	5%	10/10/2011	10/10/2014	[redacted]

*Proportion of England and Wales population, †Average discount of darbepoetin alfa over the last 3 years

In the event that demand for ESAs is increased by patients with cancer-treatment induced anaemia (CIA), as might be expected following guidance recommendation by NICE, ESA

pricing is only likely to be depressed further from additional volume-based discounting by competing manufacturers.

In summary, we are supportive of the approach taken by PenTAG based on the latest prices offered to London hospitals since it is an appropriate representation of the acquisition cost of ESAs across the UK. Furthermore, based on the new tendering arrangements aimed at allowing achievement of consistent prices across the NHS, it would be important to appropriately reflect these procurement prices for the cost-effectiveness analysis to inform any subsequent recommendations since this best reflects the relevant price to the NHS currently and in the future.

2. Biosimilars

It is important to highlight that biosimilars are not identical to originators and to ensure alignment with the recommendations of both the European Commission and MHRA.

Although not stated in the AR by PenTAG, it is important to note that two of the six ESAs licensed for the treatment of patients with CIA in the UK are biosimilars: Binocrit and Retacrit (both epoetin alfa biosimilars). It should also be noted that unlike generic drugs, biosimilars are by definition, "similar" but not identical to originator biologics. It is therefore important to make clear within the context of this technology appraisal, that biosimilars are not identical to originators and to ensure alignment with the recommendations of both the European Commission and MHRA with regard to biosimilars with clear statements regarding safety, traceability and the need to avoid automatic substitution.

3. Assessment of clinical-effectiveness

We are broadly in agreement regarding the selection of relevant evidence to assess clinical-effectiveness of ESAs.

In the absence of randomised clinical trials (RCTs) fully aligned with the label for darbepoetin alfa and other ESAs, the decision to select studies based on starting UK licensed dose is pragmatic.

We also note the assumption by PenTAG of equal efficacy for all ESAs, which underpins both the clinical- and cost-effectiveness in the AR. We believe this is a sensible approach, based on the available evidence, which is aligned with the previous NICE Technology Appraisal (TA142). In the AR, a subgroup analysis did report a statistically significant difference when comparing erythropoietin and darbepoetin alfa for the endpoint of Hb change. However, the AR includes a caution regarding interpretation of these subgroup analyses; it highlights the small number of studies per subgroup, and indicates that the statistical significance of results may appear overstated because the issues of multiple testing were not addressed. We support this statement and would like to reiterate that given the large number of subgroup analyses conducted (10) and the number of endpoints evaluated (6), some false positive results are to be expected if tested at the 5% significance level. Furthermore, in the analysis of haematological response which reports the clinically relevant endpoint of Hb decrease ≥2 g /dL, there is no difference seen between the two ESA treatment groups.

4. Assessment of cost-effectiveness

We are supportive of the empirical approach to the cost-effectiveness analysis taken by PenTAG.

The original TA142 applied a mechanistic modelling of exact Hb level over time during treatment period for the evaluation of cost-effectiveness of ESAs versus best supportive care. However, PenTAG have adopted an empirical approach in preference to modelling of Hb level over time, noting that:

(a) 'data for many required parameters is simply not available'
(b) 'it is not possible to incorporate many of the outcomes from the systematic review of clinical-effectiveness'

We are in agreement of PenTAG's findings that there are insufficient data available to conduct robust mechanistic modelling of exact Hb level over time during treatment period. We are supportive with the new empirical approach taken by PenTAG which allows for robust estimates of all necessary parameters and the use many of the outcomes from the systematic review.

5. Factual Inaccuracies

We wish to highlight the following factual inaccuracies within the AR and the recommended corrections, as described in Table 2 below.

Table 2 Factual inaccuracies in the TAR

Assessment Report Section	Factual Inaccuracy	Recommended Correction
Page 43, Table 3, Section 2.4.2.1.	Dose increase for darbepoetin alfa: "4 wks Hb increase <1 g/dl dose is doubled 4.5 µg/kg SC QW"	The label for darbepoetin alfa does not specify dose increase due to lack of response.[1] We recommend the removal of this statement.
Page 72, Section 4.2.2.2	For darbepoetin alfa the licensed weight-based, starting dose is 2.25 µg/kg in a once-weekly dose or 6.75 µg/kg once every three weeks. The maximum dose is 4.5 µg/kg per week.	For darbepoetin alfa, the licensed weight-based starting dose is 2.25 µg/kg in a once-weekly dose or 6.75 µg/kg once every three weeks. [1] We recommend the removal of the statement regarding maximum dose.
Pages 73, 745; Tables 11, 12, 31, 62, 63, 65, 66, 67; Figures 30, 31; Appendices D, G Pages 71, 121, 179 ; Tables 10, 13, 32, 33, 37; Figures 2, 3, 4, 8, 13, 18, 20, 79, 89, 90, 98, 109, 111; Appendix C	Reference: Del Mastro L, Venturini M, Lionetto R, Garrone O, Melioli G, Pasquetti W, et al. Randomized phase III trial evaluating the role of erythropoietin in the prevention of chemotherapy-induced anaemia. Journal of Clinical Oncology 1997;15(7):2715–21 is referred to as ''Del Mastro 1997" (first set of page references) and "Del Mastro 1999'' (second set of references)	Since this is a single reference, we recommend that it is referenced as such in the AR.

References:

1. Aranesp® (darbepoetin alfa) Summary of Product Characteristics. 2011. (Accessed 20/02/2014, at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-Product_Information/human/000332/WC500026149.pdf.)