Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1606 – Request to amend existing MBS item 73341 (fluorescence in situ hybridisation (FISH) test of tumour tissue from a patient with locally advanced or metastatic non-small cell lung cancer) to add brigatinib

Applicant: **Takeda Pharmaceuticals Australia 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 to include brigatinib as one of the listed medicines for the existing Medicare Benefits Schedule (MBS) item 73341 for patients with anaplastic lymphoma kinase (ALK) rearranged locally advanced or metastatic non-small cell lung cancer (NSCLC) was received from Takeda Pharmaceuticals Australia Pty Ltd by the Department of Health.

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 amending MBS item 73341 (fluorescence *in situ* hybridisation [FISH] test of tumour tissue from a patient with locally advanced or metastatic non-small cell lung cancer [NSCLC] to determine access to PBS-listed anaplastic lymphoma kinase [ALK] inhibitors) to include brigatinib.

MSAC supported the modification of existing MBS item 73341 to refer to Pharmaceutical Benefits Scheme (PBS)-subsidised ALK inhibitors as a therapeutic class rather than to list the individual PBS-subsidised medicines.

Consumer summary

Takeda Pharmaceuticals Australia Pty Ltd applied to the Medical Services Advisory Committee (MSAC) to change the description of Medicare Benefits Scheme (MBS) item 73341. This item is for the testing of tumour tissue from people with a certain type of lung cancer (non-small cell lung cancer, or NSCLC) which has spread to the lymph nodes in the middle of the chest (called locally advanced) or has spread elsewhere in the body (called metastatic). A test called fluorescence *in situ* hybridisation (FISH) is done to see whether that person can use certain medicines that are listed on the Pharmaceutical Benefits Scheme (PBS).

MBS item 73341 already lists three medicines which all come from a group of medicines called 'ALK (anaplastic lymphoma kinase) inhibitors'. This application was to add another medicine called brigatinib to this list. The Pharmaceutical Benefits Advisory Committee (PBAC) recommended listing brigatinib on the PBS in November 2019.

MSAC decided that the words 'ALK (anaplastic lymphoma kinase) inhibitors' could be used in MBS item 73341 instead of listing each of the medicines separately.

Changing this item will not change the number of people who have this test or the cost to the MBS.

MSAC's advice to the Commonwealth Minister for Health

MSAC supported changing MBS item 73341 to refer to 'ALK inhibitors' rather than list each medicine separately. This is because ALK inhibitors all achieve their effect in a similar way.

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

MSAC noted that this application is a minor submission requesting amendment of MBS item 73341 to include brigatinib as one of the listed medicines for which FISH testing of tumour tissue is used to detect anaplastic lymphoma kinase (*ALK*) gene rearrangements and thus help determine access for patients with locally advanced or metastatic NSCLC.

MSAC noted the PBAC's positive recommendation in November 2019 to list brigatinib for use as monotherapy in the treatment of patients with locally advanced (Stage IIIB) or metastatic (Stage IV) ALK-positive NSCLC. FISH is a companion diagnostic test.

MSAC advised that, rather than adding brigatinib to the list of medicines already in the MBS item descriptor (crizotinib, ceritinib and alectinib), it would be appropriate to modify the descriptor to remove the individually-listed medicines and refer to 'ALK inhibitors' as a therapeutic class.

MSAC advised amending the descriptor for MBS item 73341 as follows:

> Fluorescence in situ hybridisation (FISH) test of tumour tissue from a patient with locally advanced or metastatic non-small cell lung cancer, which is of non-squamous histology or histology not otherwise specified, with documented evidence of anaplastic lymphoma kinase (ALK) immunoreactivity by immunohistochemical (IHC) examination giving a staining intensity score >0, and with documented absence of activating mutations of the epidermal growth factor receptor (EGFR) gene, requested by a specialist or consultant physician to determine if requirements relating to ALK gene rearrangement status for access to ~~crizotinib, ceritinib, or alectinib~~ an ALK inhibitor under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.

MSAC noted that there was no request to change the testing methodology or the MBS fee.

MSAC noted that this application 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 for other medicines of the same therapeutic class. MSAC confirmed that FISH testing was the "evidentiary standard" for this application (that is, the test methodology used to detect *ALK* gene rearrangements as part of the eligibility criteria into the clinical studies supporting the clinical effectiveness of brigatinib in NSCLC).

MSAC considered that because testing for ALK rearrangement in patients with locally advanced or metastatic NSCLC for access to PBS-listed ALK inhibitors is established clinical practice in Australia, the addition of brigatinib to MBS item 73341 is unlikely to change the number of patients accessing this item. On this basis, MSAC advised that there will be no net financial impact to the MBS from the supported amendment.

4. Background

MBS item 73341 is for fluorescence *in situ* hybridisation (FISH) testing of tumour tissue in patients with NSCLC to help determine access to crizotinib, ceritinib, or alectinib.

Brigatinib was recommended at the 6-8 November 2019 PBAC meeting for use as monotherapy in the treatment of NSCLC.

5. Prerequisites to implementation of any funding advice

The National Pathology Accreditation Advisory Council (NPAAC) advised that the testing methodology is mature and that there is an external quality assurance program (EQA) available.

6. Proposal for public funding

The requested amendment to MBS item 73341 is provided in Table 1. Proposed additions are *italicised*, and deletions are marked with strikethrough.

The MBS item is amended to include 'brigatinib' as one of the listed medicines which require *ALK* gene rearrangement as a condition of access under the PBS. This will not result in a change to testing methodology, the patient population who access testing through the MBS, or to the MBS fee.

Table 1 Proposed amendments to MBS item 73341

	Category 6 – PATHOLOGY SERVICES
73341	**Group** P7 - Genetics
Fluorescence in situ hybridisation (FISH) test of tumour tissue from a patient with locally advanced or metastatic non-small cell lung cancer, which is of non-squamous histology or histology not otherwise specified, with documented evidence of anaplastic lymphoma kinase (ALK) immunoreactivity by immunohistochemical (IHC) examination giving a staining intensity score > 0, and with documented absence of activating mutations of the epidermal growth factor receptor (EGFR) gene, requested by a specialist or consultant physician to determine if requirements relating to ALK gene rearrangement status for access to crizotinib, ceritinib, ~~or~~ alectinib *or brigatinib* under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.	
Fee: $400.00 **Benefit:** 75% = $300.00 85% = $340.00	

Source: Table 1, p1 of the Minor Submission

7. Proposed intervention's place in clinical management

The applicant's proposed amendment would add brigatinib as an additional treatment option for patients with locally advanced or metastatic NSCLC and *ALK* gene rearrangements. MBS item 73341 describes the testing of tumour tissue by FISH to determine if PBS requirements relating to *ALK* gene rearrangement status are fulfilled.

8. Comparative effectiveness

Evidentiary standard

The application stated that patients enrolled in the two pivotal trials of brigatinib (Study AP26113-13-201 [201-ALTA], and Study AP26113-13-301 [ALTA-1L]) must have documented *ALK* positivity by Vysis ALK Break-Apart FISH Probe Kit (Abbott Molecular Inc). ALTA-1L also accepted *ALK* rearrangement demonstrated by Ventana ALK (D5F3) CDx immunohistochemistry (IHC) Assay (Ventana Medical Systems, Inc.). Subjects with documented *ALK* positivity by Ventana IHC assay, or other laboratory-developed test (LDT) must have sufficient tissue available for central laboratory testing with the Vysis ALK Break-Apart FISH Probe Kit. Thus, all patients enrolled in the brigatinib clinical trial program had confirmed *ALK* rearrangement status by FISH testing. Central testing was performed according to manufacturer's instructions. Consistent with the threshold in the PBS restrictions for the existing ALK inhibitors, an abnormal signal pattern in ≥ 15% of cells assessed was classified as a 'positive' result (see Table 2).

Comparison with other PBS-listed medicines

A comparison of *ALK* testing methods used in the clinical trials of brigatinib and other PBS-listed comparator treatments is presented in Table 2.

Table 1 Comparison of *ALK* rearrangement testing protocols for brigatinib, and other PBS-listed medicines

Measure	Brigatinib [1,2]	Alectinib [3]	Crizotinib [4]	Ceritinib [5]
Protocol-specified test for trial inclusion	Vysis ALK Break-Apart FISH Probe Kit Ventana ALK (D5F3) CDx IHC Assay [6]	Ventana ALK (D5F3) IHC test	ALK Break-Apart FISH assay	Vysis ALK Break-Apart FISH Probe Kit
Confirmation by central laboratory	Yes – by Vysis FISH test for patients with no prior result or a positive result by other testing method (i.e. LDT, Ventana IHC)	Yes – all samples sent to central laboratory for analysis by Vysis FISH probe kit and Ventana IHC assay	Yes – all positive samples sent to central laboratory for analysis by FISH	Only in patients without documented *ALK* positivity - by Vysis FISH test
Tumour sample for testing	FF PE tissue acquired prior to randomisation, from primary tumour or biopsied metastasis	Mandatory pre-treatment tumour samples used to centrally examine ALK status by IHC and FISH. FF tumour blocks were the preferred source, but unstained slides were also accepted	Archived or fresh tumour sample. Paraffin block(s) of adequate size to allow assessment of ALK gene fusion by FISH at a central laboratory (min 10 slides)	New tumour biopsy collected prior to enrolment and prior to first dose of study treatment
Determination of *ALK* positivity by FISH test	Split signal or single red signal (3' *ALK*), occurring in no less than 15% of 50-100 nuclei assessed	NR	≥ 15% of tumour cells with split *ALK 5' and 3'* probe signals, or isolated 3' signal	NR

Source: Table 2, p2 of the Minor Submission

Abbreviations: FF, formalin-fixed FISH, fluorescent *in situ* hybridisation; IHC, immunohistochemistry; LDT, laboratory developed test; NR, not reported; PE, paraffin-embedded

1. Study AP26113-13-201 Central Vysis FISH test report
2. Study AP26113-13-301 Clinical Study Report, section 9.5.1.1.3 pg, 52
3. Protocol for: Peters 2017
4. Protocol for: Shaw 2013
5. Shaw 2017
6. ALK rearrangement by Ventana (D5F3) IHC assay permitted in ALTA-1L with central lab confirmation by Vysis ALK FISH test

9. Financial/budgetary impacts

The application stated the inclusion of brigatinib within the wording of MBS item 73341 will not alter utilisation of this service.

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

The applicant has no further comments.

11. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website:
visit the MSAC website