Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1429 – Targeted Intraoperative Radiotherapy for Early-Stage Breast Cancer

Applicant: **Regional Health Care Group**

Date of MSAC consideration: **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

An application requesting extension of the Medicare Benefits Schedule (MBS) item for Intraoperative Radiotherapy (IORT) for early-stage breast cancer to include services delivered using the Xoft® Axxent® (California, USA) device was received by the Department of Health from the Regional Health Care Group.

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 did not support public funding of targeted intraoperative radiotherapy (IORT) using the Xoft® Axxent® device for early-stage breast cancer.

MSAC accepted the evidence of technical equivalence between the proposed (Axxent) and listed (Intrabeam) devices, but advised that this evidence did not provide a satisfactory basis to conclude clinical equivalence. Further, MSAC considered that the clinical place for IORT has not yet been fully established and that no acceptable direct or indirect evidence of comparative safety, clinical effectiveness or cost-effectiveness was presented.

Any resubmission would need to be considered by ESC and should provide evidence of long-term safety and clinical effectiveness. MSAC agreed that whole-breast external beam radiation therapy (WB-EBRT) is the appropriate comparator for Axxent, given that there has been virtually no utilisation of the existing MBS items for IORT.

MSAC requested the department follow-up with the Royal Australian and New Zealand College of Radiologists, the Royal Australasian College of Surgeons (breast surgeons) and hospitals that have purchased these devices in Western Australia and the Peter MacCallum Cancer Centre to identify what data are being collected, explain the clinical place of these devices with respect to each other and external beam radiotherapy, and explain the very low number of MBS claims to date.

MSAC also requested that the Department remind both companies of the three year review for the Intrabeam MBS listing scheduled for September 2018.

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

MSAC considered the application requesting an amendment of the existing MBS items for IORT (MBS items 15900 and 31516) for early-stage invasive breast cancer to include services delivered using the Axxent device as well as the specified Intrabeam device.

MSAC noted the application relied on acceptance of technical equivalence without any direct or indirect evidence of relative safety or effectiveness of Axxent compared with the direct comparator, Intrabeam, or the indirect comparator, WB-EBRT.

MSAC noted the claim of technical equivalence of the Axxent device to the Intrabeam device was based on *ex vivo* simulations. MSAC observed that the evaluation did not include depth-based distributions of radiation, although the drop-off in radiation was considered to be high with either device. Based on the evidence, MSAC accepted technical equivalence between the two devices with respect to the x-ray spectra, relative biological effectiveness and tissue dose distribution.

MSAC agreed that the level, quality and duration of follow-up of the Axxent evidence base was lower, poorer and shorter than the Intrabeam evidence base.

MSAC noted the clinical evidence for the Axxent device relied upon two non-comparative case series studies (Ivanov O et al 2011 and Epstein M et al 2016). MSAC queried the relevance of the Ivanov O et al 2011 study due to low quality, small sample size (n = 11) and the inclusion of a large proportion (45%) of patients with ductal carcinoma *in situ* (DCIS) rather than the proposed population of invasive ductal carcinoma. MSAC noted that the Epstein M et al 2016 study reported results as simple rates with no information on time to events or confidence intervals and follow-up was too short to make any conclusions about recurrence rates. MSAC observed that the included studies reported only breast cancer-related mortality as opposed to all-cause mortality.

MSAC acknowledged that it was not possible to determine if Axxent and Intrabeam had similar breast cancer recurrence rates given the differences in the outcome follow-up times for the devices (1.7 years for Axxent versus 5 years for Intrabeam). MSAC agreed on the lack of long term safety data for the Axxent device.

MSAC noted that an economic evaluation had not been presented to the Committee due to uncertainties around the reported outcomes. MSAC also noted the unknown costs for the Axxent device.

MSAC considered that no acceptable direct or indirect evidence of comparative safety, clinical effectiveness or cost-effectiveness was presented and as such no conclusion could be made regarding the relative safety or effectiveness of Axxent compared to Intrabeam.

MSAC agreed that WB-EBRT is the appropriate comparator for Axxent as there has been virtually no utilisation of the existing MBS items for IORT (i.e. Intrabeam). MSAC noted the limited analysis of the comparative safety and effectiveness of Axxent compared with EBRT, and considered this to be a significant omission given that WB-EBRT was pre-specified as an appropriate comparator.

Further, MSAC recalled its concerns regarding the Intrabeam evidence base (MSAC Public Summary Document [PSD] Application 1189, November 2014) and the limited evidence for long term safety and efficacy of IORT using Intrabeam compared to WB-EBRT.

MSAC recalled concerns around funding a potentially inferior treatment (Intrabeam) to one already MBS funded (EBRT). MSAC noted that the decision to list IORT using Intrabeam on the MBS – despite not being the preferred treatment – was taken specifically on the basis of improving access to treatment for the niche population that could benefit from it and who could not access WB-EBRT due to remoteness.

Overall, MSAC advised that technical equivalence between the Axxent and Intrabeam devices did not provide a satisfactory basis to conclude clinical equivalence. MSAC considered that the clinical place for IORT has not yet been fully established and after considering the strength of the available evidence in relation to the comparative safety, clinical effectiveness or cost-effectiveness does not support the extension of public funding to the use of the Axxent device for IORT for early-stage invasive breast cancer.

MSAC recalled the Committee's recommendation to conduct a review of the Intrabeam listing three years from the initial date of listing, given its limited evidence base. MSAC proposed the need to conduct this review prior to adding another similar technology onto the MBS.

MSAC also questioned the need for listing another device on the MBS, given the lack of uptake of Intrabeam (no MBS claims under Item 15900, six claims under Item 31516, between September 2015 to February 2017) – which suggests a lack of clinical need for IORT in general.

MSAC emphasised that any resubmission would need to be considered by ESC and should provide evidence of long-term safety and clinical effectiveness of Axxent. Taking into consideration that there has been virtually no utilisation of the existing MBS items for IORT, in practice WB-EBRT is the appropriate comparator for the Axxent device.

MSAC requested the Department follow-up with the Royal Australian and New Zealand College of Radiologists, the Royal Australasian College of Surgeons (breast surgeons) and hospitals that have purchased these devices to identify what data are being collected, explain the clinical place of these devices with respect to each other and external beam radiotherapy, and explain the very low number of MBS claims to date.

MSAC recalled its recommendation to review Intrabeam MBS listing three years from initial listing and requested the Department to remind both companies of the IORT review scheduled for September 2018.

4. Background

MSAC has not previously considered Targeted Intraoperative Radiotherapy for Early-Stage Breast Cancer using the XOFT® AXXENT® device.

MSAC supported public funding on the MBS for Application 1189 - Targeted intraoperative radiotherapy (T-IORT) using the Intrabeam® device at its November 2014 meeting. MBS rebates for IORT delivered during breast conserving surgery are restricted to the Intrabeam device.

5. Prerequisites to implementation of any funding advice

The Xoft® Axxent® Electronic Brachytherapy (eBx®) System is registered on the Australian Register of Therapeutic Goods (Table 1).

Table 1 Axxent device components listed on the ARTG

ARTG no.	Product no.	Product description	Product category	Sponsor
231951	NA	X-ray generator, therapeutic	Medical Device Included Class IIb	Regional Health Care Group Pty Ltd
231952	NA	X-ray tube	Medical Device Included Class IIb	Regional Health Care Group Pty Ltd
231953	NA	Balloon dissector, surgical	Medical Device Included Class IIb	Regional Health Care Group Pty Ltd

Source: Therapeutic Goods Administration, accessed 24 October 2016 www.ebs.tga.gov.au.
NA = not applicable, no. = number

6. Proposal for public funding

The Applicant sought an amendment to the 15900 and 31516 item descriptors that would make use of the Axxent device eligible for MBS funding (Table 2). The proposed fees for the amended items are unchanged from the fees associated with use of the Intrabeam device.

The Applicant's pre-MSAC response provided further amendments to the proposed MBS descriptor to include wording on x-ray photon radiation therapy devices which covers both Intrabeam® and Xoft® Axxent® devices but excludes other, e.g. electron-beam, devices:

Table 2 Proposed MBS item descriptors

15900	BREAST, MALIGNANT TUMOUR, targeted intraoperative radiotherapy, using x-ray photons, delivered at the time of breast-conserving surgery (partial mastectomy or lumpectomy) for a patient who: a) is 45 years of age or more; and b) has a T1 or small T2 (less than or equal to 3cm in diameter) primary tumour; and c) has an histologic Grade 1 or 2 tumour; and d) has an oestrogen-receptor positive tumour; and e) has a node negative malignancy; and f) is suitable for wide local excision of a primary invasive ductal carcinoma that was diagnosed as unifocal on conventional examination and imaging; and g) has no contra-indications to breast irradiation Fee: $250.00 Benefit: 75% = $187.50
31516	BREAST, MALIGNANT TUMOUR, complete local excision of, with or without frozen section histology when targeted intraoperative radiotherapy using x-ray photons is performed concurrently, if the requirements of item 15900 are met for the patient (Anaes.) (Assist.) Fee: $867.00 Benefit: 75% = $650.25

7. Summary of Public Consultation Feedback/Consumer Issues

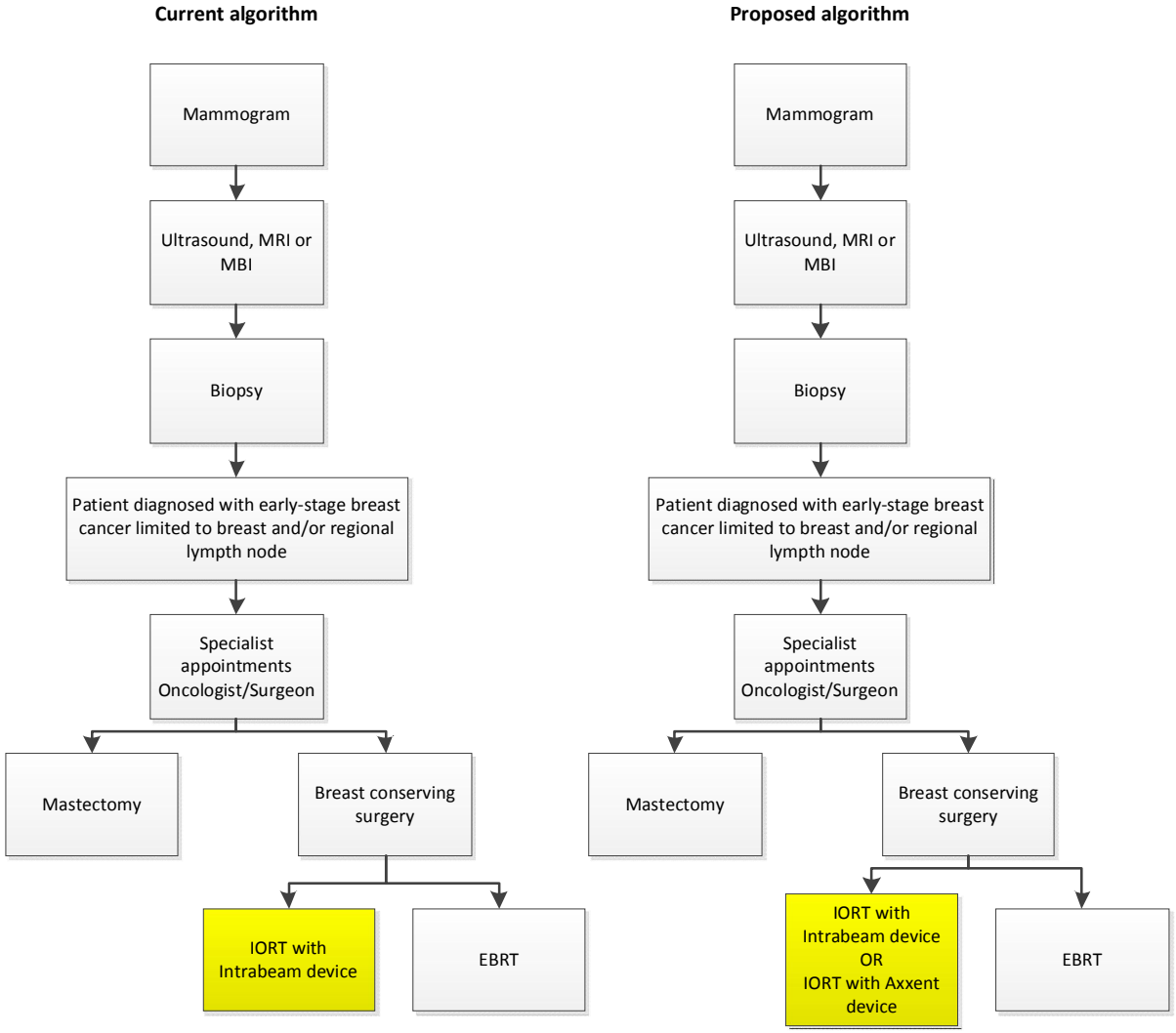
Concerns were raised following public consultation of the PICO confirmation. Key issues from the public consultation are summarised below:

- The key evidence included in the PICO confirmation includes a study on Axxent with 12 months follow-up – this is insufficient to prove clinical effectiveness. A minimum of 10 years follow-up is required. These concerns were also raised about the evidence supporting the Intrabeam device.
- Two of the three studies identified to support technical equivalence of the Axxent and Intrabeam devices are not publicly available and have not been peer-reviewed, and therefore data to support technical equivalence are limited.
- While the clinical algorithm is correct it does not allow for patients undergoing IORT with Axxent to also receive EBRT. This is expected to occur in approximately 15 per cent of patients, the same proportion as for the Intrabeam device.

8. Proposed intervention's place in clinical management

The clinical management algorithm under current and proposed funding arrangements is shown in Figure 1. The only difference between the two algorithms is that in the proposed algorithm both the Axxent and Intrabeam devices are eligible for MBS funding for patients who receive IORT in conjunction with their breast conserving surgery. Under current arrangements, only the Intrabeam device is listed for MBS funding.

Figure 1 Clinical management algorithm for the proposed intervention relative to current clinical practice



Note: Differences between the current and proposed algorithms are highlighted in yellow.
EBRT = external beam radiation therapy, IORT = intraoperative radiation therapy, MBI = molecular breast imaging, MRI = magnetic resonance imaging.

9. Comparator

The nominated primary comparator is IORT with the Intrabeam device, the nominated secondary comparator is whole-breast EBRT.

10. Comparative safety

Each of the included studies reported safety outcomes; key outcomes include infection, seroma, haematoma, dehiscence, skin necrosis, and erythema. Overall, and irrespective of device, most adverse events were mild and resolved with minimal intervention.

Due to a lack of comparative evidence and low level of consistency between studies, the relative risk associated with use of the Axxent device compared to the Intrabeam could not be determined for any outcome.

11. Comparative effectiveness

The effectiveness of each device was measured by the rate of recurrence of local breast cancer and deaths due to breast cancer after treatment (mortality). Three of the five included studies reported local cancer recurrence, and two studies reported mortality.

Rate of recurrence of invasive ductal carcinoma in the Axxent studies was 1.2 per cent. Rate of recurrence in the Intrabeam study ranged from 0.9 to 1.3 per cent. No deaths due to breast cancer were reported for the Axxent device. The mortality rate due to breast cancer in the Intrabeam study was 1.5 per cent.

Included studies, for both devices, reported short follow-up times Axxent (20 months) and Intrabeam (28 months). The lack of 10-year data means only preliminary effectiveness evidence has been reported.

Results from three *ex vivo* simulations (only one of which had been published) found dosimetric equivalence between the two devices.

Calculations conducted by an independent expert indicated that the Axxent delivers radiation at a higher dose rate compared to Intrabeam for all applicator sizes. This will affect the time taken to deliver treatment but is not expected to affect the relative clinical effectiveness of the devices. The Intrabeam device has a steeper dose drop-off than the Axxent device; however this is unlikely to affect clinical effectiveness.

Results from one publication concluded there is no significant difference in relative biological effectiveness (RBE) for all tissue types modelled.

Additional advice from the Peter MacCallum Cancer Centre stated that the Axxent device is designed to inflate evenly and it is expected to maintain a spherical shape with uniform dose distribution during the procedure; however, it should be noted that no data have been identified to confirm this assertion. In instances where the applicator does not maintain a spherical shape due to obstruction, advice from the breast radiation oncologist at the Peter MacCallum Cancer Centre is that the patient would be considered ineligible for IORT and would be considered for EBRT.

Overall, evidence indicated the devices are likely to have technical equivalence; however no data were identified to confirm uniformity of dose around the balloon applicators.

Clinical Claim

The primary clinical claim was that the dose distribution, relative biological effectiveness and health outcomes of the Axxent device are equivalent to those of the Intrabeam device. The primary health outcome is the prevention of local recurrence of breast cancer. Secondary health outcomes are comparable mortality rates, adverse events and toxicity.

12. Economic evaluation

No economic evaluation was presented for this Assessment.

13. Financial/budgetary impacts

No financial implications were presented for this Assessment.

14. Key issues from ESC for MSAC

ESC considered the application requesting an amendment of the existing MBS items for intraoperative radiotherapy (IORT) to allow use of the Xoft Axxent device as well as the specified Intrabeam device.

ESC noted that while initially the applicant had suggested two options for the revised MBS descriptors - one which specified the two branded devices and another generic option - the applicant suggested dismissal of the generic descriptor option in the pre-ESC response, as it allowed for other forms of radiation (e.g. electron based radiotherapy) to be claimed. ESC suggested specifying x-ray photon radiation therapies in the generic descriptor could cover both devices.

ESC advised that the application relied on acceptance of 'technical equivalence', in the absence of any direct or indirect evidence on relative safety or effectiveness of Axxent compared with Intrabeam. ESC noted that the quality of the Axxent evidence base was lower level, of poor quality and with a shorter duration of follow-up than the Intrabeam evidence base (which itself had its own issues). ESC noted the limited RCT evidence in regards to the Intrabeam device (i.e. the current MBS items) - particularly regarding long term safety and efficacy of IORT using Intrabeam compared to WB-EBRT. ESC also noted a previous MSAC recommendation (Public Summary Document for Application 1189: Targeted intraoperative radiotherapy [IORT] for early breast cancer) to review IORT in 3 years from the initial date of listing.

ESC observed that there were issues regarding the applicability and extrapolation of the clinical evidence which relied upon two non-comparative case series studies for the Axxent device (Ivanov 2011 and Epstein 2016). ESC expressed concerns around the suitability of reported outcomes in these studies. ESC advised excluding data from the Ivanov 2011 study entirely, due to issues with lower quality, small sample size (n = 11) and the large proportion (45%) of patients with ductal carcinoma *in situ* (DCIS) in the study, who are outside the proposed population. ESC noted that the Epstein 2016 study reported results as simple rates with no information on time to events or confidence intervals. ESC considered that the follow-up was too short to make any conclusions about recurrence rates. ESC did not accept that Axxent and Intrabeam had similar breast cancer recurrence rates given the differences in the outcome follow-up times for the devices (1.7 years for Axxent versus 5 years for Intrabeam). ESC questioned the lack of long term safety data and the fact that the included studies reported only breast cancer-related mortality as opposed to all-cause mortality. Overall, ESC did not accept claims of the non-inferior safety and effectiveness of the devices and advised that no statement could be made regarding relative safety or effectiveness of Axxent device compared to Intrabeam.

ESC noted that the evidence base for Intrabeam was of higher quality compared with Axxent and that the EBRT evidence base had the highest quality of all.

ESC considered WB-EBRT to be the effective comparator for Axxent, given that there has been virtually no utilisation of the existing MBS items for IORT (i.e. Intrabeam). There was, however, insufficient analysis of the comparative safety and effectiveness of Axxent compared to WB-EBRT (with absence of direct comparison and imbalance in the evidence base cited as reasons), which ESC believes to be a significant omission given that EBRT was pre-specified as an appropriate comparator. To illustrate this point, ESC highlighted

examples of potentially relevant level I and level II evidence for WB-EBRT that could have been included in the report.

ESC considered that any decision to expand the existing MBS items to include Axxent would be on the basis of perceived technical equivalence of Axxent and Intrabeam, and not on a demonstration of clinical equivalence. ESC noted that MSAC does not have a policy on how to deal with evaluations that rely on technical comparisons rather than clinical comparisons. While ESC noted that technical equivalence is accepted by certain decision makers (e.g. Prostheses List Advisory Committee [PLAC] decisions about devices) there are no direct precedents for MSAC to do the same. Further, ESC noted it was also unclear how technically similar the devices would need to be should MSAC accept technical equivalence as a surrogate for clinical equivalence.

ESC observed that the assessment report indicated the Axxent and Intrabeam devices to have equivalence in terms of dose delivery. ESC noted that radiation dose specified in this application (20 Grays) is the same for both the devices and so this aspect of the devices could be considered technically equivalent. However, ESC noted differences between the devices in other respects, in particular (i) the use of a saline-filled balloon by the Axxent device versus a fixed sphere for the Intrabeam, and (ii) the requirement to suture the Axxent device in place during dose delivery. Theoretically, these administration differences could give rise to different safety issues for the Axxent relative to the Intrabeam. Consequently, on balance ESC was unsure if these devices could be considered truly technically equivalent on the basis of the currently available evidence.

ESC noted that the Royal Australian and New Zealand College of Radiologists, during their feedback to PASC, was not supportive of IORT (Axxent or Intrabeam) and considered the technology to be immature.

ESC noted that no economic assessment was included in the contracted assessment. However, ESC expressed uncertainties with regards to downstream costs associated with the management of adverse effects (e.g. recurrence), which are currently unknown for the Axxent device. ESC also discussed the preclusion of an economic analysis and provision of information on out of pocket costs, given all the uncertainties.

ESC noted the very low uptake of the original Intrabeam MBS items. ESC considered that there would be no impact on the MBS if Axxent replaced Intrabeam, but noted the likelihood of cost savings if Axxent replaced WB-EBRT (based on the budget impact analysis reported for MSAC Application 1189).

ESC acknowledged the issues faced by patients in accessing EBRT and the requirement for long periods of time away from home for patients living in rural and remote areas. However, ESC questioned whether listing the Axxent device would improve access for patients given the very low uptake of the Intrabeam device. ESC believes that both devices are portable and so the portability of Axxent may not make much difference to the access issues. Additionally, IORT (with Axxent or Intrabeam) must be delivered by a radiation oncologist and a medical physicist, which may limit access in rural and regional areas.

ESC noted consumer concerns that a potentially inferior procedure may be offered to patients due to their location, socioeconomic factors and other concerns. There was also consumer concern about the uncertain safety of the device and the lack of information on out of pocket costs.

15. Other significant factors

Alternative IORT devices use electrons as their radiation source. IORT with electrons (IOERT) was outside the scope of the Assessment; however, if the MBS descriptor were not sufficiently narrowly specified, IOERT may become eligible for MBS funding.

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

The applicant had no comment.

17. Further information on MSAC

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