



Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1560 – 17p deletion testing by fluorescence *in situ* hybridization for access to ibrutinib in patients with previously untreated chronic lymphoid leukaemia or small lymphocytic lymphoma

Applicant: Janssen-Cilag Pty Ltd

Date of MSAC consideration: MSAC 77th Meeting, 28-29 November 2019

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

1. Purpose of application

An application requesting an amendment to the Medicare Benefits Schedule (MBS) item 73343 to broaden the reimbursement of the fluorescence *in situ* hybridization (FISH) test for the detection of 17p deletion (*del(17p)*) for all patients with chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL) requiring treatment, agnostic of line of therapy.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC supported the modification of existing MBS item 73343, to expand the eligible population for this test to include previously untreated patients and to limit the testing to no more frequently than one test per year.

MSAC advised that implementation of this advice should not necessarily be impeded by the implementation of its related advice from Application 1544.

Consumer summary

Janssen-Cilag Pty Ltd applied for public funding through the Medicare Benefits Schedule (MBS) for a genetic test in people with chronic lymphoid leukaemia (CLL) or small lymphocytic lymphoma (SLL), which are two closely related blood cancers. The test is called fluorescence *in situ* hybridisation (FISH). It is done to see if a person with CLL or SLL has a deletion of a short amount of genetic material in their chromosome 17 (*del(17p)*). If such a person has such a deletion, then it means they may be able to safely and effectively use certain medicines that are listed on the Pharmaceutical Benefits Scheme (PBS). These medicines (idelalisib, ibrutinib and venetoclax) work better than alternative medicines in people with *del(17p)*.

Consumer summary

People with CLL or SLL who have *del(17p)* and who did not respond to or no longer respond to one or more other cancer treatments before can already get idelalisib, ibrutinib and venetoclax through the PBS. This is called second-line treatment.

This application was for FISH testing in people who have never been treated before for CLL or SLL. Ibrutinib would be the first treatment they have (called first-line treatment). MSAC considered the evidence and advised that FISH testing at the time that a patient's CLL or SLL is diagnosed is sufficiently accurate to help determine eligibility for first-line ibrutinib.

The application depended on whether the Pharmaceutical Benefits Advisory Committee (PBAC) decided to fund ibrutinib on the PBS as first-line treatment. In November 2019, PBAC recommended ibrutinib be listed as a first-line treatment.

MSAC's advice to the Commonwealth Minister for Health

MSAC supported public funding of FISH testing for *del(17p)* for people who have just been diagnosed with CLL or SLL, so they can access first-line ibrutinib on the PBS.

3. Summary of consideration and rationale for MSAC's advice

This application was to extend *del(17p)* testing by fluorescence *in situ* hybridisation (FISH) to patients with a new diagnosis of chronic lymphoid leukaemia (CLL) or small lymphocytic lymphoma (SLL) for access to ibrutinib. Testing is currently available for patients with relapsed or recurrent CLL or relapsed or recurrent SLL to access idelalisib, ibrutinib or venetoclax (MBS item 73343).

MSAC noted that, in November 2019, the Pharmaceutical Benefits Advisory Committee (PBAC) made a positive recommendation for extending the listing for ibrutinib to previously untreated patients with CLL or SLL with *del(17p)*.

MSAC noted that this was a minor application that had bypassed its Evaluation Sub-Committee (ESC). This is because MSAC has already accepted the comparative safety, clinical effectiveness and cost-effectiveness for this type of genetic testing at a later time point of CLL or SLL (MBS item 73343). MSAC confirmed that FISH testing using a threshold level of **redacted**% of nuclei in the sample harbouring the deletion was the "evidentiary standard" for this application (that is, the test methodology used to determine *del(17p)* status as part of the eligibility criteria into the clinical study supporting the clinical effectiveness of ibrutinib in first-line CLL or SLL) and also the approach most widely used currently in Australian pathology laboratories.

MSAC noted there is a concurrent application (Application 1544) for using genome-wide microarray (GWMA) technology which can detect *del(17p)* amongst many other pathogenic variants. MSAC accepted that microarray testing may eventually supersede FISH, but noted that FISH is still suitable for detecting *del(17p)* as per this application.

MSAC considered the current fee of \$230.95 to be too low to cover the true cost of the test as it is currently performed as part of a CLL panel. However, since FISH may eventually be superseded by microarray testing, MSAC considered it suitable to leave the fee as is until such time as its related advice from Application 1544 is implemented.

MSAC considered that retesting is not necessary after a positive test result, but that there is a need to retest after a negative result at each relapse, as per the International Working Group on CLL guideline. MSAC therefore advised that such testing be limited to no more frequently than one test per year. MSAC advised that, as a result of supporting more than one test per patient, the net financial estimates in the application need not be further adjusted for any decreases in the current low MBS billing rates for *del(17p)* testing after relapse.

MSAC supported the following wording changes (in red) to the descriptor for MBS item 73343. MSAC supported including lymph node tissue, in line with the type of samples likely taken during initial diagnosis.

MBS item 73343

Category 6 – PATHOLOGY SERVICES

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 ~~or lymph node tissue 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.

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

Other issues

MSAC noted the PBAC's request to consider tumour protein 53 (*TP53*) testing in this context, as patients with CLL or SLL with a *TP53* mutation carry a similar poor prognosis as patients with *del(17p)*. The *TP53* gene is located on chromosome 17p. Thus, *TP53* function is lost in patients with *del(17p)*, but patients may lose *TP53* function even with an intact chromosome 17p due to other types of mutations. FISH can detect translocations and insertions/deletions, but is unable to detect other types of genetic variations. In this context, MSAC also considered including immunoglobulin heavy chain (*IGHV*) hypermutation status, as this has favourable prognostic value for patients with CLL or SLL. However, MSAC advised that a separate application for *TP53* and *IGHV* genetic testing be prepared to cover patients with CLL or SLL, as genetic sequencing is required to detect these mutations and so cannot be considered under the current application, which is for FISH. There is also a need to consider the optimal timing of these test alternatives, noting the small incremental yield of the proposed additional testing.

4. Background

In April 2017, MSAC supported the listing of *del(17p)* testing as a codependent test to support access to the kinase inhibitors idelalisib and ibrutinib, which were both earlier recommended by PBAC for listing on the PBS for the treatment of patients with relapsed or refractory CLL or relapsed or refractory SLL whose disease is characterised by a chromosome 17p deletion (see PSD for Application 1456, MSAC 69th Meeting, 6-7 April 2017).

In November 2018, MSAC supported amending MBS item 73343 to include *del(17p)* deletion testing in patients with relapsed or refractory CLL to determine access to venetoclax under the PBS (see PSD for Application 1456, MSAC 74th Meeting, 22-23 November 2018).

5. Prerequisites to implementation of any funding advice

The Applicant stated that the FISH test is widely accessible in Australia, and in clinical practice the test would be requested by specialists or consultant physicians (haematologist/oncologist), and qualified pathologists in National Association of Testing Authorities (NATA) accredited pathology testing laboratories would deliver the service. The

Royal College of Pathologists of Australasia (RCPA) accredits laboratories for pathology training, approves supervised training undertaken in an accredited laboratory and conducts examinations leading to certification as a qualified pathologist and Fellow of the College (FRCPA).

The Applicant confirmed with the RCPA and the Australasian Society of Diagnostic Genomics (ASDG) that a quality assurance program, run by these pathology groups is already in place for FISH testing in NATA accredited laboratories. The QAP module qualitatively assesses laboratory performance in the detection of *TP53* deletions at *17p13.1* in CLL using FISH (<https://rcpaqap.com.au/product/molecular-haematology-module-12/>).

Based on this information provided by RCPA and ASDG, the Applicant advised that FISH testing for *del(17p)* in previously untreated patients with CLL or SLL would be covered by the existing QAP as it will be conducted in the same NATA accredited laboratories, by the same pathologists, and according to the same standards as per current practice for patients with relapsed or refractory CLL or relapsed or refractory SLL.

6. Proposal for public funding

The proposed amendment to MBS item 73342 is summarised in Table 1.

The Applicant's proposed amendment would broaden the reimbursement of the FISH test for the detection of *del(17p)* for all patients with CLL or SLL requiring treatment, agnostic of line of therapy. Note the fee and benefit remain unchanged to the current MBS item 73343.

Table 1 Proposed amendment to MBS item 73343

| Category 6 – PATHOLOGY SERVICES |
|--|
| <p>Proposed item descriptor:</p> <p>Detection of 17p chromosomal deletions by fluorescence in situ hybridisation, in a patient with chronic lymphocytic leukaemia or small lymphocytic lymphoma, and testing is via a peripheral blood, or bone marrow or lymph node tissue sample, requested by a specialist or consultant physician, to determine if the requirements for access to ibrutinib, idelalisib or venetoclax on the Pharmaceutical Benefits Scheme are fulfilled.</p> <p>Explanatory notes: This test is not intended for monitoring purposes. This item number should not be used more than once per year per patient.</p> <p>Fee: \$230.95 Benefit: 75% = \$173.25 85% = \$196.35</p> |

Source: Table 3.1, p7 of the Minor Submission

Pre-MSAC response

The Applicant responded to the PBAC request for advice from MSAC on the following questions:

Whether to extend the proposed PBS restriction to include TP53 mutations as an alternative to del(17p)?

The Applicant supported the inclusion of this test outcome in the proposed PBS restriction wording provided that broadening the restriction to include the *TP53* mutation positive population would not negatively impact the timing of the PBS listing of ibrutinib in the requested *del17p* population and the MBS listing of the FISH test for *del(17p)*.

Whether to limit the proposed extension to the restriction to those TP53 mutations detected by this method or to be method agnostic?

The Applicant stated it would support the PBS restriction criteria wording for ibrutinib to be method agnostic. Below are its two options of suggested wording under the clinical criteria for this scenario:

1. The patient must show evidence of one or more 17p chromosomal deletions and/or TP53 mutations as demonstrated by an appropriate test. The presence of 17p deletion and/or TP53 mutation without any signs of active disease is not an indication for treatment.
OR
2. The patient must show evidence of one or more TP53 aberrations as demonstrated by an appropriate test. The presence of TP53 aberrations without any signs of active disease is not an indication for treatment.

... the likely increase in the proportion of patients eligible for ibrutinib via the proposed restriction beyond relying on del(17p) alone?

Consistent with the pre-PBAC response, the Applicant proposed that, should the PBS listing for ibrutinib include both TP53 mutations and del(17p), the prevalence be adjusted to **redacted**%.

Whether consideration should be given to modifying the existing PBS restrictions which mention “Evidence of one or more 17p chromosomal deletions demonstrated by fluorescence in situ hybridisation (FISH)” for medicines in CLL or SLL?

The Applicant stated that, should the MSAC and the PBAC agree that the PBS restriction wording for IBR be agnostic to testing methodology, it would seem appropriate that other existing PBS listed restriction wording for other medicines which specify del(17p) and/or TP53 mutations be modified.

7. Proposed intervention’s place in clinical management

The modification of existing MBS item 73343 to allow FISH testing for the detection of del(17p) for all patients with CLL or SLL requiring treatment, regardless of treatment line, would enable the identification of patients with a high clinical need who would benefit from first-line treatment with ibrutinib instead of chemoimmunotherapy, whilst also identifying patients with a normal karyotype who may otherwise be managed with chemoimmunotherapy.

8. Comparative effectiveness

Evidentiary standard

The application stated that patients enrolled in the pivotal trial of first-line ibrutinib (iLLUMINATE) must have documented del(17p) by Vysis CLL FISH Probe Kit (Abbott Molecular Inc). A threshold level of **redacted**% to determine del(17p) was used at the screening stage into the trial. This means that the patient tested positive for del(17p) if more than **redacted**% of nuclei in the sample harboured the del(17p).

This FISH test and threshold is the same as that used to support the existing MBS item.

9. Financial/budgetary impacts

An epidemiological approach was utilised to estimate the utilisation of the FISH test if it was reimbursed for the detection of del(17p) in patients with previously untreated CLL or previously untreated SLL (Table 2).

Table 2 Utilisation estimates of the FISH test (MBS item 73343) in patients with previously untreated CLL or previously untreated SLL who require treatment

| Data | Year 1 2020 | Year 2 2021 | Year 3 2022 | Year 4 2023 | Year 5 2024 | Year 6 2025 |
|---|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Australian population | 26,037,356 | 26,452,147 | 26,866,209 | 27,279,046 | 27,690,209 | 28,099,273 |
| Incident population with previously untreated CLL or previously untreated SLL | | | | | | |
| Incidence of CLL ^a | 1,652 | 1,697 | 1,745 | 1,792 | 1,839 | 1,887 |
| Incidence of SLL ^b | 306 | 313 | 320 | 326 | 333 | 339 |
| Total incidence of CLL or SLL | 1,958 | 2,010 | 2,065 | 2,118 | 2,172 | 2,226 |
| Proportion of patients to be tested using MBS 73343, % | redacted% | redacted% | redacted% | redacted% | redacted% | redacted% |
| Patients to be tested using MBS 73343, n | redacted | redacted | redacted | redacted | redacted | redacted |
| Prevalent population with previously untreated CLL or previously untreated SLL | | | | | | |
| Prevalent population with CLL or SLL | 10,337 | | | | | |
| Proportion of patients to be tested using MBS 73343, % | redacted% | | | | | |
| Patients to be tested using MBS 73343, n | redacted | | | | | |
| Proportion of patients to be tested using MBS 73343 over time, % | redacted% | redacted% | redacted% | redacted% | redacted% | redacted% |
| Patients to be tested using MBS 73343, n | redacted | redacted | redacted | redacted | redacted | redacted |
| Total population with previously untreated CLL or previously untreated SLL tested for <i>del(17p)</i> by FISH (MBS Item 73343) | | | | | | |
| Incident (n) | redacted | redacted | redacted | redacted | redacted | redacted |
| Prevalent (n) | redacted | redacted | redacted | redacted | redacted | redacted |
| Total (n) | redacted | redacted | redacted | redacted | redacted | redacted |

Source: Table 4.2, p12 of the pre-MSAC response

^a (AIHW, Australian Cancer Incidence and Mortality (ACIM) books, 2017)

^b Data Request to AIHW

The applicant estimated that the yearly cost of amending MBS item 73343 to broaden the reimbursement of the FISH test for detection of *del(17p)* for all patients with CLL or SLL patients will range from a high of \$redacted in Year 1 (year 2020) to a low of \$redacted in Year 6 (Year 2025) for a cumulative cost of \$redacted over the first 6 years (Table 3).

Table 3 Estimated cost to the MBS of the proposed amendment to MBS item 73343

| Data | Year 1 2020 | Year 2 2021 | Year 3 2022 | Year 4 2023 | Year 5 2024 | Year 6 2025 |
|---|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
| Patients who will utilise the test (n) | redacted | redacted | redacted | redacted | redacted | redacted |
| Fee for MBS 73343 with 85% benefit (\$) | \$redacted | \$redacted | \$redacted | \$redacted | \$redacted | \$redacted |
| Total (\$) | \$redacted | \$redacted | \$redacted | \$redacted | \$redacted | \$redacted |

Source: Table 5.1, p13 of the pre-MSAC response

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

The applicant had no comment.

11. Further information on MSAC

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