

Applicant Submitted Proposed Protocol  
For  
Targeted Intraoperative Radiotherapy for  
Early Breast Cancer  
(INTRABEAM®)  
Carl Zeiss Pty Ltd

Medical Service Advisory Committee  
Application 1189

For Consideration by  
Protocol Advisory Subcommittee (PASC)

February 2014

## 1) Title of Application

Targeted intraoperative radiotherapy (IORT) for early breast cancer.

## 2) Purpose of application

*Please indicate the rationale for the application and provide one abstract or systematic review that will provide background.*

The rationale of targeted intraoperative radiotherapy (IORT) is to accurately target the tissues where there is the highest risk of cancer returning. IORT is a form of partial breast irradiation involving the application of radiotherapy (using the INTRABEAM<sup>®</sup> device) to the tissues surrounding a breast cancer in the operating theatre after surgical removal of the tumour (breast-conserving surgery, partial mastectomy or lumpectomy).

IORT can also be applied as a second procedure at some time after surgery.

## 3) Population and medical condition eligible for the proposed medical services

*Provide a description of the medical condition (or disease) relevant to the service.*

Early stage breast cancer.

*Define the proposed patient population that would benefit from the use of this service. This could include issues such as patient characteristics and /or specific circumstances that patients would have to satisfy in order to access the service.*

Patients suitable for this modality instead of EB-WBRT should meet the following criteria: aged 45 years+; pathologically documented invasive breast cancer; considered by the surgeon to be suitable for breast conserving surgery; no contraindication to breast irradiation.

*Indicate if there is evidence for the population who would benefit from this service i.e. international evidence including inclusion / exclusion criteria. If appropriate provide a table summarising the population considered in the evidence.*

The evidence for this application is primarily based on the following two published papers. The patient population in these papers is in line with the intended Australian patient population.

- Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomised, non-inferiority phase 3 trial. Vaidya JS, Joseph DJ, Tobias JS, Bulsara M, Wenz F, Saunders C, Alvarado M, Flyger HL, Massarut S, Eiermann W, Keshtgar M, Dewar J, Kraus-Tiefenbacher U, Sütterlin M, Esserman L, Holtveg HM, Roncadin M, Pigorsch S, Metaxas M, Falzon M, Matthews A, Corica T, Williams NR, Baum M. *Lancet*. 2010 Jul 10;376(9735):91-102.
- Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. Vaidya JS, Wenz F, Bulsara M, Tobias JS, Joseph DJ, Keshtgar M, Flyger HL, Massarut S, Alvarado M, Saunders C, Eiermann W, Metaxas M, Sperk E, Sütterlin M, Brown D, Esserman L, Roncadin M, Thompson A, Dewar JA, Holtveg HM, Pigorsch S, Falzon M, Harris E, Matthews A, Brew-Graves C, Potyka I, Corica T, Williams NR, Baum M; on behalf of the TARGIT trialists' group. *Lancet*. 2013 Nov 8. pii: S0140-6736(13)61950-9.

The main patient criterion for this international (including Australia), prospective, randomised, non-inferiority phase III trial was women aged 45 years or older with invasive ductal breast carcinoma undergoing breast-conserving surgery.

*Provide details on the expected utilisation, if the service is to be publicly funded.*

The expected utilisation of this service will be estimated based on:

- The current incidence of breast cancer treated with breast-conserving surgery (partial mastectomy or lumpectomy);
- The percentage of these patients who currently have external beam whole breast radiation therapy (EB-WBRT);
- The percentage of these patients who would have access to IORT in the short and long-term.

Additional, an estimate will be attempted of patients who are unable or unwilling to have EB-WBRT, due to such factors as living in a remote geographical area.

The claims on the following MBS Item numbers give some indication of the potential population.

#### 31512

BREAST, MALIGNANT TUMOUR, complete local excision of, with or without frozen section histology (Anaes.) (Assist.)

Fee: \$650.15 Benefit: 75% = \$487.65

There were 6,958 claims in the 2012-13 Financial Year for MBS Item 31512.

#### 15221

RADIATION ONCOLOGY TREATMENT, using a single photon energy linear accelerator with or without electron facilities - each attendance at which treatment is given - 1 field - treatment delivered to primary site (breast)

Fee: \$59.65 Benefit: 75% = \$44.75 85% = \$50.75

There were 326 claims in the 2012-13 Financial Year for MBS Item 15221.

#### 15236

RADIATION ONCOLOGY TREATMENT, using a single photon energy linear accelerator with or without electron facilities - each attendance at which treatment is given - 2 or more fields up to a maximum of 5 additional fields (rotational therapy being 3 fields) - treatment delivered to primary site (breast)

The fee for item 15221 plus for each field in excess of 1, an amount of \$37.95

There were 19,215 claims in the 2012-13 Financial Year for MBS Item 15236.

### **4) Intervention – proposed medical service**

*Provide a description of the proposed medical service.*

The application sphere of the INTRABEAM® system is inserted into the surgical cavity and a deep surgical purse string suture is inserted in the subcutaneous plane to bring together the target breast tissue so that it applies well to the surface of the PRS applicator sphere and

holds it in place during treatment. The skin should be gently everted and held away from the delivery device by a couple of stay sutures to prevent direct contact with the sphere. It is important to keep the skin at a distance from the applicator, which is easily achieved during the surgical procedure. If necessary, protective caps may be fashioned by the surgeon to protect deep or superficial structures. In particular if the deep margin of excision is considered within range of the left anterior descending branch of the coronary artery, the surface of the applicator sphere should be covered with a protective cap at the chest wall. Care must be taken however, to not inadvertently shield areas of tissue that require treatment.

The dose delivered to the breast tissue is approximately 20Gy at 0.2mm. The time required varies depending on the size of the applicator but ranges between approximately 10-30 minutes.

After completion of radiation, the conforming stitches are removed and the skin is sutured in the usual manner. Strict haemostasis should be obtained following the removal of the INTRABEAM device. The wound should be closed in the usual fashion to achieve a good cosmetic result. The rapid attenuation of the radiation dose allows the treatment to be carried out in the routine theatre.

*If the service is for investigative purposes, describe the technical specification of the health technology and any reference or "evidentiary" standard that has been established.*

This service is not for investigative purposes.

*Indicate whether the service includes a registered trademark with characteristics that distinguish it from any other similar health technology.*

This service includes the use of a registered trademarked device, the INTRABEAM® Photon Radiosurgery (PRS) device by Carl Zeiss Surgical (Oberkochen, Germany).

*Indicate the proposed setting in which the proposed medical service will be delivered and include detail for each of the following as relevant: inpatient private hospital, inpatient public hospital, outpatient clinic, emergency department, consulting rooms, day surgery centre, residential aged care facility, patient's home, laboratory. Where the proposed medical service will be provided in more than one setting, describe the rationale related to each.*

The proposed setting for the delivery of this service, when provided as part of a breast conserving surgery, is an operating theatre with the patient classified as an inpatient in either a private or public hospital.

*Describe how the service is delivered in the clinical setting. This could include details such as frequency of use (per year), duration of use, limitations or restrictions on the medical service or provider, referral arrangements, professional experience required (e.g.: qualifications, training, accreditation etc.), healthcare resources, access issues (e.g.: demographics, facilities, equipment, location etc.).*

Details of the delivery of this service include:

- IORT is usually delivered as part of the breast conserving surgical procedure.
- IORT is delivered by a Radiation Oncologist. A Medical Physicist is also required in order to calibrate the device. The Breast Surgeon, the Radiation Oncologist and the Medical Physicist are required to go through the Targit Accreditation Training Certification short course before performing the service.

- An individual patient has only one treatment that is delivered as part of the breast conserving surgery. Alternatively, IORT can be delivered post-surgery as a boost procedure (once per individual patient).
- The dose delivered to the breast tissue is approximately 20Gy at 0.2mm. The time required varies depending on the size of the applicator but ranges between approximately 10-30 minutes.
- The INTRABEAM® device is very portable only requiring a stand and control cart. Consequently, given the portability of the device and the ability to deliver IORT without special 'shielding', it has the potential to be used in any operating theatre that is suitable for breast conserving surgery.
- The relative low cost of the INTRABEAM® System, compared to the linear accelerator required to deliver EB-WBRT, makes it possible to provide this proposed service in more geographically remote locations.

## 5) Co-dependent information (if not a co-dependent application go to Section 6)

*Please provide detail of the co-dependent nature of this service as applicable.*

This is not a co-dependent service.

## 6) Comparator – clinical claim for the proposed medical service

*Please provide details of how the proposed service is expected to be used, for example is it to replace or substitute a current practice; in addition to, or to augment current practice.*

It is intended that this service will be provided as an alternative to the current practice of EB-WBRT.

## 7) Expected health outcomes relating to the medical service

*Identify the expected patient-relevant health outcomes if the service is recommended for public funding, including primary effectiveness (improvement in function, relief of pain) and secondary effectiveness (length of hospital stays, time to return to daily activities).*

- The primary health outcome (effect) is the prevention of the local recurrence of breast cancer.
- Secondary health outcomes are improved cosmesis and reduced toxicity compared to EB-WBRT.
- Other outcomes include a reduced time spent in the hospital setting by the patient and a more rapid return to daily activities.

Overall, outcomes that could be taken into account include local and regional recurrence, time to metastasis, progression-free and overall survival, quality of life and side effects including changes in long-term coronary artery disease risk. Patient preference and patient reported outcomes may also affect the economic evaluation.

*Describe any potential risks to the patient.*

IORT may cause redness and soreness of the skin of the breast, tenderness or painful sensations within the breast, or redness of the skin of the breast, and firmness of the breast tissue at the surgical site. These side effects gradually disappear after treatment has finished, but may also continue for several months. The feeling of firmness tends to be greatest between the third and sixth month post-surgery, and decline thereafter.

Participants who received IORT in the TARGIT-A Trial were observed to have a slightly high risk of fluid formation at the lumpectomy site than those who received standard whole breast radiation therapy. This fluid was easily managed with aspiration (drainage) using a needle and was not associated with an increased risk of infection.

Complications arising from IORT have been shown in the TARGIT-A Trial to be identical to patients who received EB-WBRT. These complications include swelling (edema), scarring, skin ulceration, radiation-induced tissue death (fat necrosis), and delayed wound healing. Some of these treatments may limit the ability of physical examination and mammograms to evaluate the breast for a cancer recurrence and may require that the patient undergo additional studies to evaluate the breast.

*Specify the type of economic evaluation.*

The economic evaluation will be a cost-effectiveness analysis based on a published US analysis. An Australian based cost-minimisation analysis will also be provided based on the non-inferior primary outcome results of the two key published papers.

## **8) Fee for the proposed medical service**

*Explain the type of funding proposed for this service.*

As a service rendered in an in-patient setting, the type of funding proposed for this service is a fee for the providers.

*Please indicate the direct cost of any equipment or resources that are used with the service relevant to this application, as appropriate.*

The direct equipment costs associated with this service are:

- A depreciation cost for the capital (the INTRABEAM<sup>®</sup> device including stand and cart); and
- A cost per procedure for equipment (applicator, drapes, etc).

*Provide details of the proposed fee.*

As with all new MBS Items, the proposed fee for this service will be based on the time taken and the expertise required to perform the service and will be in line with the MBS fee for 'similar' services.

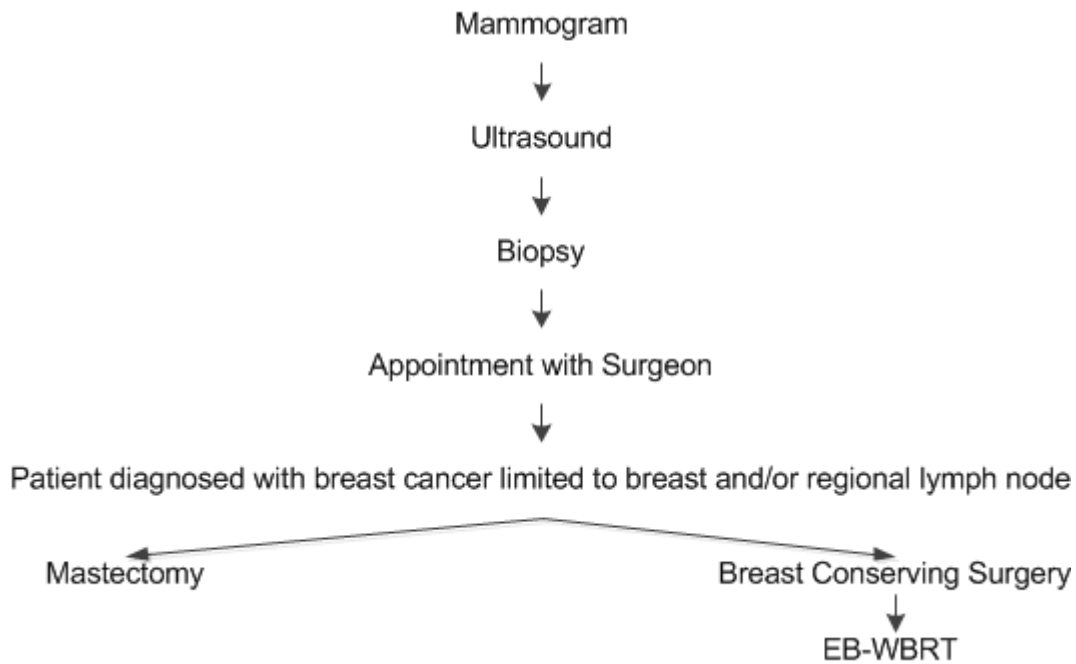
However, there are a number of 'unique' funding issues that need to be taken into account and explored as part of the submission. These include:

- The comparator, EB-WBRT, is delivered using a linear accelerator in an out-patient setting. The cost of this service is covered by a combination of MBS fee, the Radiation Oncology Health Programme Grant (ROHPG) and, the Medicare (out-patient) Safety Net (EMSN). In contrast, the proposed service is delivered in an in-patient setting using equipment not covered by the ROHPG and as part of a current surgical procedure.

## **9) Clinical Management Algorithm - clinical place for the proposed intervention**

*Provide a clinical management algorithm (e.g.: flowchart) explaining the current approach (see (6) Comparator section) to management and any downstream services (aftercare) of the eligible population/s in the absence of public funding for the service proposed preferably with reference to existing clinical practice guidelines.*

Current clinical management algorithm - existing clinical practice guidelines



NBCC Recommended follow-up schedule

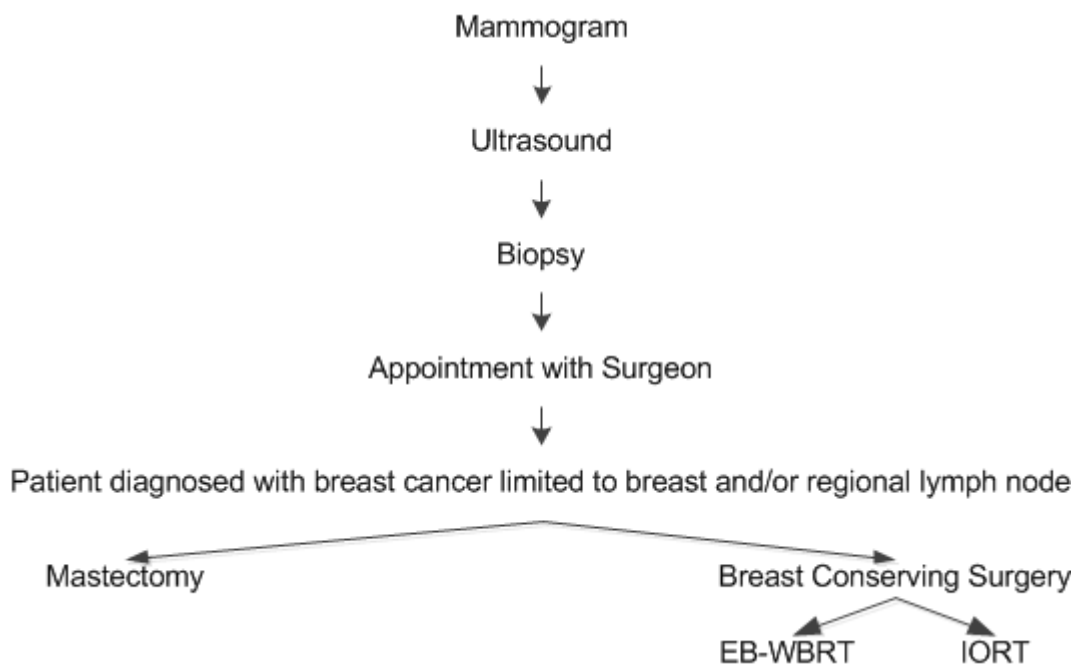
	1-2 Years	3-5 Years	After 5 Years
History & Exam	Every 3 months	Every 6 months	Every year
Mammography (& ultrasound if indicated)	At 6-12 months after radiotherapy for conserved breast	Every year	Every year

Chest X-ray: Only if clinically indicated

Bone Scan, blood count & biochemistry: Only if clinically indicated

*Provide a clinical management algorithm (e.g.: flowchart) explaining the expected management and any downstream services (aftercare) of the eligible population/s if public funding is recommended for the service proposed.*

Clinical management algorithm – including proposed service



NBCC Recommended follow-up schedule

	1-2 Years	3-5 Years	After 5 Years
History & Exam	Every 3 months	Every 6 months	Every year
Mammography (& ultrasound if indicated)	At 6-12 months after radiotherapy for conserved breast	Every year	Every year

Chest X-ray: Only if clinically indicated

Bone Scan, blood count & biochemistry: Only if clinically indicated

**10) Regulatory Information**

*Please provide details of the regulatory status. Noting that regulatory listing must be finalised before MSAC consideration.*

The details of registration (including certificates) of all medical devices and capital equipment used as part of this service were supplied in the original MSAC Application document.

- The INTRABEAM® device is TGA registration under ARTG 138540.
- The TGA-approved indication is: Intended for use in surgery to deliver radiotherapy through the use of low voltage x-rays.

**11) Decision analytic**

*Provide a summary of the PICO as well as the health care resource of the comparison/s that will be assessed, define the research questions and inform the analysis of evidence for consideration by MSAC*

Key Research Questions

- For selected patients with early breast cancer, is a single dose of radiation therapy delivered at the time breast conserving surgery using targeted intraoperative radiation



therapy (IORT) non-inferior based on local recurrence, as the current standard of care, EB-WBRT (delivered by a linear accelerator over a period of weeks after breast conserving surgery)?

- For selected patients with early breast cancer, is a single dose of radiation therapy delivered some time after breast conserving surgery using targeted intraoperative radiation therapy (IORT) non-inferior based on local recurrence, as the current standard of care, EB-WBRT (delivered by a linear accelerator over a period of weeks after breast conserving surgery)?

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### Key Evidence

The key evidence for the submission will be from:

- (i) Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial.

Vaidya JS, Wenz F, Bulsara M, Tobias JS, Joseph DJ, Keshtgar M, Flyger HL, Massarut S, Alvarado M, Saunders C, Eiermann W, Metaxas M, Sperk E, Sütterlin M, Brown D, Esserman L, Roncadin M, Thompson A, Dewar JA, Holtveg HM, Pigorsch S, Falzon M, Harris E, Matthews A, Brew-Graves C, Potyka I, Corica T, Williams NR, Baum M; on behalf of the TARGIT trialists' group.

Lancet. 2013 Nov 8. pii: S0140-6736(13)61950-9.

- (ii) Long-term results of targeted intraoperative radiotherapy (Targit) boost during breast-conserving surgery.

Vaidya JS, Baum M, Tobias JS, Wenz F, Massarut S, Keshtgar M, Hilaris B, Saunders C, Williams NR, Brew-Graves C, Corica T, Roncadin M, Kraus-Tiefenbacher U, Sütterlin M, Bulsara M, Joseph D.

Int J Radiat Oncol Biol Phys. 2011 Nov 15;81(4):1091-7.

- (iii) Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomised, non-inferiority phase 3 trial.

Vaidya JS, Joseph DJ, Tobias JS, Bulsara M, Wenz F, Saunders C, Alvarado M, Flyger HL, Massarut S, Eiermann W, Keshtgar M, Dewar J, Kraus-Tiefenbacher U, Sütterlin M, Esserman L, Holtveg HM, Roncadin M, Pigorsch S, Metaxas M, Falzon M, Matthews A, Corica T, Williams NR, Baum M.

Lancet. 2010 Jul 10;376(9735):91-102.

These key papers will be supplemented by the results of literature searches in Medline, Embase and the Cochrane Library.

### PICO

Patients: Women with early stage breast cancer who have a primary tumour less than 2 cm diameter with no nodal metastases.

Intervention: IORT – single dose

Comparator: EB-WBRT (possibly mastectomy for women living in remote areas). Possible other potential comparators include partial-breast radiotherapy, Mammasite, and brachytherapy.

Outcomes: Equivalent effectiveness in terms of prevention of the local recurrence of breast cancer compared to EB-WBRT;

Improved cosmesis and reduced toxicity compared to EB-WBRT; and

Decreased treatment time compared to EB-WBRT.

## 12) Healthcare resources

*Provide a list of the health care resources whose utilisation is likely to be impacted should the proposed intervention be made available as requested whether the utilisation of the resource will be impacted due to differences in outcomes or due to availability of the proposed intervention itself.*

It is anticipated that the main change in resources use will result from the replacement of the delivery of treatment using EB-WBRT (the comparator) with IORT. A crude indication of the current funding for a course of EB-WBRT using Dual Photon 3D-CRT (50Gy over 25 fractions), is as follows:

	Description	MBS per attendance*	HPG per attendance	Number of attendances	Total
MBS15550	Simulation	\$658.60	\$101.94	1	\$760.54
MBS15562	Dosimetry	\$1,120.75	\$107.44	1	\$1,228.19
MBS15251	Treatment	\$59.65	\$55.97	25	\$2,890.50
MBS15266	Treatment	\$126.65		25	\$3,166.25
MBS15705	Verification	\$76.60		8	\$612.80
<u>Total</u>					\$8,658

\* As at Aug'13

This funding estimate does not include any fees charged in excess of the MBS Scheduled Fee amount.

Note: It is anticipated that full details of the resources used for EB-WBRT will be available as a result of MSAC Application 1182 - assessment of intensity modulated radiation therapy for cancer treatment delivery.

### IORT – delivery of treatment costs (when performed as part of a breast conserving procedure)

Capital equipment: The INTRABEAM® system including stand and cart.

Consumables: Applicators, drapes, etc..

Other: Intra-operative ultrasound

Set-up time: to be determined

Breast Surgeon: Approximately an additional 10 minutes wound preparation compared to current procedure.

Medical Physicist: 30 minutes

Radiation Oncologist: 30 minutes

Operating theatre: Additional 45 minutes

All fees will be determined as part of the submission and in consultation with the relevant clinicians (Craft Groups and colleges).

### 13) Questions for public funding

*Please list questions relating to the safety, effectiveness and cost-effectiveness of the service / intervention relevant to this application, for example:*

- Which health / medical professionals provide the service
- Are there training and qualification requirements
- Are there accreditation requirements

#### Service Providers

- (i) Breast Surgeon
- (ii) Radiation Oncologist
- (iii) Medical Physicist

#### Training and Qualification Requirements

Prior to the first procedure all service providers are required to have a Targit Academy Training Certificate.