



Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1456 – 17p deletion testing for access to venetoclax in patients with relapsed or refractory chronic lymphoid leukaemia

Applicant: AbbVie Pty Ltd

Date of MSAC consideration: MSAC 74th Meeting, 22-23 November 2018
MSAC 70th Meeting, 27 July 2017
MSAC 69th Meeting, 6-7 April 2017

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, [visit the MSAC website](#)

1. Purpose of application

This streamlined codependent application requested:

- an amendment to the Medicare Benefits Schedule (MBS) item 73343 allowing its use to determine eligibility for treatment with venetoclax in patients with relapsed/refractory chronic lymphocytic leukaemia; and
- Pharmaceutical Benefits Scheme (PBS) Authority Required listing of venetoclax in combination with rituximab as a treatment for relapsed or refractory CLL patients

2. MSAC's advice to the Minister – November 2018 consideration

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost effectiveness, MSAC supported amending MBS item 73343 to include 17p deletion testing in patients with relapsed/refractory chronic lymphoid leukaemia to determine access to venetoclax under the Pharmaceutical Benefits Scheme.

Summary of consideration and rationale for MSAC's advice – November 2018

In April 2017, MSAC deferred the application requesting modification of an MBS item to allow patients with chronic lymphocytic leukaemia (CLL) to undergo 17p deletion or *TP53* mutation testing until such time as the Pharmaceutical Benefits Advisory Committee (PBAC) makes a positive recommendation regarding the listing of venetoclax. MSAC foreshadowed its support for including venetoclax in the item descriptor.

MSAC noted the PBAC's positive recommendation in November 2018 to list venetoclax for the treatment of patients with relapsed or refractory CLL who are unsuitable for treatment or retreatment with a purine analogue, which includes patients who have 17p deletions. MSAC noted that the *TP53* mutation testing was not included in item 73343, and that the requested PBS-listing of venetoclax was for an earlier line of therapy than was considered in July 2017 (ie not waiting until patients had failed a kinase inhibitor).

The proposed listing for item 73343 is as follows:

Detection of 17p chromosomal deletions by fluorescence *in situ* hybridisation, in a patient with relapsed or refractory chronic lymphocytic leukaemia or small lymphocytic lymphoma, on a peripheral blood or bone marrow sample, requested by a specialist or consultant physician, to determine if the requirements for access to idelalisib, ibrutinib, or venetoclax on the Pharmaceutical Benefits Scheme are fulfilled.

There is no change to the proposed MBS fee, costs to the MBS or testing strategy. Utilisation is not expected to increase, as patients that will be tested for eligibility to venetoclax would have otherwise been tested for eligibility to ibrutinib or idelalisib.

3. MSAC's advice to the Minister – July 2017 consideration

MSAC agreed that despite receiving an application to list 17p deletion testing for access to treatment with venetoclax, no change to the MBS listing for 17p deletion testing was necessary. MSAC noted that the PBS listing recommended by the July 2017 PBAC meeting reserved use of venetoclax to patients in whom kinase inhibitor (idelalisib or ibrutinib) treatment had already failed. MSAC noted that, as 17p deletion testing was required before a patient could access idelalisib or ibrutinib, the 17p deletion status of any patient eligible for venetoclax would already have been established.

Summary of consideration and rationale for MSAC's advice – July 2017

In April 2017, MSAC recommended the listing of 17p deletion testing as a codependent test to support access to the kinase inhibitors idelalisib and ibrutinib, both recently recommended by PBAC for listing on the PBS for the treatment of patients with relapsed or refractory (R/R) chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL) whose disease is characterised by a 17p chromosomal deletion or *TP53* gene mutation. MSAC noted that the PBAC was due to consider venetoclax for patients with highly refractory CLL with no other suitable treatment options at its July 2017 meeting, and that 17p deletion testing was submitted as a codependent test with the proposed PBS listing. At this meeting MSAC considered amendment of the previously recommended item for 17p deletion testing to help determine access to venetoclax, in addition to idelalisib and ibrutinib, in R/R CLL patients.

MSAC noted that the PBAC had recommended the PBS listing of venetoclax for the treatment of relapsed or refractory CLL in patients who have failed a kinase inhibitor, without necessarily requiring evidence that these patients have a 17p deletion. MSAC advised that its previously supported MBS item descriptor need not include venetoclax, since eligibility for ibrutinib or idelalisib on the basis of 17p deletion would have been established before considering venetoclax.

MSAC also advised that there was no need to amend its previously supported MBS item descriptor for 17p deletion testing of patients with R/R CLL or SLL. MSAC noted that, in this case, fluorescence *in situ* hybridisation (FISH) should be specified as the test methodology. At its April 2017 meeting, the Committee had noted that the FISH approach was supported by the strongest evidence, and is the only methodology that would be covered by a Quality Assurance Program. MSAC also confirmed that, although the FISH methodology is specified here, in principle, items should not be specific to particular methodologies unless there are important consequences for test accuracy and clinical utility and labs that meet accepted performance standards should be free to select the appropriate test methodologies.

4. MSAC's advice to the Minister – April 2017 consideration

After considering the available evidence in relation to safety, clinical effectiveness and cost-effectiveness, MSAC deferred the application requesting modification of an MBS item to allow patients with chronic lymphocytic leukaemia (CLL) to undergo 17p deletion or *TP53* mutation testing until such time as the Pharmaceutical Benefits Advisory Committee (PBAC) makes a positive recommendation regarding the listing of venetoclax.

MSAC foreshadowed that, if PBAC subsequently decides to recommend to the Minister that venetoclax be listed on the Pharmaceutical Benefits Scheme (PBS), the committee would support the listing of a new MBS item for 17p deletion (not *TP53* mutation) testing in patients with relapsed or refractory CLL to help determine eligibility for PBS-subsidised venetoclax. MSAC advised that it would support an expedited MSAC process of re-consideration if PBAC subsequently recommends PBS listing of venetoclax.

Summary of consideration and rationale for MSAC's advice – April 2017

MSAC considered a streamlined codependent submission accompanying the submission to the March 2017 PBAC meeting requesting the PBS listing of venetoclax (Venclexta®, AbbVie) for the treatment of patients with relapsed or refractory chronic lymphocytic leukaemia (CLL) and with a 17p deletion or a *TP53* mutation.

MSAC noted that CLL is the most common form of leukaemia and, although considered to be a slowly progressing cancer, genetic markers can be used to provide useful prognostic information. MSAC highlighted that one such marker is the presence of a 17p deletion, which affects 5-8% of CLL patients who are chemotherapy naïve and 30-37% of patients with disease progression after first-line treatment. MSAC noted that, according to the applicant, patients with a 17p deletion have substantially inferior prognosis, with a shorter survival period and marked resistance to first-line chemotherapy. Of patients with a confirmed 17p deletion, more than 80% also exhibit mutations in the *TP53* allele, which may also be indicative of poor prognosis.

MSAC noted that the submission requested a modification of MBS item 73314 to allow patients with CLL to access 17p deletion or *TP53* mutation testing. This MBS item states “characterisation of gene rearrangement or the identification of mutations within a known gene rearrangement, in the diagnosis and monitoring of patients with laboratory evidence of (a) acute myeloid leukaemia; or (b) acute promyelocytic leukaemia; or (c) acute lymphoid leukaemia; or (d) chronic myeloid leukaemia.” This list of leukaemias does not include CLL. MSAC noted that the applicant claimed that the proposed change would enable identification of:

- CLL patients with poor prognosis who were likely to be resistant to fludarabine (which is frequently used as part of first-line treatment)
- patients eligible to access PBS-subsidised treatment with venetoclax (or idelalisib + rituximab).

MSAC emphasised that, while 17p deletion testing provides prognostic information and is predictive of patients' responses to purine analogue-based chemotherapy, it does not appear to be predictive of patients' responses to venetoclax treatment.

MSAC acknowledged that the applicant included *TP53* mutation testing as part of their submission in light of previous advice from the Department which recommended consistency between the PBS listing of venetoclax and similar therapies such as idelalisib which was recommended for PBS listing by the PBAC in July 2016. MSAC noted that this was also in

line with the PBS restriction proposed by the applicant for the PBS listing of venetoclax, which specified that eligible CLL patients includes those with a 17p deletion or *TP53* mutation. MSAC highlighted however, that the applicant was willing to accept MBS listing of 17p deletion testing alone if the PBAC deemed that the inclusion of patients with *TP53* mutation in the PBS listing for venetoclax was not appropriate. MSAC noted that, consistent with the advice in relation to testing in the context of idelalisib in CLL, the Department advised of the likelihood that only 17p mutation testing would be included in any PBS restriction for venetoclax. MSAC noted that this was partly the result of the small but uncertain number of patients harbouring a *TP53* mutation with normal 17p status and hence, the size of this population. MSAC also recalled that the methods associated with *TP53* mutation testing were more complex and expensive than 17p deletion testing. Hence, MSAC limited its consideration to the MBS listing of 17p deletion testing alone in the proposed population.

MSAC noted that evidence of 17p deletion has been included as one of the restriction criteria for the PBS-subsidised use of idelalisib (in combination with rituximab) and ibrutinib, which were recommended for PBS listing in the relapsed or refractory CLL or SLL patient population by the PBAC in July 2016 and January 2017, respectively. MSAC also recalled advice supporting a new MBS item for genetic testing to help determine eligibility for ibrutinib and idelalisib following requests by the PBAC. MSAC advised that it would support the inclusion of 17p deletion testing on the MBS to support PBS listing of idelalisib (PBAC had not recommended the PBS listing of ibrutinib at the time) and foreshadowed that testing would be confined to the smaller eligible population solely for access to the PBS drug after the development of refractory or relapsed disease, rather than the broader population at initial diagnosis.

MSAC also advised that the clinical utility of 17p deletion testing had been established by the evidence presented to the PBAC. In its consideration of the current submission, MSAC highlighted that the key data provided to support the PBS listing of venetoclax was derived from the M13-982 clinical trial which included patients with relapsed or refractory CLL harbouring a 17p deletion. MSAC noted that, as part of this trial, 17p deletion testing was performed using fluorescence *in situ* hybridisation (FISH) methodology using the Vysis CLL Probe Kit (Abbott Molecular), which has been listed in the Australian Register of Therapeutic Goods by the Therapeutic Goods Administration. MSAC noted that the trial demonstrated high overall response rates to venetoclax (77%), prolonged progression-free survival and a high proportion (87%) of patients remaining alive 12 months after commencing treatment. MSAC highlighted however, that as this was an open-label, non-comparative study, the comparative benefit in progression free survival or overall survival could not be determined directly.

MSAC reviewed the data presented to support the analytical specificity (percentage of signals that hybridise to the correct locus and no other location) and sensitivity (percentage of scoreable interphase nuclei with the expected normal region signal pattern) of 17p deletion testing using the Vysis CLL Probe Kit (Abbott Molecular) and considered that both were high. MSAC was concerned that, while this data indicated that the overwhelming majority of patients harbouring a 17p deletion would be correctly identified, no data to support the clinical specificity and sensitivity of the test was included in the submission. In turn, MSAC was uncertain whether or not these high values would be replicated as part of clinical practice in Australian laboratories. MSAC also recalled it had foreshadowed a need for the implementation of a Quality Assurance Program (QAP) for this testing as recommended by the Royal College of Pathologists of Australasia (RCPA). MSAC noted that the Department

is currently working with RCPA to establish this program. A QAP would only cover laboratories performing this method by FISH.

MSAC noted that advice from the RCPA highlighted that 17p deletion testing can be performed using either FISH or microarray methods and that FISH testing of 17p deletion is an “essential minimum requirement for the management of CLL patients”. MSAC advised that 17p deletion testing using FISH methods was supported by the strongest evidence, with the evidentiary basis for using microarray methods noted as being comparatively weaker. MSAC also considered the possibility of allowing patients to access 17p deletion testing through conventional cytogenetic testing items such as item 73290, currently funded on the MBS. The committee noted however, that these methods are unlikely to be as sensitive as FISH techniques and expressed concern about the potential for false negative results and consequential under-treatment.

MSAC noted that, when estimating the cost to the MBS of listing this service, the applicant assumed that all eligible patients would be tested at both the first-line setting and the relapsed or refractory setting. MSAC noted that the total cost to the MBS of 17p deletion testing would be below \$**redacted** per year across the five years projected, with an overall five-year cost to the MBS of \$**redacted**.

MSAC discussed whether or not the proposed testing should be restricted to only those patients who have relapsed or are refractory to first-line treatment or whether all patients should be eligible for testing at the point of diagnosis. MSAC noted that, if restricted to patients who have relapsed or are refractory to treatment, this would be more consistent with the other recommended PBS listings. However, MSAC advised that 17p deletion testing (and possibly other molecular testing) at initial diagnosis of CLL and small lymphocytic lymphoma (SLL) is also likely to yield benefits, particularly with respect to clinical utility, given that test results influence subsequent patient management and frequency of monitoring. In addition, based on advice from the RCPA, MSAC highlighted that 17p deletion testing is often recommended in the initial work-up of patients with CLL and SLL to inform the management plan. The Department noted that the use of molecular testing for prognostic purposes would require an evaluation of relevant clinical data. This dataset was not considered in the PBAC’s evaluation of ibrutinib and idelalisib clinical trials. MSAC noted that 17p deletion testing at initial diagnosis would be likely to affect the extent of utilisation of the service. The committee therefore requested that the Department find an appropriate sponsor to bring forward an application which would enable the committee to consider the case for implementing molecular testing (17p deletion and possibly other tests) at diagnosis to support management of CLL and SLL.

MSAC foreshadowed that, if PBAC subsequently decides to recommend to the Minister that venetoclax be listed on the Pharmaceutical Benefits Scheme (PBS), the committee would support the listing of a new MBS item for 17p deletion (not *TP53* mutation) testing in patients with relapsed or refractory CLL to help determine eligibility for PBS-subsidised venetoclax. MSAC advised that it would support an expedited MSAC process of re-consideration if PBAC subsequently recommends PBS listing of venetoclax.

MSAC also advised that, to support an extension to microarray methods of testing, a targeted health technology assessment should be completed to examine its analytical validity compared with FISH testing.

5. Background

November 2018 Consideration

Application 1456 was previously considered at the April 2017 and July 2017 MSAC meetings.

In July 2017, MSAC agreed that despite receiving an application to list 17p deletion testing for access to treatment with venetoclax, no change to the MBS listing for 17p deletion testing was necessary as the PBS listing recommended by the July 2017 PBAC meeting reserved use of venetoclax to patients in whom kinase inhibitor (idelalisib or ibrutinib) treatment had already failed.

In April 2017, MSAC deferred the application requesting modification of an MBS item to allow patients with chronic lymphocytic leukaemia (CLL) to undergo 17p deletion or *TP53* mutation testing until such time as the Pharmaceutical Benefits Advisory Committee (PBAC) makes a positive recommendation regarding the listing of venetoclax.

April 2017 Consideration

MSAC has not previously considered 17p deletion testing of patients with relapsed or refractory chronic lymphoid leukaemia (CLL) for access to venetoclax.

The Department accepted this as a ‘streamlined’ application, based on previous MSAC support for 17p deletion testing to help determine access to PBS-subsidised idelalisib or ibrutinib (currently in implementation). Therefore, any MBS-funded testing to help determine access to venetoclax would be via an amendment to the MBS item implemented in the context of these other PBS medicines. As the previous MSAC support in the context of access to idelalisib and ibrutinib did not extend to *TP53* gene mutations, this aspect of the codependent application for testing to help determine access to PBS-subsidised venetoclax was not part of the streamlined arrangements and there was no separate evidence base provided to enable a separate MSAC assessment.

As the TGA-approved indication for venetoclax is limited to CLL, the application did not request consideration of 17p deletion testing for small lymphocytic lymphoma for access to venetoclax.

6. Prerequisites to implementation of any funding advice

As part of the clinical trial program for venetoclax, fluorescent *in situ* hybridisation (FISH) testing to assess 17p deletions was performed using the Vysis CLL Probe Kit (Abbott Molecular).

The Vysis CLL Probe Kit is currently TGA-approved and marketed in Australia, with the approved purpose outlined as being “For the determination of acquired genetic alterations in human clinical specimens” (ARTG inclusion number 196286).

7. Proposal for public funding

The application requested modification of MBS item 73314 to allow patients with CLL to access 17p deletion or *TP53* mutation testing through the MBS. The modification to MBS item 73314 is shown in bold text in Table 1, with FISH testing being covered under the ‘characterisation of gene rearrangement’ wording and *TP53* mutation testing being covered under the ‘identification of mutations within a known gene rearrangement’ wording.

The application did not seek any alteration to the MBS fee.

Table 1 Amendment to MBS item 73314 proposed in the application

MBS item 73314: Characterisation of gene rearrangement or the identification of mutations within a known gene rearrangement, in the diagnosis and monitoring of patients with laboratory evidence of:

- (a) acute myeloid leukaemia; or
- (b) acute promyelocytic leukaemia; or
- (c) acute lymphoid leukaemia; or
- (d) chronic myeloid leukaemia; or
- (e) chronic lymphocytic leukaemia**

Fee: \$230.95 Benefit: 75% = \$173.25 85% = \$196.35

8. Proposed intervention's place in clinical management

Chronic lymphocytic leukaemia is the most common form of leukaemia. There were 1,161 new cases of CLL reported in Australian in 2012 (AIHW, 2016). There are more male patients diagnosed with CLL than female patients, with 745/1,161 (64%) of the Australian incident cases reported in 2012 being reported in men. The incident rate for CLL increases markedly with age, with very low incidence reported in patients less than 40 years of age, increasing steadily to an incidence rate of 37.6/100,000 in patients over 85.

The poor prognosis of the subgroup of CLL patients harbouring a 17p deletion or *TP53* mutation, coupled with their poor response to many of the chemotherapeutic agents most frequently used to treat CLL, results in there being a significant unmet clinical need for CLL treatments that have a therapeutic effect in 17p deletion and/or *TP53* mutation patients.

The application is seeking PBS-listing of venetoclax in combination with rituximab as a treatment for relapsed or refractory CLL patients who may be harbouring a 17p deletion or *TP53* mutation. The primary role of 17p deletion and/or *TP53* mutation testing in CLL patients is to provide prognostic information for CLL patients and for identifying patients resistant to chemoimmunotherapy regimens frequently used in the management of patients with CLL.

9. Comparator

The comparator for the proposed testing is no testing.

10. Comparative safety

The clinical utility (and thus the comparative safety, the comparative effectiveness and the comparative cost-effectiveness) of the 17p deletion test for the intended codependent purposes with CLL therapies that do not involve a purine analogue has been established by the strength of evidence previously considered by the PBAC.

11. Comparative effectiveness

The application stated that there is a high degree of consistency regarding both the methodological approach used (FISH) and specimen type tested (peripheral blood or bone marrow) across the clinical trials reporting on the efficacy of venetoclax and alternative CLL treatments recently developed (idelalisib + rituximab and ibrutinib).

The key clinical trial assessing the efficacy and safety of venetoclax in relapsed or refractory CLL harbouring a 17p deletion used the Vysis CLL Probe Kit at a threshold level of **redacted**% to determine the 17p deletion status of patients at the screening stage.

The results of the assessment of analytical specificity are outlined in Table 2.

Table 2 Assessment of analytical specificity of probes in Vysis CLL probe kit

Probe	Target	No. of metaphase chromosome signals - Hybridised to target	No. of metaphase chromosome signals - Total hybridised signals	Specificity, % (95%CI)
Vysis LSI TP53 SpectrumOrange	17p13.1	200	200	100 (98.17,100)
Vysis LSI ATM SpectrumGreen	11q22.3	200	200	100 (98.17,100)
Vysis LSI D13S319	13q14.3	200	200	100 (98.17,100)
Vysis LSI 13q34 SpectrumAqua	13q34	200	200	100 (98.17,100)
Vysis CEP 12 SpectrumGreen	12p11.1-q11	200	200	100 (98.17,100)

Source: Table 8 (p. 8) of Vysis CLL Probe Kit Package Insert

The results of the assessment of analytical sensitivity are outlined in Table 3.

Table 3 Assessment of analytical sensitivity of probes in Vysis CLL probe kit

Probe	Number of interphase nuclei - With expected signal pattern	Number of interphase nuclei - Scoreable signals	Sensitivity, % (95% CI)
Vysis LSI TP53 SpectrumOrange	4899	5000	97.98 (97.55, 98.35)
Vysis LSI ATM SpectrumGreen	4934	5000	98.68 (98.32, 98.98)
Vysis LSI D13S319	4930	5000	98.60 (98.23, 98.91)
Vysis CEP 12 SpectrumGreen	4947	5000	98.94 (98.62, 99.21)

Source: Table 9 (p. 9) of Vysis CLL Probe Kit Package Insert

Based on the data outlined in Table 2 and Table 3, the application stated that the Vysis CLL probes used to assess patient 17p deletion status prior to enrolment in the venetoclax clinical trial program have very high specificity (100%) and sensitivity (>97%) values. Based on the performance characteristics of the Vysis CLL Probe Kit, it was expected that the majority of patients enrolled in the key clinical trial of venetoclax in patients harbouring a 17p deletion (M13-982) would have been correctly identified as harbouring a 17p deletion.

Clinical claim

The application stated that, in broader clinical practice, the high performance characteristics of the Vysis CLL Probe Kit would precisely identify patients that harbour a 17p deletion (true positive) and would benefit from treatment with venetoclax instead of chemoimmunotherapy, whilst also being able to precisely identify patients with a normal karyotype (true negative) who may otherwise be managed with chemoimmunotherapy.

12. Economic evaluation

Cost-effectiveness was considered by the PBAC.

13. Financial/budgetary impacts

To estimate the cost to the MBS of listing 17p deletion testing for CLL patients, the application assumed that:

- 100% of patients will have an assessment of 17p deletion or *TP53* mutation testing at both the first-line and relapsed or refractory settings.
- 75% of 17p deletion or *TP53* mutation testing will be funded through the MBS, if funded. MSAC noted that, based on PBS dispensing data, 68% of patients have CLL treatment dispensed through private hospitals. Using an MBS-funded 17p deletion testing rate of 75% would account for some shifting of patient management, treatment and 17p deletion testing from the public to the private hospital setting.
- There is currently no 17p deletion testing being funded using MBS items 73290 or 73314.

The application's estimates of the total number of 17p deletion tests and overall cost to the MBS associated with proposed listing over five years are provided in Table 4. These estimates show that the estimated cost remains below \$redacted per year across five years, with an overall five-year cost of \$redacted.

Table 4 Estimated cost to the MBS of the proposed listing

Table redacted

The cost of 17p deletion or *TP53* mutation testing would be higher in the first-line setting (\$redacted over five years) than in the relapsed or refractory settings where testing to determine patient eligibility to access PBS-listed venetoclax or idelalisib + rituximab is required (\$redacted over five years). Also, the role of 17p deletion or *TP53* mutation testing, and cost of testing to the MBS, would be the same irrespective of whether venetoclax is funded or not. This is because 17p deletion testing has a widely accepted role in managing patients with CLL even if treatment with venetoclax or idelalisib + rituximab is not being considered.

14. Other significant factors

Nil.

15. Applicant's comments on MSAC's Public Summary Document

AbbVie welcomes the decision of MSAC and is working with the Department of Health on the earliest possible MBS listing.

16. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: [visit the MSAC website](#)