Review of TA502; Ibrutinib for treating relapsed or refractory mantle cell lymphoma

TA502 was published in 2018 and scheduled to be considered for review in 2020.

Decision

1. TA502 remains relevant and an update is not needed.

Rationale

2. Overall, no new evidence has been identified that is likely to change the existing recommendations in TA502 therefore it is concluded that an update is not needed.

   TA502 includes an optimised recommendation for ibrutinib as a treatment option for treating relapsed or refractory mantle cell lymphoma in adults, if they have had only 1 previous line of therapy. The full marketing authorisation for ibrutinib allows it to be used in people with relapsed or refractory mantle cell lymphoma regardless of number of previous lines of therapy. The committee noted that the clinical evidence available suggested greater efficacy in patients who had ibrutinib after only 1 previous line of therapy, compared with 2 or more therapies.

   The company's base case analysis ICER for the full population of people with relapsed or refractory mantle cell lymphoma was £62,650 per QALY gained. The company conducted scenario analyses which resulted in ICERs of above £59,000 per QALY gained in all but 1 of the scenarios. It was noted that the ICER for patients in the second line was £49,849 per QALY gained. In addition, it was concluded that this ICER may be a conservative estimate because updated clinical data suggested that the economic model underestimated survival in this subgroup. The end-of -life criteria were met, therefore the threshold to be considered a cost-effective use of NHS resources was £50,000 per QALY gained. The committee concluded that the most plausible ICER for the second-line population was likely to be lower than £50,000 per QALY gained.

In TA502 the main area of uncertainty was around the lack of direct comparative data against standard of care in clinical practice. An indirect comparison was used in TA502 and no new evidence has been identified that directly compares ibrutinib against standard care or placebo. Furthermore, no relevant evidence was identified in a population having third or later-line treatment. Overall, no relevant new evidence was identified that is likely to change the existing recommendations.

Summary of new evidence and implications for review

Has there been any change to the price of the technology(ies) since the guidance was published?

3. The list price for ibrutinib has not changed. In TA502, the company agreed a patient access scheme. This is still in place.

Are there any existing or proposed changes to the marketing authorisation that would affect the existing guidance?

4. No proposed changes to the market authorisation for ibrutinib.

Were any uncertainties identified in the original guidance? Is there any new evidence that might address this?

5. The main uncertainties in TA502 were related to a lack of direct comparative data against standard of care. In addition, there was uncertainty related to the overall survival data obtained from the pivotal study, due to crossover. No new evidence that might address this issue has been identified.

Are there any related pieces of NICE guidance relevant to this appraisal? If so, what implications might this have for the existing guidance?

6. There have been no new technology appraisals in this disease area since publication.

7. The search strategy from the original ERG report was adapted for the Cochrane Library, Medline, Medline In-Process and Embase. References from January 2015 to January 2021 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 above. See Appendix C for further details of ongoing and unpublished studies.

Equality issues

8. The original guidance noted the potential equality issue raised by the company and patient groups that ibrutinib would offer an alternative to less effective but better tolerated chemotherapy agents for older or frailer people. It also noted the issue raised that oral administration allows an effective treatment option for people without access or transport to an infusion unit and significantly reduces multiple hospital visits. The committee acknowledged that access to ibrutinib may enhance treatment in these groups of people.

Decision paper sign off

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Appendix A – Information from existing guidance

Original remit

To appraise the clinical and cost effectiveness of ibrutinib (Imbruvica) within its marketing authorisation for treating relapsed or refractory mantle cell lymphoma in adults.

Current guidance

1.1 Ibrutinib is recommended as an option for treating relapsed or refractory mantle cell lymphoma in adults, only if:

- they have had only 1 previous line of therapy and
- the company provides ibrutinib with the discount agreed in the commercial access agreement with NHS England.

1.2 This recommendation is not intended to affect treatment with ibrutinib that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

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.	A review of the appraisal will be planned into the NICE's work programme.	No
The decision to review the guidance should be deferred.	NICE will reconsider whether a review is necessary at the specified date.	No
The guidance should be Cross referred 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 remains relevant 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

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 remains relevant and an update is not needed.	The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider.	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

Relevant Institute work

Published

None.

In progress

KTE-X19 for treating relapsed or refractory mantle cell lymphoma. NICE technology appraisal guidance. Publication expected 24 February 2021.

Details of changes to the marketing authorisation for the technology

Marketing authorisation and price considered in original appraisal

Ibrutinib has a marketing authorisation in the UK for the treatment of adults 'with relapsed or refractory mantle cell lymphoma'.

“Ibrutinib is available at the list price of £4,599.00 for 90×140-mg capsules (£51.10 per capsule) and £6,132.00 for 120×140-mg capsules (£51.10 per capsule; excluding VAT, British national formulary [BNF] June 2016).”

Proposed marketing authorisation (for this appraisal) and current price

BNF (accessed 18 January 2021) says “Mantle cell lymphoma (specialist use only)”.

emc (accessed 18 January 2021) says “IMBRUVICA as a single agent is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL).”

BNF (accessed 18 January 2021) lists the following prices:

Active ingredients	Size	Unit	NHS indicative price
Ibrutinib 420 mg	28	tablet (POM)	£4292.40

Active ingredients	Size	Unit	NHS indicative price
Ibrutinib 560 mg	28	tablet (POM)	£5723.20

Registered and unpublished trials

Trial name and registration number	Details
A Prospective, Multicenter, Open Label Single Arm Phase IV Clinical Trial to Assess Safety of ImbruvicaTM (Ibrutinib Capsules 140 mg) in Indian Patients With Chronic Lymphocytic Leukemia or Mantle Cell Lymphoma Who Have Received at least One Prior Therapy or Chronic Lymphocytic Leukemia With 17p Deletion NCT03190330; CR108316; 54179060LYM4005	The primary purpose of this study is to evaluate the post-marketing safety of ImbruvicaTM (ibrutinib capsule 140 milligram [mg]) under actual conditions of use, and to understand the incidence of adverse events (AEs) (serious and non-serious AEs). Phase 4, currently recruiting. Estimated primary completion date: September 29th 2021.

Trial name and registration number	Details
A Phase 3b, Multicenter, Open-label, PCI-32765 (Ibrutinib) Long-term Extension Study NCT01804686; CR100955; 2012-004225-24 (EudraCT Number); PCI-32765CAN3001	The purpose of this study is to collect long-term safety and efficacy data for participants treated with PCI-32765 (Ibrutinib) and to provide ongoing access to PCI-32765 for participants who are currently enrolled in PCI-32765 studies that have been completed according to the parent protocol, are actively receiving treatment with PCI-32765, and who continue to benefit from PCI-32765 treatment. Phase 3b, enrolling by invitation. Estimated primary completion date December 31st 2026.