



Australian Government
Medical Services Advisory Committee

Public Summary Document

Application No. 1163.1 – Testing for HER2 status in gastric cancer for access to trastuzumab

Applicant: Roche Products Pty Ltd

Date of MSAC consideration: MSAC 64th Meeting, 30-31 July 2015

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, see at www.msac.gov.au

1. Purpose of application and links to other applications

In February 2011, an integrated co-dependent application requesting Medicare Benefits Schedule (MBS) listing of *in situ* hybridisation for detection of amplification of the human epidermal growth factor receptor 2 (HER2) gene in gastric cancer and Pharmaceutical Benefits Schedule (PBS) listing for trastuzumab in HER2-positive metastatic gastric cancer (encompassing the stomach or the gastro-oesophageal junction) was received from Roche Products Pty Limited.

This application proposed a co-dependent package of two types of health technology (a pathology test and a medicine) subsidised through two different programs and therefore required advice from the Medical Services Advisory Committee (MSAC) to be coordinated with that of the Pharmaceutical Benefits Advisory Committee (PBAC).

Both PBAC and MSAC deferred the co-dependent application. In February 2015, the applicant submitted a second application for consideration.

2. MSAC's advice to the Minister

After considering the outstanding issues regarding testing for HER2 status in gastric cancer for access to trastuzumab, MSAC confirmed that, following the July 2015 PBAC recommendation to list trastuzumab in the PBS for this indication, MSAC supported public funding via a new MBS item for *in situ* hybridisation (ISH) testing of HER2 status in gastric cancer.

MSAC advised that the MBS item descriptor should reflect the attributes indicated by the following option, noting that the detail of the text for the item descriptor and item structure would be finalised by the Department:

- An in situ hybridization (ISH) test of tumour tissue from a patient with metastatic adenocarcinoma of the stomach or gastro-oesophageal junction,
- with documented evidence of human epidermal growth factor receptor 2 (HER2) overexpression by immunohistochemical (IHC) examination giving a staining intensity score of 2+ or 3+ on the same tumour tissue *unless biopsy or resection specimens are not available and so paraffin embedded cell blocks need to be used*,
- requested by, or on the advice of, a specialist or consultant physician who manages the treatment of the patient to determine if the requirements relating to human epidermal growth factor receptor 2 (HER2) gene amplification for access to trastuzumab under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.

MSAC had no objection to the proposed MBS fee of \$315.40.

MSAC re-affirmed that the definition of HER2 positivity to be reflected in the PBS restriction to help determine eligibility for PBS-subsidised trastuzumab should be:

Patient must have evidence of human epidermal growth factor receptor 2 (HER2) gene amplification as demonstrated in the tumour material by both (a) immunohistochemistry (IHC)2+ OR IHC3+ AND (b) in situ hybridisation (ISH) results based on both more than 6 copies of HER2 AND the ratio of HER2:chromosome 17 being more than 2.

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

MSAC considered the outstanding issues arising from its November 2012 consideration and from the July 2015 PBAC recommendation to list trastuzumab.

MSAC noted the eligible population for trastuzumab confirmed by PBAC of patients with metastatic (Stage IV) HER2-positive adenocarcinoma of the stomach or gastro-oesophageal junction. MSAC did not consider it necessary to expand the testing population to also include patients with inoperable locally advanced or recurrent (Stage III) gastric cancer as requested by the applicant because the turnaround time for testing would not unnecessarily delay the decision to start trastuzumab, and earlier testing would unnecessarily increase the risk of starting trastuzumab in non-metastatic gastric cancer.

MSAC agreed with the applicant's request to require simply that HER2 testing be performed on tumour material. MSAC no longer considered it necessary to state a preference that HER2 testing be performed on metastatic tissue when available, considering that this issue is best determined by clinicians and pathologists on a case-by-case basis.

MSAC also agreed with the applicant's request, as re-emphasised in its pre-MSAC response, to not state a preference for dual probe testing over single probe testing, again considering that this issue is best determined by pathologists on a case-by-case basis.

MSAC confirmed that the MBS item descriptor should specify the prerequisite results of the immunohistochemistry (IHC) test to initiate ISH testing. For cases without tissue blocks, MSAC agreed that cell blocks could be tested by ISH without pre-screening by IHC.

MSAC accepted advice from its ESC that the retesting rate was within acceptable limits (5%) and would not have an appreciable effect on the economic evaluation, or the financial implications for the MBS. MSAC confirmed that there was no need to account for resampling in the MBS item descriptor. MSAC also noted that the July 2015 PBAC meeting had raised

the possibility of extending its recommended risk-share arrangements for trastuzumab to also include HER2 ISH testing, but decided against supporting this option because it is currently not an option for MBS-listed items.

MSAC affirmed its suggestion that data should be collated across standardised reports to the requesting oncologists to confirm eligibility of individuals for trastuzumab, including: diagnosis and staging of disease, IHC result, HER2 copy number from ISH, HER2 to chromosome ratio from ISH, and nature of specimen (whether cell block or not).

4. Background

The applicant first requested a PBS listing for trastuzumab in HER2-positive metastatic gastric cancer in 2011. At that time PBAC rejected the submission on the basis of ‘unacceptably high and uncertain incremental cost-effectiveness ratios’ and advised that any future resubmission would also have to be considered by MSAC.

In November 2012, a co-dependent resubmission was considered by both PBAC and MSAC. PBAC deferred its decision until MSAC could advise on the optimal testing algorithm to be used in Australia. MSAC deferred the decision to list HER2 ISH testing until such a time as the PBAC made a decision regarding the PBS listing for trastuzumab. MSAC also provided advice to PBAC about the relevant matters identified by MSAC that should be addressed in any subsequent consideration.

The table below summarises the key recommendations about the potential MBS listing made by MSAC in the November 2012 consideration and the position taken on each by the applicant in its second co-dependent application.

MSAC issue	Applicant's position
Matters largely settled	
Preference for testing tumour specimens, not cytology specimens.	The Applicant agreed and provided suggested explanatory notes to accompany the MBS item descriptor.
The definition of HER2 test positive should be both (a) IHC2+ or IHC3+ and then (b) ISH results based on both >6 copies of HER2 and the ratio of HER2:chromosome 17 being >2.	The Applicant accepted the MSAC recommendations for the definition of HER2 positivity.
The proposed MBS item should therefore be made a pathologist determinable service.	The Applicant agreed that the MBS item should be made a pathologist determinable service.
The proposed MBS item descriptor should allow any accepted type of ISH testing.	The Applicant agreed that the MBS item descriptor should allow for any accepted type of ISH to be used.
The sensitivity analyses of the economic evaluation should appropriately examine the likely extent of proportions of false positive test results and false negative test results.	<p>The Applicant revised the structure of the economic model to include some consideration of the consequences of false positive and false negative test results. The new model does not completely reproduce the testing algorithm proposed for use in Australia, and the model uses the accuracy of ISH alone as a proxy for the accuracy of IHC testing followed by ISH testing for those with IHC scores 2+ and 3+ only.</p> <p>The sensitivity analyses reported by the Applicant are only marginally different to the \$45,000-75,000/QALY gained base-case ICER.</p>
Pathology practice should be optimised to ensure HER2 testing for metastatic gastric cancer is limited to laboratories with expertise and back-up by requiring that the one laboratory performs both the IHC and ISH testing on the specimen.	The Applicant supported a centralised approach to performing HER2 testing in Australia.
Matters requiring further consideration by MSAC	
A centralised approach should also be developed to facilitate the collation of data across standardised reports to the requesting oncologists on the IHC score, the number of HER2 copies and the ratio of HER2 to chromosome 17.	The Applicant offered to work with the Department and professional bodies to develop appropriate data collection and standardised reporting tools that will comply with any specific data collation requirements outlined by MSAC to facilitate optimisation of testing.
The eligible patient population for HER2 testing would have Stage IV (metastatic) adenocarcinoma of the stomach or gastro-oesophageal junction (metastatic gastric cancer) and that there was no need or basis to further enrich the population eligible for testing.	The Applicant requested that the eligible population for HER2 testing for gastric cancer should be expanded to include all patients with inoperable locally advanced, recurrent or metastatic gastric cancer, with the intention that these patients would be tested at the time of diagnosis. The Applicant argued that this is

MSAC issue	Applicant's position
Matters largely settled	
	a pragmatic approach to testing, and is comparable to the approach endorsed by MSAC for EGFR testing for patients with non-small cell lung cancer (Application 1161).
The proposed MBS item descriptor should indicate a preference for testing the metastasis rather than the primary tumour.	The Applicant requested that the MBS item descriptor should not specify a preference for testing tissue from the metastasis over testing the primary tumour. It noted that this is consistent with the testing regimen used in the ToGA trial, in which tissue from either the primary tumour or a metastasis could be used for HER2 testing.
The proposed MBS item descriptor should refer to dual probe rather than single probe testing.	The Applicant requested that the use of a single- or dual-probe is not specified in the proposed MBS item descriptor. Based on the findings of the GaTHER study, the Applicant believed that specifying the use of dual-probe testing is not appropriate. Consequently, it did not include a reference to the use of either a dual-probe or single-probe approach in its proposed MBS item descriptor.
The economic evaluations and financial analyses presented to PBAC should include a re-sampling (new biopsy or new extraction from resected tissue) rate of 5% to reflect the rate of indeterminate results from the initial test, for example, due to excessive heterogeneity.	The Applicant incorporated the cost of retesting due to indeterminate results into the cost of HER2 testing. In the base-case and sensitivity analyses, 5% of the population are retested at both testing stages. Retested patients receive a second IHC test cost of \$74.50 and a second ISH test cost of \$315.40. Retested patients were not assigned additional costs for patient episode initiation or specimen retrieval, storage or enrichment. Resampling in the case of insufficient tissue was not costed in the financial impact analysis.
Wording of the proposed MBS item for HER2 ISH testing.	<p>The Applicant proposed the creation of a new MBS item for confirmatory HER2 ISH testing in gastric cancer patients. The new wording complied with the recommendations made by MSAC, except for the following:</p> <ul style="list-style-type: none"> • Did not include a preference for testing the metastasis rather than the primary tumour • Did not explicitly require dual-probe rather than single-probe testing. • Expanded the eligible population from metastatic gastric cancer only, to all patients with inoperable locally advanced, recurrent or metastatic gastric cancer.
Cost to the MBS of the proposed listing	In the current application, the cost to the MBS

MSAC issue	Applicant's position
Matters largely settled	
	of the requested listing increased by \$45,694 (Year 1, 2016) over the cost in the 2012 application. This increase in cost was primarily due to including a 5% retesting rate and using an alternative source for the IHC diagnostic yield (Australian AGC testing program replaces ToGA and GaTHER data).

5. Prerequisites to implementation of any funding advice

In the setting of advanced gastric cancer, trastuzumab may be delivered in either an inpatient or outpatient setting and is TGA-approved to be co-administered in addition to cisplatin and a fluoropyrimidine.

Prerequisite immunohistochemistry (IHC testing) should be performed in a National Association of Testing Authorities accredited laboratory. The low volume of cases and range of unique gastric cancer-specific issues (such as heterogeneity of expression within tumour samples) ideally would require laboratory participation in the Royal College of Pathologists of Australasia quality assurance program. Given the heterogeneity of receptor expression in tissue samples, experts recommend that ISH is performed with access to the IHC test/slide to guide the direction of reading (where possible).

6. Proposal for public funding

The Applicant agreed with MSAC that testing should be limited to biopsy and resection specimens. The Applicant also agreed that if biopsy and resection specimens are not available, then paraffin embedded cell blocks may be used for ISH testing, without the requirement for IHC testing as a prerequisite.

In addition, the Royal College of Pathologists of Australasia (RCPA) provided its opinion on this issue in a letter dated March 2015, and strongly recommended that testing on cytology samples be permitted, as this may be the only material available from metastatic deposits.

The Applicant proposed the creation of a new MBS item for confirmatory HER2 ISH testing in gastric cancer patients. The revised wording for the proposed MBS item descriptor is presented below.

Proposed MBS item descriptor for HER2 ISH testing in gastric cancer patients

Category [6] – [Pathology services]

MBS [XXXXXX]

An in situ hybridization (ISH) test of tumour tissue from a patient with **inoperable, locally advanced, recurrent or metastatic adenocarcinoma of the stomach or gastro-oesophageal junction** requested by, or on the advice of, a specialist or consultant physician who manages the treatment of the patient to determine if the requirements relating to human epidermal growth factor receptor 2 (HER2) gene amplification for access to trastuzumab under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.

Fee: \$315.40 **Benefit:** 75% = \$236.55 85% = \$268.10

Explanatory notes:

In situ hybridization (ISH) testing should be performed on biopsy or resection specimens. If biopsy or resection specimens are not available then paraffin embedded cell blocks may be used.

If biopsy or resection specimens are available then benefits for item XXXXXX are payable only when prerequisite immunohistochemistry (IHC) testing for HER2 overexpression is scored at 2+ or 3+.

If biopsy or resection specimens are not available and testing is performed on paraffin embedded cell blocks the requirement for prerequisite IHC testing does not apply.

If biopsy or resection specimens are available then benefits for item XXXXXX are payable only when performed on the same specimen and in the same laboratory as the prerequisite immunohistochemistry (IHC) testing for HER2 overexpression.

The PBS restriction for trastuzumab through the PBS is as a treatment for HER2 positive, metastatic (equivalent to stage IV) adenocarcinoma of the stomach or gastro-oesophageal junction, in patients who have not received prior treatment for advanced disease, in combination with cisplatin and either capecitabine or 5-fluorouracil, with a WHO performance status of 2 or less. HER2 positivity must be demonstrated by being both (a) IHC2+ or IHC3+ and then (b) ISH results based on both >6 copies of HER2 and the ratio of HER2: chromosome 17 being >2.

Note: The current MBS fee for ISH testing in breast cancer is \$315.40. It is proposed that this fee is appropriate to apply to ISH testing in gastric cancer. Abbreviation: IHC = immunohistochemistry; ISH = In situ hybridization; HER2=human epidermal growth factor receptor 2

The proposed item descriptor and explanatory notes complied with the recommendations from MSAC's 2012 consideration in the following ways:

- requires that HER2 ISH testing be performed only when prerequisite immunohistochemistry (IHC) testing for HER2 overexpression is scored at 2+ or 3+;
- requires that HER2 ISH testing be performed on the same specimen and in the same laboratory as the prerequisite IHC testing;
- allows any accepted type of ISH testing, as the type of ISH testing is not specified;
- limits HER2 testing to biopsy or resection specimens, and thus exclude the possibility of testing of cytology specimens. However, if no other more suitable specimen is available then paraffin embedded cell blocks may be used, in which the prerequisite IHC testing is not required; and

- the definition of HER2 test positive in metastatic gastric cancer should be both (a) IHC2+ or IHC3+ and then (b) ISH results based on both >6 copies of HER2 and the ratio of HER2:chromosome 17 being >2.

The proposed item descriptor did not comply with the recommendations from MSAC’s 2012 consideration in the following ways:

- does not include a preference for testing the metastasis rather than the primary tumour;
- does not explicitly require dual-probe rather than single-probe testing; and
- expands the eligible population from metastatic gastric cancer only (as requested by MSAC, PSD p. 12) to all patients with inoperable locally advanced, recurrent or metastatic gastric cancer.

The Applicant agreed that the MBS item should be made a pathologist determinable service (Section B HER2 testing p. 2 and 14). The cost of the proposed MBS item for HER2 ISH testing in gastric cancer is \$315.40. This is the same cost that was used in the 2012 application and is the same as the MBS fee of for ISH testing in breast cancer (MBS item 73332).

7. Summary of Public Consultation Feedback/Consumer Issues

Refer to Public Summary Document 1163 from November 2012.

8. Proposed intervention’s place in clinical management

Refer to Public Summary Document 1163 from November 2012.

9. Comparator

Refer to Public Summary Document 1163 from November 2012.

10. Comparative safety

Refer to Public Summary Document 1163 from November 2012.

11. Comparative effectiveness

Refer to Public Summary Document 1163 from November 2012.

12. Economic evaluation

The revised economic evaluation presented by the Applicant compares the situation in which both HER2 testing and trastuzumab are available, versus the current situation, in which neither HER2 testing or trastuzumab are available, as shown below.

Proposed scenario	Testing is performed to determine a patient’s HER2 status, and patients with a positive HER2 test result* are considered to be ‘High HER2’. ‘High HER2’ patients with metastatic disease are treated with trastuzumab in conjunction with cisplatin and 5-FU (HCF) and patients with a negative HER2 test result are treated with cisplatin and 5-FU (CF) alone.
Comparator scenario	HER2 testing and trastuzumab are not available, a patient’s HER2 status is not known and all metastatic patients are treated with CF (as currently occurs in clinical practice)

* defined as IHC2+/ISH+ or IHC3+/ISH+, where ISH positivity is defined as both >6 copies of HER2 and the ratio of HER2:chromosome 17 being >2

As shown in the figure below, the model structure considers both HER2 positive and HER2 negative patients and incorporates the efficacy and relevant costs associated with testing and treatment. The updated economic also incorporates diagnostic accuracy and sensitivity analyses of varying testing strategies (including FISH, CISH and SISH).

Structure of the economic model (Figure redacted)

Adjustments to the economic model relevant to testing presented in the current application were as follows:

- 5% of existing samples are re-tested for HER2 status in the base-case evaluation (and appropriate incremental costs included); and
- Storage and enrichment cost are captured in the MBS item fee for ISH testing and the requirements for additional patient biopsies is negligible; therefore the analyses presented do not include an additional costs associated with re-biopsy, professional attendances, storage and enrichment.

13. Financial/budgetary impacts

The cost to the MBS of the proposed listing in both the previous 2012 application and in the current application is presented below.

Cost to the MBS (excluding co-payments)

Cost description	2016	2017	2018	2019	2020
Cost to MBS in current application	\$(redacted)	\$(redacted)	\$(redacted)	\$(redacted)	\$(redacted)
Cost to MBS in 2012 application	\$(redacted)	\$(redacted)	\$(redacted)	\$(redacted)	\$(redacted)
Difference in cost to MBS	\$(redacted)	\$(redacted)	\$(redacted)	\$(redacted)	\$(redacted)

The updated financial impact calculations use data from the Australian AGC testing program rather than from ToGA and GaTHER to determine the results of IHC testing. As a consequence, (redacted)% of patients are either IHC2+ or IHC3+ and therefore eligible to receive ISH testing, compared with only (redacted)% in the 2012 estimates. This increase in the number of HER2 tests being performed is on top of the additional 5% of the population assigned retesting costs due to indeterminate results and contributes to the increased cost to the MBS in the updated estimates.

14. Key issues from ESC for MSAC

ESC noted that one of the issues (whether the incremental effectiveness of trastuzumab should be estimated by the intention-to-treat analysis or a subgroup analysis of the ToGA trial) raised in the fit-for-purpose co-dependent re-application had been expedited to the April 2015 MSAC meeting because of the importance of the MSAC advice for the PBAC consideration. None of the remaining issues for MSAC consideration centred on comparative safety, comparative effectiveness or comparative cost-effectiveness because these had either largely been settled in 2012, or were more central issues for PBAC consideration with respect to the trastuzumab component of the co-dependency.

ESC therefore addressed the matters requiring further consideration by MSAC, following the order used for the table provided in the background section above.

Collation of data

ESC noted that the applicant supported the concept of data collection via a standardised report to requesting oncologists on the IHC score, the number of HER2 copies and the ratio of HER2 to chromosome 17 to show whether HER2 positivity had been met in order to be eligible for trastuzumab. ESC also noted that MSAC had proposed additional data collection in the context of EGFR testing, BRAF testing and ALK testing. ESC advised that MSAC should identify the objectives of any additional data collection in this context. Liaison with appropriate pathology expertise on standardised reporting and data collection would then be appropriate, noting that the RCPA has structured reporting guidelines for gastric cancer.

Population eligible for testing

ESC noted that MSAC had foreshadowed limiting MBS-funded testing of patients to those with metastatic (stage IV) gastric cancer, whilst the applicant sought to expand this to also include patients with inoperable or locally advanced or recurrent gastric cancer. The main justifications offered for this expansion were local and international clinical guidelines; the high proportion (81%) of the added population who would progress to stage IV disease and thus become eligible for trastuzumab if HER2 positive; and the rapidly progressive nature of the disease. It was also suggested that the increased costs of testing the wider group of patients might be outweighed by the costs of retrieving tissue blocks from archive or additional biopsy procedures if all patients had to have metastatic cancer before HER2 testing is conducted, but no quantification of this trade-off was attempted, including in the financial estimates. ESC noted that the Applicant's response to the critique estimated an increased cost to the MBS to include this expansion in the range of \$105,000 to \$200,000 per year. ESC supported the expansion, noting that it would involve a relatively small population which would mostly become eligible with disease progression.

Source of tested specimen

ESC noted that MSAC had foreshadowed a preference for testing the metastasis, whilst the applicant and the RCPA both proposed that no preference be expressed. The main justification offered was the practical concern that it may be inappropriate to obtain material from some metastases and material obtained from other metastases may be insufficient. Neither the ToGA trial protocol nor current clinical guidelines specify a preference for HER2 testing based on the metastasis. Studies by Bozetti 2011 and Shibata 2014 were presented to show concordance greater than 97% between distant metastatic sites of gastric cancer and matched histological specimens from the primary tumours. Other studies by Gumusay 2015, Selcukbiricik 2014, and Ieni 2014 were included in the critique of the application suggesting lower rates of concordance, with a further suggestion that discordant results were mostly due to being HER2-positive in the primary tumour and HER2- negative in the metastasis. ESC noted the points made by the Applicant in its response to the critique that these studies did not necessarily include patients with distant metastases. Overall, ESC considered that comparison of results of specimens from the primary tumour and other sites might provide some reassurance that a patient testing HER2-negative in the primary tumour may not have the metastasis also tested, noting that this possibility of multiple testing was not included in the economic or financial modelling. ESC supported the omission of any preference to testing the metastasis, noting the practical concerns of obtaining specimens from the metastasis and the reassurance that testing of both sources should be minimal.

Number of probes in testing

ESC noted that MSAC had foreshadowed limiting MBS-funded testing to dual probe rather than single probe testing, whilst the applicant sought not to remove any specification of the number of probes in the MBS item descriptor. The main justification offered was that the authors of the Australian GaTHER study had concluded that reliance on the HER2 to

chromosome 17 ratio resulted in reduced concordance than the HER2 copy number. However, if the MSAC recommended definition of HER2 positivity, which has been accepted by both the applicant and the RCPA, requires reporting of both the HER2 to chromosome 17 ratio and the HER2 copy number, it was not clear how this justification is relevant.

Re-sampling to resolve indeterminate results from the initial test

ESC noted that the second co-dependent application underestimated the costs of addressing indeterminate results by only estimating the costs of conducting a second IHC and second ISH test, but that this underestimate would not be likely to have a material effect on the economic evaluation, or the financial implications for the MBS.

Wording of the MBS item descriptor

In addition to the issues already addressed, ESC noted that an issue for MSAC related to the prerequisite results of the IHC test to initiate ISH testing. One option would be to include these details in the text of the MBS item descriptor to make it enforceable, as MSAC had recommended in the context of ALK testing. The alternative option, as proposed by the applicant, is to include these details in the explanatory notes, where they provide guidance only. ESC noted that the HER2 in gastric cancer context was more complex because it allowed for certain circumstances where prerequisite IHC testing would not apply, which resulted in lengthier text on the issue. ESC supported including these details in the explanatory notes.

Cost to the MBS

In addition to the issues already addressed, ESC noted that the estimates of the cost of testing to the MBS had reasonably increased by a small extent to reflect updated prevalence data and a 5% retesting rate.

15. Other significant factors

Nil.

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

Roche welcomes MSAC's support for a new MBS item for in situ hybridisation (ISH) testing of HER2 status to determine eligibility for PBS-subsidised trastuzumab for the treatment of patients with metastatic gastric cancer.

17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website at: www.msac.gov.au.