



**Australian Government**  

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**Medical Services Advisory Committee**

**Minutes from MSAC 69th Meeting, 6-7 April 2017**

**Application No. 1479R – Substitution of  $^{68}\text{Ga}$ -DOTA-peptide PET/CT scanning in lieu of Octreotide for patients undergoing somatostatin receptor diagnostic imaging under MBS item 61369**

**MSAC's advice to the Minister**

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC supported substitution of  $^{68}\text{Ga}$ -DOTA-peptide positron emission tomography (PET)/ computed tomography (CT) scanning in lieu of radioactive indium-labelled octreotide ( $^{111}\text{In}$ -octreotide) single-photon emission computed tomography (SPECT)/ CT for the diagnosis of gastroenteropancreatic neuroendocrine tumours (GEP NETs).

MSAC accepted that in contrast to  $^{111}\text{In}$ -octreotide SPECT/CT, the proposed imaging service is associated with a lower radiation dose, has superior diagnostic accuracy (higher sensitivity) and is less expensive.

**Summary of consideration and rationale for MSAC's advice**

MSAC considered the application requesting MBS listing of  $^{68}\text{Ga}$ -DOTA-peptide PET/CT scanning for the diagnosis of GEP NETs. MSAC noted that the application was referred to the committee by the MBS Review Taskforce for targeted assessment and that full economic evaluation through the PICO Advisory Sub-Committee (PASC) and the Evaluation Sub-Committee (ESC) was not deemed necessary.

MSAC noted that GEP NETs express somatostatin receptors on their cell surface and that in turn, they can be detected through somatostatin receptor scintigraphy (SRS), an imaging procedure which involves the pre-administration of a radiolabelled somatostatin analogue, which binds to the somatostatin receptor, followed by a PET/CT scan. MSAC noted that the only approved diagnostic radiopharmaceutical for SRS in Australia is OctreoScan® ( $^{111}\text{In}$ -octreotide), currently listed in conjunction with SPECT imaging under MBS item 61369 ± CT imaging (claimed separately under MBS item 61505). MSAC acknowledged the use of this MBS item as the comparator in the submission. MSAC noted that the proposed imaging service is expected to completely replace this existing MBS SRS item. MSAC highlighted that the application did not request changes to the eligible population for this item and hence, the only population in scope was patients with:

- suspected GEP NETs based on biochemical evidence and negative conventional imaging; or
- surgically amenable GEP NETs to exclude additional disease sites.

There are currently three different DOTA peptides which are used in conjunction with  $^{68}\text{Ga}$  ( $^{68}\text{Ga}$ ) for PET/CT imaging of GEP NETS. MSAC noted that in Australia, the DOTA-D-Phe<sup>1</sup>-Tyr<sup>3</sup>-Thr<sup>8</sup>-octreotate (DOTATATE) peptide is coupled to the radioactive  $^{68}\text{Ga}$  isotope. MSAC highlighted that while the  $^{68}\text{Ga}$ -DOTA-peptide is not listed on the Australian Register of Therapeutic Goods (ARTG), the radioactive  $^{68}\text{Ga}$  isotope generators are commercially available and

Good Manufacturing Practice (GMP) compliant. MSAC highlighted that, based on advice from the Therapeutic Goods Administration (TGA), radionuclide generators are not captured by the definition of therapeutic goods under the *Therapeutic Goods Act 1989* and are more appropriately considered as part of the manufacturing process.

In its consideration of the evidence presented to support the comparative safety and efficacy of the proposed imaging service, MSAC noted that no direct comparative studies were identified. MSAC also noted that while the gold standard for the diagnosis of GEP NETS is histopathology, the systematic review evidence presented to support the diagnostic accuracy of the proposed imaging, consisted of a composite reference standard which included the results from histopathology and/or conventional imaging and/or clinical follow-up of at least one year.

MSAC noted that the evidence presented to support the safety of the proposed imaging service was largely derived from the findings of three single-centre studies, none of which identified any serious adverse reactions associated with the procedure. MSAC noted that  $^{68}\text{Ga}$ -DOTATATE PET was associated with a significantly lower radiation dose of approximately 3-4 millisieverts (mSv) compared with 12 mSv for  $^{111}\text{In}$ -octreotide SPECT (Hartmann H et al 2009). MSAC also acknowledged that the potential long-term effects of exposure to ionising radiation associated with the procedure are unlikely to be of major concern to patients with GEP NETs, given their reduced life expectancy. MSAC considered the applicant's claim that the proposed imaging is also superior in safety due to faster acquisition time and acknowledged that while  $^{111}\text{In}$ -octreotide SPECT/CT requires approximately two days to complete,  $^{68}\text{Ga}$ -DOTATATE PET/CT can be completed within 90-120 minutes. MSAC summarised that the proposed imaging service has a similar safety profile to  $^{111}\text{In}$ -octreotide SPECT, with a lower radiation dose and faster acquisition time.

MSAC considered the evidence presented to support the comparative effectiveness of the proposed service, largely derived from systematic review findings which compared  $^{68}\text{Ga}$ -DOTATATE PET/CT (Deppen SA et al 2016b),  $^{68}\text{Ga}$ -DOTA-peptide PET/CT (Geijer H & Breimer LH 2013) and  $^{111}\text{In}$ -Octreotide SPECT/CT with the aforementioned composite reference standard for patients with NETs. MSAC acknowledged that although this population was broader than that proposed by the applicant, the majority of patients in the reviewed studies had GEP NETs specifically. MSAC noted that both  $^{68}\text{Ga}$ -DOTATATE PET/CT and  $^{68}\text{Ga}$ -DOTA-peptide PET/CT were more sensitive than  $^{111}\text{In}$ -octreotide SPECT/CT, with sensitivity values of 91%, 93% and 80%, respectively. However, all three imaging procedures had similar specificity values. MSAC also considered the positive predictive value (PPV) and negative predictive value (NPV) of these imaging procedures, assuming a 59% prevalence (proportion of patients with a clinically-diagnosed NET). MSAC noted that while the PPV of the imaging procedures was similar, their NPV varied by more than 10%. At a 59% prevalence, the NPV for the different imaging procedures was:  $^{68}\text{Ga}$ -DOTATATE PET/CT 87.5%;  $^{68}\text{Ga}$ -DOTA-peptide PET/CT 90.1%; and  $^{111}\text{In}$ -octreotide SPECT/CT 76.6%. This indicated that approximately 23% of patients who received a negative  $^{111}\text{In}$ -octreotide SPECT/CT result would actually have the disease compared to approximately 10% of patients with the  $^{68}\text{Ga}$ -based PET/CT imaging. MSAC considered that this almost 50% reduction in the rate of false negative results was likely to be of clinical significance. MSAC noted that although there was no evidence presented in the submission to support the applicant's claim that the proposed imaging would reduce the need for repeat testing, the committee highlighted that the lower rates of false negative results may lead to a reduction in downstream testing.

MSAC also considered the findings of an updated meta-analysis conducted as part of the application, which highlighted that 38% of patients who had a prior  $^{111}\text{In}$ -octreotide SPECT/CT scan and 36% who had a prior  $^{111}\text{In}$ -octreotide SPECT  $\pm$  CT, had a change in management after undergoing imaging with  $^{68}\text{Ga}$ -DOTA-peptide PET/CT. MSAC highlighted a number of clinical scenarios associated with changes in patient management in these instances including:

- Approximately half of GEP NET patients who are histopathology-positive but with a false negative  $^{111}\text{In}$ -octreotide SPECT/CT result could become eligible for somatostatin analogue

(SSA) therapy or peptide receptor radionuclide therapy (PRRT) after <sup>68</sup>Ga-DOTA-peptide PET/CT due to its better NPV compared to <sup>111</sup>In-octreotide SPECT/CT.

- GEP NET patients who are histopathology-positive but with an SRS-negative result according to <sup>68</sup>Ga-DOTA-peptide PET/CT are likely to be directed away from PRRT and SSA therapy (due to a lack of somatostatin receptor expression on the tumour cell surface).
- Identification of the primary tumour site with <sup>68</sup>Ga-DOTA-peptide PET/CT imaging in patients in whom it is otherwise not detected are likely to be directed to surgical resection.
- Identification of further metastases with <sup>68</sup>Ga-DOTA-peptide PET/CT imaging may lead to patients receiving PRRT instead of, or in addition to, surgical intervention.

MSAC noted that according to indirect comparative evidence of the 5-year survival rates of patients who received the various treatments, surgical resection was associated with the best survival outcomes, followed by long acting release (LAR) SSA and PRRT (Bodei L et al 2014; Saglam S et al 2015). MSAC summarised that compared to no treatment, the treatment of GEP NETS with surgery, SSA or PRRT appears to be more effective.

MSAC noted that the total projected cost (MBS costs plus patient contribution costs) of listing the proposed imaging is \$446,511 for 445 services in year 1, increasing to \$953,240 for 951 services in year 5. Despite the proposed service having a lower schedule fee (\$953) than the existing <sup>111</sup>In-octreotide SPECT (\$2,015.75), the proposed listing is expected to increase the net cost to the MBS due to trended reductions in the use of <sup>111</sup>In-octreotide SPECT ± CT i.e. the number of <sup>111</sup>In-octreotide SPECT services (and associated costs) anticipated to be offset by the proposed imaging is projected to decrease over time. MSAC noted when taking these cost offsets into account, the total projected cost of listing the proposed imaging is \$290,269 in year 1, increasing to \$905,177 in year 5. However, MSAC considered that the utilisation estimates used to calculate the financial impact of listing the proposed imaging service were uncertain and noted the applicant's comment that the projected increase in the number of services (almost double) over the first 5 years of listing was likely to be an overestimate given that the incidence of the disease is relatively static. MSAC noted that the cost of the radio-isotope specified in the current MBS item 61369 exceeds the MBS rebate and hence the observed decline in use of this item may be attributed, in part, to this.

MSAC also noted that as <sup>68</sup>Ga-DOTATATE PET scanning is currently performed in a number of Australian public hospitals, MBS listing of the proposed service may result in cost shifting from state and territory health budgets to the MBS, as the service and hence the use of the specific isotope would now be MBS funded, rather than funded through public hospital budgets. As well there may be some transfer of services into true private settings following MBS funding. MSAC noted that in their pre-MSAC response, the applicant highlighted that such a shift would be unlikely due to the short half-life of the tracer (68 minutes) requiring an onsite <sup>68</sup>Ga generator. Due to the cost of these generators, this is anticipated to only be feasible for large centres with significant infrastructure, radiopharmaceutical expertise and a critical mass of patients.

MSAC acknowledged the applicant's concern that currently, item 61505 (CT scan) cannot be claimed in conjunction with PET imaging procedures even though it can be co-claimed with item 61369 (general nuclear medicine/SPECT). The applicant highlighted that CT imaging provides essential information such as anatomical localisation which contributes to the high diagnostic accuracy of PET imaging. The applicant noted that this is of particular importance in this population, as not all GEP NETs express a significant number of somatostatin receptors and may subsequently be undetected by <sup>68</sup>Ga-DOTA-peptide PET alone.

MSAC supported the decision to list <sup>68</sup>Ga-DOTA-peptide PET/CT scanning in lieu of <sup>111</sup>In-octreotide SPECT/CT, noting that the proposed imaging was likely to be more effective than the comparator due to improved diagnostic accuracy (increased sensitivity) which is likely to lead to changes in management with more appropriate use of targeted therapies (e.g. surgical resection, SSA therapy, PRRT) and should improve outcomes for patients. In addition, the procedure is

associated with significantly lower radiation, is less expensive and faster to conduct than the comparator. MSAC noted that due to the small sample size of the eligible population, there should be no restrictions on the number of services (i.e. repeat studies) per patient.