Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1621 – Amendment to MBS Item 73344 for c-ROS proto-oncogene 1 (ROS1) fluorescence in situ hybridisation (FISH) testing to identify ROS1 to determine patient eligibility for entrectinib under the Pharmaceutical Benefits Scheme (PBS)

Applicant: **Roche Products Pty Ltd**

Date of MSAC consideration: **MSAC 78th Meeting, 3 April 2020**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, visit the MSAC website

1. Purpose of application

An application for a streamlined codependent consideration requested:

- Pharmaceutical Benefits Schedule (PBS) listing of entrectinib for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) who are *ROS* proto-oncogene 1 (*ROS1*)-positive in tumour tissue
- an amendment of Medicare Benefits Schedule (MBS) item 73344 to include entrectinib in the list of medicines for fluorescence *in situ* hybridization (FISH) testing to help determine eligibility for access to PBS subsidised treatment.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to the safety, clinical effectiveness and cost-effectiveness of testing the *ROS* proto-oncogene 1 (*ROS1*) in non-small cell lung cancer (NSCLC) tumour tissue, MSAC supported the modification of existing MBS item 73344 to include reference to entrectinib in alignment with the PBS listing of this medicine as recommended by the Pharmaceutical Benefits Advisory Committee (PBAC) in March 2020.

The MSAC-supported descriptor was:
Fluorescence in situ hybridization (FISH) test of tumour tissue from a patient with locally advanced or metastatic non-small-cell lung cancer (NSCLC), which is of non-squamous histology or histology not otherwise specified, with documented evidence of ROS proto-oncogene 1 (ROS1) immunoreactivity by immunohistochemical (IHC) examination giving a staining intensity score of 2+ or 3+; and with documented absence of both activating mutations of the epidermal growth factor receptor (EGFR) gene and anaplastic lymphoma kinase (ALK) immunoreactivity by IHC, requested by a specialist or consultant physician to determine if requirements relating to ROS1 gene rearrangement status for access to crizotinib ***or entrectinib*** *under the Pharmaceutical Benefits Scheme are fulfilled.*

Consumer summary

Roche Products Pty Ltd submitted an application to fund fluorescence *in situ* hybridization (FISH) testing through the Medicare Benefits Schedule (MBS) for *ROS* proto-oncogene 1 (*ROS1*) gene rearrangements (fusions) in patients with non-small cell lung cancer (NSCLC). This testing will help patients know whether they can access the medicine entrectinib under the Pharmaceutical Benefits Scheme (PBS).

FISH testing allows certain genetic changes to be detected. In this case, FISH is used to find *ROS1* fusions. *ROS1* is an oncogene, which means it is a gene that can contribute to poor cancer outcomes. *ROS1* fusions are found in some people with NSCLC, and these people can respond well to medicines like entrectinib.

In March 2020, the Pharmaceutical Benefits Advisory Committee (PBAC) recommended listing entrectinib on the PBS for treating some people with NSCLC who also have *ROS1* fusions.

MSAC's advice to the Commonwealth Minister for Health

The Medical Services Advisory Committee (MSAC) has previously advised that *ROS1* gene rearrangement testing is safe, clinically effective and cost-effective in patients with NSCLC. As the PBAC has recommended the listing of entrectinib on the PBS, MSAC supported the funding of *ROS1* fusion testing to help patients know whether they have access to PBS-subsidised entrectinib.

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

MSAC noted that this application was an amendment to MBS Item 73344 for *ROS1* FISH testing to identify *ROS1* gene rearrangements, to help determine patient eligibility for entrectinib under the PBS.

MSAC noted that the March 2020 PBAC meeting recommended that entrectinib, another tyrosine kinase inhibitor, be listed on the PBS for patients with *ROS1*-positive NSCLC.

MSAC recalled that it previously determined *ROS1* gene rearrangement testing to be safe, clinically effective and cost effective in patients with NSCLC, which resulted in MBS item 73344, implemented in 1 January 2019.

MSAC agreed with the applicant's proposals that there should be no consequential change to the MBS fee, costs to the MBS, or testing strategy. MSAC also noted that utilisation is not expected to increase, as patients who will be tested for eligibility for entrectinib would have otherwise been tested for eligibility for crizotinib.

Other discussion
MSAC separately noted that *ROS1* testing is already increasing because it is also used to help determine access to PBS-subsidised pembrolizumab, for those patients with NSCLC who are found not to have *ROS1* gene rearrangements.

4. Background

In July 2018, MSAC supported MBS funding for FISH testing for *ROS1* rearrangements in patients with locally advanced or metastatic NSCLC to determine access to crizotinib under the PBS (see Public Summary Document [PSD] for Application 1454, MSAC 73rd Meeting,

26-27 July 2018). This resulted in the implementation of MBS item 73344 for *ROS1* testing in NSCLC patients on 1 January 2019.

MSAC first considered Application 1454 at its November 2017 meeting. MSAC deferred its advice until the PBAC recommended the PBS listing of crizotinib for this population.

ALK FISH testing was considered by MSAC at its November 2013 and November 2014 meetings. At the November 2014 MSAC consideration, *ALK* FISH testing was supported for patients with locally advanced or metastatic, non-squamous or histology not otherwise specified (NOS) NSCLC with a documented absence of *EGFR* activating mutations and ALK immunoreactivity by IHC.

5. Proposal for public funding

The application proposed a minor amendment to the MBS item descriptor for *ROS1* FISH testing that will facilitate its use in determining patient eligibility to access entrectinib under the PBS (Table 1). Proposed additions are in **bold** text. No change was sought to the current MBS fee for *ROS1* testing by FISH.

Table 1: Proposed amendment to MBS listing for ROS1 FISH testing under item 73344

Category 6 – PATHOLOGY SERVICES
MBS item: 73344 Fluorescence in situ hybridization (FISH) test of tumour tissue from a patient with locally advanced or metastatic non-small-cell lung cancer (NSCLC), which is of non-squamous histology or histology not otherwise specified, with documented evidence of ROS proto-oncogene 1 (ROS1) immunoreactivity by immunohistochemical (IHC) examination giving a staining intensity score of 2+ or 3+; and with documented absence of both activating mutations of the epidermal growth factor receptor (EGFR) gene and anaplastic lymphoma kinase (ALK) immunoreactivity by IHC, requested by a specialist or consultant physician to determine if requirements relating to ROS1 gene rearrangement status for access to crizotinib **or entrectinib** under the Pharmaceutical Benefits Scheme are fulfilled. **Fee:** $400.00 **Benefit:** 75% = $300.00 85% = $340.00

Source: Table 4, p8 of the minor submission

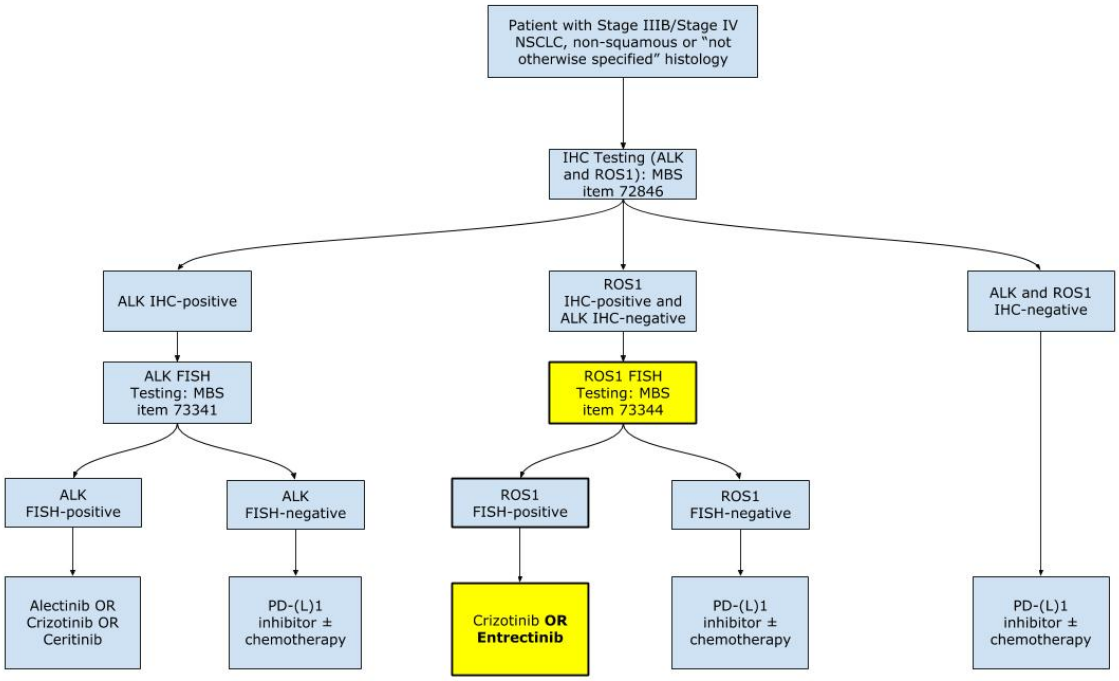
6. Proposed intervention's place in clinical management

No change to the testing algorithm for NSCLC patients was proposed.

The place of *ROS1* testing in the selection of first-line systemic treatment options for patients with NSCLC with the availability of entrectinib on the PBS is outlined in the clinical management algorithm provided at Figure 1. The context of *ROS1* testing by FISH within the molecular testing cascade and use of ROS1 inhibitors in *ROS1*-positive patients are highlighted in yellow.

The requirement for patients to have undergone testing for *EGFR* mutations, ALK immunohistochemical and ROS1 immunohistochemical screening prior to *ROS1* FISH testing represented in Figure 1 is broadly consistent with MSAC's previous advice regarding the place of *ROS1* testing by FISH and the item descriptor for MBS item 73344.

Figure 1: Clinical management algorithm with the availability of entrectinib as an alternative treatment to crizotinib



The proposed role of entrectinib is as an alternative treatment to crizotinib, rather than a subsequent treatment to crizotinib. This is supported by the clinical criterion outlined in the proposed PBS restriction for entrectinib specifying that a "patient must not have received prior treatment with a c-ROS proto-oncogene 1 (*ROS1*) receptor tyrosine kinase inhibitor for this condition". An assessment of the clinical efficacy of entrectinib in patients that have received prior treatment with a ROS1-inhibitor was presented as part of the major submission to the PBAC and does not support sequential use of crizotinib followed by entrectinib. As such, there is no basis for re-testing *ROS1*-positive patients treated with crizotinib in order to determine if they are suitable for subsequent treatment with entrectinib.

7. Comparative effectiveness

Comparison of testing strategies employed in clinical trials of ROS1-inhibitors
A summary of the *ROS1* gene rearrangement strategies performed across the nonrandomised studies of entrectinib and crizotinib to support PBS-listing in *ROS1*-positive patients is provided in Table 2.

Table 2: Comparison of ALK gene rearrangement testing in ROS1-inhibitor studies

	Entrectinib			Crizotinib			
Study ID (in major PBAC submission)	ALKA	STARTRK-1	STARTRK-2	PROFILE 1001	Wu et al (2018), referred to as 0012-01 in crizotinib PBAC submission	EUCROSS	METROS
Phase	1	1/2a	2	1	2	2	2
Permitted *ROS1* testing methodology(ies) outlined in study protocol/publication	IHC, FISH	IHC, FISH, NGS, qPCR	NGS, Sanger sequencing, RT-PCR, NanoString, EdgeSeq	FISH, NGS	RT-PCR	FISH	FISH
Local laboratory testing permitted	Yes	Yes	Yes	NR	NR	No	No
Confirmatory central laboratory testing required	Yes (by FISH)	Yes	Yes (Centralised NGS testing used to determine patient eligibility)	NR	Yes (3 regional laboratories established)	Yes	Yes

Source: ALKA: Study Protocol, pp. 6,139-6,333 of ALKA CSR; STARTRK-1: Study Protocol, pp. 7,089-7,309 of STARTRK-1 CSR; STARTRK-2: CSR, p.3,029; PROFILE 1001: (Shaw et al. 2014), pp. 1,965-6; Wu et al (2018), p.1,406; EUCROSS: p.2 of (Michels et al. 2019); METROS: p. 7 of (Landi et al. 2019)
Abbreviations: IHC = immunohistochemistry; FISH = fluorescence *in situ* hybridisation; NGS = next-generation sequencing; NR = not reported; qPCR = real time polymerase chain reaction; RT-PCR = reverse transcription polymerase chain reaction

FISH testing was permitted for the identification of *ROS1* gene rearrangements in NSCLC patients enrolled in the ALKA and STARTRK-1 studies (entrectinib) and the PROFILE 1001, EUCROSS and METROS studies of crizotinib (Table 3). FISH testing was not used for the assessment of *ROS1*-positivity in the STARTRK-2 study of entrectinib, nor the Phase 2 trial of crizotinib reported by Wu et al. (2018).

The number of *ROS1*-positive patients with NSCLC that enrolled in the ALKA and STARTRK-1 studies by testing methodology is summarised in Table 3. Results are also presented for the primary efficacy endpoint reported in the major PBAC submission (objective response rate) reported in these studies. These data show a high degree of consistency with regard to patient response to treatment regardless of whether *ROS1* testing was undertaken using FISH or next-generation sequencing (NGS).

Table 3: ROS1 testing methodology and object response rate reported in entrectinib studies

	ALKA (N=9)	STARTRK-1 (N=7)	STARTRK-2 (N=37)
ROS1 testing methodology			
FISH	9 (100%)	redacted (redacted%)	Not permitted
NGS	0	redacted (redacted%)	37 (100%)
Objective response rate, % (95% CI)	redacted% (redacted%)	redacted% (redacted%)	redacted% (redacted%)
Responders, n (%)	redacted (redacted%)	redacted (redacted%)	redacted (redacted%)
Non-responders, n (%)	redacted (redacted%)	redacted (redacted%)	redacted (redacted%)

Source: ROS1 testing methodology: p. 1 (ALKA) and p. 4 (STARTRK-1) of TGA Submission Section 2.7.3: Summary of Clinical Efficacy (CCOD 31 May 2018) Supporting Data; Objective response rate: Table 2-20 of major PBAC submission

Molecular testing used in STARTRK-2 study

The clinical development of entrectinib was undertaken in patients with locally advanced or metastatic solid tumours irrespective of tumour type. Based on its ability to inhibit cell signalling when there are molecular alterations encoded by the *NTRK1*, *NTR2*, *NTRK3*, *ROS1*

and *ALK* genes, patients were enrolled in the clinical development studies of entrectinib on the basis of having a solid tumour with a molecular alteration in a gene known to be inhibited by entrectinib.

Based on results reported in the ALKA and STARTRK-1 studies, the STARTRK-2 study enrolled patients across multiple solid tumour types ("baskets") based on the presence of an *NTRK1/2/3*, *ALK* or *ROS1* gene rearrangement. The STARTRK-2 study was designed such that each "basket" could be analysed as a separate cohort, i.e. an assessment of efficacy and safety of entrectinib by specific gene rearrangement type.

Reflecting the design of the STARTRK-2 study which enrolled patients with multiple gene rearrangement types, simultaneous testing for multiple gene rearrangements was undertaken using a gene panel. All patients enrolled in the STARTRK-2 study were allocated to a specific "basket" based on the results of a proprietary *NTRK1/2/3*, *ROS1* and *ALK* gene rearrangements assay (Trailblaze Pharos™) developed by Ignyta Inc.

The *NTRK1/2/3*, *ROS1* and *ALK* gene rearrangements assay (Trailblaze Pharos™) used in the STARTRK-2 study was a NGS test used for the detection of gene rearrangements in the *NTRK1/2/3, ROS1* and *ALK* genes. Testing was performed on RNA obtained from formalin-fixed paraffin-embedded (FFPE) human solid tissue specimens.

This *NTRK1/2/3, ROS1* and *ALK* gene rearrangements assay (Trailblaze Pharos™) was approved by the US FDA as an investigational device for use in the STARTRK-2 study (IDE G160133). All molecular testing of formalin-fixed, paraffin-embedded (FFPPE) solid tissue samples used to determine patient eligibility to enrol in the STARTRK-2 study, as well as allocate patients to a specific "basket", was performed at a centralised laboratory at Ignyta Inc in San Diego USA. The laboratory at Ignyta Inc. was accredited per the College of American Pathologists and Clinical Laboratory Improvement Amendments requirements (CAP/CLIA accredited).

In 2017, Roche (the applicant) reached a definitive merger agreement with Ignyta Inc. As part of this merger, Roche acquired the rights to entrectinib from Ignyta Inc. **Redacted**.

Data on the ability of the *NTRK1/2/3, ROS1* and *ALK* gene rearrangements assay (Trailblaze Pharos™) to identify gene rearrangements compared with an alternative testing methodology was presented to the FDA as part of obtaining permission to use Trailblaze Pharos™ as an investigational device for use in the STARTRK-2 study. The assessment of the **redacted**.

Table 4: Results of assessment of analytical accuracy of the NTRK1/2/3, ROS1 and ALK gene rearrangements assay (Trailblaze Pharos™)

		Orthogonal method[b]			Agreement rates			
		Positive	Negative	Total	Rate	n/N	%	95% CI
NGS[a]	Positive	redacted	redacted	redacted	redacted	redacted	redacted	redacted
	Negative	redacted	redacted	redacted	redacted	redacted	redacted	redacted
	Total	redacted	redacted	redacted	redacted	redacted	redacted	redacted

[a] *NTRK1/2/3, ROS1* and *ALK* gene rearrangements assay (Trailblaze Pharos™)
[b] Reverse transcription polymerase PCR (RT-PCR), followed by Sanger sequencing
Source: p. 3,096 or STARTRK-2 CSR
Abbreviations: OPA = overall percent agreement; NPA = negative percent agreement; PPA = positive percent agreement

Based on the results of the assessment of analytical accuracy presented in Table 4, the applicant concluded that the molecular testing results used to enrol patients in the STARTRK-2 were robust and that patients allocated to each "basket" (including patients with NSCLC randomised to the *ROS1* basket) were accurately identified as harbouring a gene rearrangement: 100% positive percent agreement between the *NTRK1/2/3, ROS1* and *ALK* gene rearrangements assay (Trailblaze Pharos™) and RT-PCR followed by Sanger sequencing.

A comparison of the *NTRK1/2/3, ROS1* and *ALK* gene rearrangements assay (Trailblaze Pharos™) with *ROS1* testing by FISH was not undertaken by the applicant.

MSAC has previously considered the comparative analytical performance of *ROS1* gene rearrangement testing with NGS versus FISH, with the results outlined in the Public Summary Document (PSD) for MSAC Application 1454 (Table 6).

Table 5: Assessment of ROS1 testing with NGS versus FISH previously considered by MSAC

Study	N [a]	NGS	FISH	*ROS1* pos n (%)	Sensitivity	Specificity
Pfarr 2016	159	Ion Torrent AmpliSeq™ (ThermoFisher) with RNA Lung Cancer Fusion Panel	ZytoLight SPEC *ROS1* probe	8/135 (6%)	100%[b]	100%[b]
Lira 2014	295	Custom *ROS1* target sequence (NanoString Technologies)	ZytoLight SPEC *ROS1* probe	4/46 (9%)	100%	100%
Reguart 2017	108	nCounter Prep Station™ and Digital Analyzer™	ZytoLight SPEC *ROS1* probe	27/79 (35%)	70%	96%

FISH = fluorescent in-situ hybridisation; IHC = immunohistochemistry; NGS = next-generation sequencing; NPV = negative predictive value; pos = positive; PCR = polymerase chain reaction; PPV = positive predictive value; RNA = ribonucleic acid; *ROS1* = *ROS* proto-oncogene 1; RT-PCR = reverse transcription polymerase chain reaction.
[a] May be higher than the denominator in the results due to failed tests, inadequate tumour samples or some tests carried out on a subset of total samples.
[b] Only a subset of positive and negative cases were verified using FISH.
Source: Table 6, p10 of MSAC Application 1454 PSD

A targeted literature review undertaken by the applicant also identified a publication comparing *ROS1* testing results using NGS with FISH undertaken in an Australian setting (Rogers et al. 2017), but not outlined in the results presented above. The results of *ROS1* testing performed on 51 FFPE clinical samples using NGS and FISH reported in this Australian study are presented in Table 6.

Table 6: Assessment of ROS1 testing with NGS versus FISH in Australian setting

		FISH			Agreement rates		
		Positive	Negative	Total	Rate	n/N	%
NGS[a]	Positive	2	1	3	PPA	2/2	100
	Negative	0	48	48	NPA	48/49	98
	Total	2	49	51	OPA	50/51	98

[a] RNA-NGS (ThermoFisher NGS Colon and Lung Cancer Research Panel)
Source: Result of *ROS1* testing for FISH versus ThermoFisher NGS p. 2 or supplement to (Rogers et al. 2017)
Abbreviations: OPA = overall percent agreement; NPA = negative percent agreement; PPA = positive percent agreement

In relation to the results comparing *ROS1* gene rearrangement testing performed using NGS and FISH summarised above, the applicant concluded that these testing methodologies have comparable, and at least non-inferior, performance characteristics. Subsequently, the identification of *ROS1* gene rearrangements using the *NTRK1/2/3, ROS1* and *ALK* gene rearrangements assay (Trailblaze Pharos™) in the STARTRK-2 study would be expected to be consistent with testing results had they been undertaken using FISH.

In the absence of the future availability of the 'evidentiary standard' used to identify *ROS1*-positive study participants with NSCLC enrolled in the STARTRK-2 study, the applicant concluded that *ROS1* testing using FISH represents a valid methodology for identifying these patients eligible to receive entrectinib under the PBS.

Further, the applicant quoted from the PSD for MSAC Application 1454 (p. 3): "MSAC noted that FISH testing is the reference method for *ROS1* testing and as such its analytical validity has been assumed".

8. Financial/budgetary impacts

The application presented data on the number of items processed for *ROS1* gene rearrangement testing by FISH since listing on the MBS on 1 January 2019 (Table 7).

Table 7: Number of items processed for MBS Item 73344: January 2019-August 2019

	State/territory								Total
	NSW	VIC	QLD	SA	WA	TAS	ACT	NT	
Items processed: 73344	26	7	15	3	NR	NR	2	NR	52

Source: Medicare item reports: http://medicarestatistics.humanservices.gov.au/statistics/mbs_item.jsp
Abbreviation: NR = not reported

As demonstrated by the information in Table 7, the number of *ROS1* tests by FISH (52) since listing in January 2019 is low. Any amendment to MBS item 73344 allowing its use to determine patient eligibility to access entrectinib under the PBS is not expected to drive further uptake in the number of *ROS1* tests by FISH claimed under the MBS. This is because testing is already required to access crizotinib and there is no role for repeat *ROS1* testing in the management of NSCLC patients. As such, no increase is expected in the cost of *ROS1* testing to the MBS as a result of amending MBS item 73344 as requested.

9. Applicant comments on MSAC's Public Summary Document

Roche welcomes the MSAC's decision to recommend an amendment of Medicare Benefits Schedule (MBS) item 73344 to include entrectinib in the list of medicines for fluorescence in situ hybridization (FISH) testing to help determine eligibility for access to PBS subsidised treatment.

10. Further information on MSAC

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