NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Technology Appraisal Review Proposal paper

Review of TA322; Lenalidomide for treating myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality

Original publication date:	September 2014
Review date	September 2017
Existing recommendations:	Recommended To see the complete existing recommendations and the original remit for TA322, see Appendix A.

1. Proposal

The guidance should be transferred to the 'static guidance list'. That we consult on this proposal.

2. Rationale

No new evidence or trials have emerged that are expected to substantially change the recommendations in TA322.

3. Summary of new evidence and implications for review

New evidence is not expected to lead to a change in the recommendations in the original guidance. The main uncertainties in the appraisal were:

- the proportion of people eligible for the patient access scheme (PAS), that is, they remain on treatment beyond 26 cycles and
- the overall survival and health related quality of life benefits generated by lenalidomide.

Since the appraisal, data provided by the company suggest that the PAS is operating without any problems. The average proportion of patients on treatment at 26 cycles is greater than that estimated by the company in the appraisal, therefore improving the value proposition of lenalidomide to the NHS. The company do not have plans to change the PAS.

The estimates of overall survival used in the appraisal were taken from trial evidence which was deemed uncertain by the committee. The evidence suggested that there was not a statistically significant difference in terms of overall survival for those on lenalidomide compared with placebo. Since the appraisal a meta-analysis of over

2000 patients, examined the efficacy and safety results of lenalidomide. The results of this study found that treatment with lenalidomide significantly improved overall survival (HR=0.62) compared with placebo, erythropoiesis-stimulating agents or thalidomide. This finding is unlikely to change the current recommendation.

Two relevant ongoing trials were identified, both looking at the safety and efficacy of lenalidomide. One trial is collecting overall survival outcomes for lenalidomide, however it is a single arm trial and so it is not expected that results from this trial could help to resolve the uncertainty of the overall survival benefits for lenalidomide compared with best supportive care.

In conclusion much of the new evidence relates to the use of lenalidomide in a broader population than its marketing authorisation (people with del 5q), and of the evidence which is relevant to this population nothing is likely to change the previous recommendation.

Has there been any change to the price of the technology since the guidance was published?
No
Are there any existing or proposed changes to the marketing authorisation that would affect the existing guidance?
No
Were any uncertainties identified in the original guidance? Is there any new evidence that might address this?
The main area of uncertainty in this appraisal was whether the patient access scheme would be realised in clinical practice. With the complex patient access scheme only becoming operational after 26 treatment cycles, when they would receive any further treatment for no cost. Evidence of the proportion of people surviving to this marker would help to alleviate some of the uncertainty in the economic analysis. The economic model in the appraisal suggested that the ICER was sensitive to changes in the proportion of patients that were eligible for the PAS. If the proportion of patients on treatment after 26 cycles was less than 27% then the ICER would be greater than £30,000 per QALY gained.
Are there any related pieces of NICE guidance relevant to this appraisal? If so, what implications might this have for the existing guidance?
See Appendix C for a list of related NICE guidance.
Additional comments
None

The search strategy was adapted from the original ERG report and the scoping page strategy for the original topic and was re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from January 2012 onwards were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section below. See Appendix C for further details of ongoing and unpublished studies.

4. Equalities issues

During the appraisal comments were received from consultees about the Jehovah's Witness group who are unable to receive blood transfusion for religious reasons. The recommendations were not amended for people unable to receive blood transfusions, because no representations had been made or evidence received about the pathway of care for this group of people. Therefore, the clinical and cost-effectiveness of lenalidomide in this patient population could not be determined, meaning an alternative recommendation could not be made.

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GE paper sign off: Meindert Boysen, 17 August 2017

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Appendix A – Information from existing guidance

5. Original remit

To appraise the clinical and cost effectiveness of lenalidomide within its licensed indication for the treatment of myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality in people with red blood cell transfusion dependence.

6. Current guidance

1.1 Lenalidomide is recommended as an option, within its marketing authorisation, that is for treating transfusion-dependent anaemia caused by low or intermediate-1 risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate, with the following condition:

> The drug cost of lenalidomide (excluding any related costs) for people who remain on treatment for more than 26 cycles (each of 28 days; normally a period of 2 years) will be met by the company.

7. Research recommendations from original guidance

6.1 The Committee noted that the cost effectiveness of lenalidomide compared with standard care for people with low- or intermediate-1-risk MDS associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate, was sensitive to whether the patient access scheme would be realised in clinical practice. The Committee agreed that it would be critical to generate evidence to support the following:

> The proportion of people who become eligible for the patient access scheme, that is, that they remain on treatment beyond 26 cycles.
>
> The benefit of lenalidomide after 26 cycles, that is the associated overall survival and health related quality of life for those who remain on treatment beyond 26 cycles

8. Cost information from original guidance

Lenalidomide is available in 21-day packs of 10 mg and 5 mg capsules at net prices of £3780 and £3570 respectively (excluding VAT; 'British national formulary' [BNF] edition 67). The cost of a 28-day cycle of treatment with 10 mg of lenalidomide (excluding VAT) is £3780. Costs may vary in different settings because of negotiated procurement discounts.

Appendix B – Explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

Options	Consequence	Selected – 'Yes/No'
A review of the guidance should be planned into the appraisal work programme. The review will be conducted through the specify STA or MTA process.	A review of the appraisal will be planned into the NICE's work programme.	No
The decision to review the guidance should be deferred to specify date or trial.	NICE will reconsider whether a review is necessary at the specified date.	No
A review of the guidance should be combined with a review of a related technology appraisal. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the specified related technology.	No
A review of the guidance should be combined with a new technology appraisal that has recently been referred to NICE. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the newly referred technology.	No
The guidance should be incorporated into an on-going clinical guideline.	The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review. This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.	No

Appendix B

Options	Consequence	Selected – 'Yes/No'
The guidance should be updated in an on-going clinical guideline[1].	Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn. Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).	No
The guidance should be transferred to the 'static guidance list'.	The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review.	Yes
The guidance should be withdrawn	The guidance is no longer relevant and an update of the existing recommendations would not add value to the NHS. The guidance will be stood down and any funding direction associated with a positive recommendation will not be preserved.	No

[1] Information on the criteria for NICE allowing a technology appraisal in an ongoing clinical guideline can be found in section 6.20 of the guide to the processes of technology appraisal.

Appendix C – other relevant information

Relevant Institute work

Published

Azacitidine for the treatment of myelodysplastic syndromes, chronic myelomonocytic leukaemia and acute myeloid leukaemia (2011) NICE technology appraisal guidance 218. *Review decision April 2014 - move to the static list.*

Haematological cancers: improving outcomes (2016) NICE guideline NG47

Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy (2009) NICE technology appraisal guidance 171. *Review decision November 2012: "TA129 and TA171 will be moved to the 'static guidance list' … A part review of TA171 for the treatment of multiple myeloma following treatment with bortezomib will be scheduled into the technology appraisals work programme."*

In progress

None were identified.

Referred - QSs and CGs

None were identified.

Suspended/terminated

Multiple myeloma - lenalidomide (post bortezomib) (partial review TA171) NICE technology appraisal guidance [ID667]. Publication date to be confirmed. *5 May 2017: "The release of the Final Appraisal Determination for this topic has been delayed. In light of comments from consultees over the impact of this guidance on the overall multiple myeloma treatment pathway, NICE Guidance Executive has requested that these issues are explored further by the appraisal committee."*

Multiple myeloma (newly diagnosed) - lenalidomide NICE technology appraisal guidance [ID474]. Publication date to be confirmed. *14 July 2015: "The company holding the marketing authorisation for lenalidomide have informed NICE that it would not be appropriate to make a submission for this Technology Appraisal without a patient access scheme (PAS). The company have stated that a PAS will not be agreed with the Department of Health within a time frame that would currently enable it to be considered as part of the appraisal. In recognition of the exceptional circumstances, NICE has agreed that the appraisal can be suspended until a PAS has been agreed with the Department of Health."*

Lymphoma (mantle cell, relapsed, refractory) - lenalidomide NICE technology appraisal guidance [ID739]. Publication date to be confirmed. *6 November 2015: "The Appraisal Committee was due to meet on 16 February 2016 to discuss the use of lenalidomide for treating relapsed or refractory mantle cell lymphoma. The*

company has indicated that they will not be making a submission for this appraisal. Consequently, NICE will suspend the appraisal whilst we consider the next steps."

Multiple myeloma - lenalidomide (maintenance, post autologous stem cell transplantation) NICE technology appraisal guidance [ID475]. Publication date to be confirmed. *8 December 2016: "Suspended, NICE have agreed to reschedule the Single Technology Appraisal for lenalidomide as maintenance treatment of multiple myeloma after autologous stem cell transplantation (ID475). Celgene have advised NICE that they do not yet have access to the required data and therefore their submission is still in development. We will provide an update once we can confirm rescheduling dates."*

Details of new products

Drug (company)	Details (phase of development, expected launch date)	In topic selection
Epoetin alfa for treating anaemia in people with myelodysplastic syndromes. Janssen-Cilag.	May 17: Licensed in EU for the treatment of symptomatic anaemia (haemoglobin concentration of ≤10 g/dL) in adults with low- or intermediate-1-risk primary MDS who have low serum erythropoietin (<200 mU/mL).	[redacted]
Darbepoetin alpha (Aranesp) for the treatment of anaemia in adults patients with low transfusion demand in low or intermediate-1- risk myelodysplastic syndromes. Amgen.	Phase III.	[redacted]

1. Details of changes to the indications of the technology

Indication and price considered in original appraisal	Proposed indication (for this appraisal) and current price
The cost of a 28 day cycle of treatment with 10 mg of lenalidomide (excluding VAT) is £3780. Lenalidomide has a marketing authorisation 'for the treatment of patients with transfusion‑dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate'	The cost in eBNF June 2017 is the same. The indication remains the same.

2. Registered and unpublished trials

Trial name and registration number	Details
A Post-authorization, Non-interventional, Safety Study of Patients With Myelodysplastic Syndromes (MDS) Treated With Lenalidomide NCT02279654	Phase not given, currently recruiting. Estimated enrolment: 1800 Estimated primary completion date: December 2021
Randomized Phase III Trial Comparing the Frequency of Major Erythroid Response (MER) to Treatment With Lenalidomide (Revlimid®) Alone and in Combination With Epoetin Alfa (Procrit®) in Subjects With Low- or Intermediate-1 Risk MDS and Symptomatic Anemia NCT00843882	Phase III, ongoing not recruiting. Primary outcome measure: MER (Major Erythroid Response) defined as sustained transfusion independence in transfusion-dependent patients or a rise in hemoglobin > 2 g/dL in transfusion-independent patients with anemia for a minimum of 8 consecutive weeks Estimated enrolment: 252 Estimated primary completion date: September 2017

Trial name and registration number	Details
Revlimid 5 mg Capsules Special Use-results Surveillance (All-case Surveillance) NCT02921802	Phase not given, ongoing not recruiting. Primary outcome measure: adverse events. Estimated enrolment: 4626 Estimated primary completion date: June 2020

3. Relevant services covered by NHS England specialised commissioning

Lenalidomide for this indication was added to the Cancer Drugs Fund (CDF) in August 2014. It is no longer on the current list (June 2017).

When the new CDF system began in July 2016, the NHS England website said the following: “Of the 41 treatments remaining from the old CDF, 39 have transferred to the new arrangements pending NICE appraisal/reconsideration or assessment by NHS England for use of off label cancer drugs. There are two treatments that have been given two months’ notice of removal from the CDF. For one of these, lenalidomide, the manufacturer (Celgene) has confirmed that at the end of the two-month notice period they are willing to provide the drug free of charge via their ‘Single named patient use and compassionate supply programme’ on a case by case basis.” It isn’t clear from the press release which indication this refers to, as lenalidomide was also on the CDF for ‘2nd line treatment of multiple myeloma in patients who have contraindications to the use of Bortezomib’.

Appendix D – References

Lian, X. Y. et al (2016). Efficacy and Safety of Lenalidomide for Treatment of Low-/Intermediate-1-Risk Myelodysplastic Syndromes with or without 5q Deletion: A Systematic Review and Meta-Analysis. *PloS one*, *11*(11), e0165948.