



Medical Services Advisory Committee

Public Summary Document

Application No. 1146 – Capsule Endoscopy for the Diagnosis of Suspected Small Bowel Crohn Disease

Applicant: Given Imaging Pty Ltd
Date of MSAC consideration: 27 July 2011

1. Purpose of application

The application was submitted by Given Imaging Pty Ltd on 25 February 2010.

Although the application was received from a single proprietary manufacturer, MSAC's usual approach is to consider assessments across a 'generic' group of related products because an MBS item usually described a professional service, not a particular brand of technology.

MSAC noted that there are other brands of capsule endoscopy technologies available from manufacturers in Japan, Korea and China that were not reported in the assessment. However, in the absence of any comparative evidence across the various forms of capsule endoscopy mentioned, MSAC could only assume that all brands available in the Australian market could be regarded as meeting appropriate technical standards.

Capsule endoscopy is a non-invasive diagnostic test, usually conducted in an outpatient setting, in which the gastrointestinal system is visualised via a camera inside an ingested capsule. The test visualises the gastrointestinal tract mucosa to diagnose a range of conditions such as obscure gastrointestinal bleeding (OGIB), coeliac disease, small bowel tumours and Peutz-Jeghers syndrome.

Capsule endoscopy is an extension of use of an existing intervention. MSAC agreed that in the absence of histopathology as a standard against which to assess patients with Crohn disease, any 'positive' capsule endoscopy finding is not really a confirmed diagnosis but rather another indication in relation to the likelihood of the disease for the clinician to consider in determining treatment options.

Crohn disease is a chronic inflammatory bowel disease that may affect any portion of the gastrointestinal tract but, in cases of small bowel involvement, typically affects the terminal ileum. Most patients with isolated small bowel Crohn disease are diagnosed using colonoscopy with ileoscopy; however diagnosis can be difficult due to the inaccessibility of the small bowel.

2. Background

Capsule endoscopy is currently funded through the MBS for two indications: for the investigation of OGIB (MBS item 11820) and for the conduct of small bowel surveillance of a patient with Peutz-Jeghers syndrome (MBS item number 11823). Both of these MBS items originated following recommendations by MSAC. Capsule endoscopy for investigation of OGIB originally received interim MBS funding following consideration by MSAC in 2003 (Application 1057). MSAC reconsidered this indication in 2007 with MSAC recommending full MBS listing. The use of capsule endoscopy for Peutz-Jeghers syndrome was considered by

MSAC in 2007 (Application 1119).

3. Prerequisites to implementation of any funding advice

The capsules are TGA approved; there are no specific conditions on its TGA certification.

Capsule endoscopy is usually performed in an outpatient setting. Consistent with other MBS listings of capsule endoscopy, it is presumed that any capsule endoscopy service will only attract a MBS benefit when performed by a specialist or consultant physician with endoscopic training recognised by The Conjoint Committee for the Recognition of Training in Gastrointestinal Endoscopy (and Medicare Australia is notified of that recognition).

4. Proposal for public funding

Although not directly specified in the application, the proposed MBS item descriptor implied by the application is summarised below:

Category 2 - DIAGNOSTIC PROCEDURES AND INVESTIGATIONS

CAPSULE ENDOSCOPY to evaluate suspected small bowel Crohn disease, using a capsule endoscopy device approved by the Therapeutic Goods Administration. This is restricted to patients with no known Crohn disease (ie, it is not for patients with known Crohn disease with suspected small bowel involvement). The procedure includes the administration of the capsule, imaging, image reading and interpretation, and all attendances for providing the service on the day the capsule is administered (not being a service associated with double balloon enteroscopy).

Medicare benefits are only payable for this item if:

(a) the service is performed by a specialist or consultant physician with endoscopic training that is recognised by The Conjoint Committee for the Recognition of Training in Gastrointestinal Endoscopy and Medicare Australia notified of that recognition; and

(b) the patient to whom the service is provided:

(i) is aged 10 years or over; and

(ii) has suspected Crohn disease on the basis of evidence of underlying inflammation, as indicated by elevated Erythrocyte Sedimentation Rate and/or C-Reactive Protein or other inflammatory markers tested at least twice over at least six weeks, and ongoing symptoms of diarrhoea and/or abdominal pain; and

(iii) no evidence of strictures on small bowel radiology; and

(c) a colonoscopy with attempted ileoscopy and small bowel radiology have been performed on the patient and have not confirmed the diagnosis of Crohn disease; and

(d) the service is performed within 6 months of the colonoscopy, attempted ileoscopy and small bowel radiology

Fee: \$1,961.95 Benefit: 75% = \$1,471.50, 85% = \$1,890.75

Capsule endoscopy is restricted to patients with suspected but unconfirmed nonstricturing small bowel Crohn disease, as indicated by ongoing symptoms suggestive of Crohn disease such as abdominal pain, diarrhoea, extraintestinal symptoms or raised inflammatory markers on blood tests.

MSAC noted Evaluation Sub-committee (ESC) advice that MSAC consider whether there should be a limit to the number of times the capsule endoscopy for Crohn could be used as there is an issue of ongoing monitoring and the question of whether there should be any repeat testing in a patient who is not confirmed as having Crohn disease, such as in the event of flaring up of symptoms, and that any item descriptor could be more restrictive in these circumstances, eg. to once per lifetime or no more frequently than on an annual basis, although a gastroenterologist may be able to confirm intent.

MSAC also noted ESC advice that Item 11820 is directly relevant to the procedure and that in the event of public funding, one option might be to amend this descriptor rather than create a new one. While the existing item may potentially cover those with undiagnosed Crohn disease affecting the small bowel who initially present clinically with OGIB, Crohn disease can present with a diverse range of clinical symptoms and signs depending on the part/extent of the gastrointestinal tract that is affected and as such gastrointestinal bleeding may not always be part of the clinical picture. On balance, an amendment is likely to become too complicated and ESC

acknowledged a separate descriptor might be best to specify the intended purpose for Crohn disease in a way that is clearly distinguishable from the uses that are already funded, capture the issue of restricting its repeated use in an individual, and enable tracing of the number of uses per patient for the specific new purpose. If necessary, the current items might need amendment to exclude this proposed new use.

MSAC noted that capsule endoscopy must be restricted to patients who have had the following conventional diagnostic tests:

Blood tests for inflammatory markers such as **erythrocyte sedimentation rate** (ESR) or C-reactive protein (CRP)

and

Colonoscopy

and

Attempted ileoscopy (as part of colonoscopy)

and

Small bowel radiology:

Small Bowel Follow Through (SBFT)

or

small bowel enteroclysis (SBE)

or possibly

Abdomen CT +/- enterography

or possibly

MRI +/- enterography

However, MSAC agreed with ESC that the term “small bowel radiology” was ambiguous and implied that CT and/or MRI be included as prerequisite tests rather than alternative tests. This has consequences for clear communication of the intended patient group for public funding of capsule endoscopy as proposed. In addition, MSAC noted ESC advice to consider whether this small bowel radiology would be able to identify bowel strictures which may be important to reduce the risk of capsule retention and associated retrieval surgery.

Consistent with other MBS listings of capsule endoscopy, it is presumed that capsule endoscopy services will only be reimbursed for public funding when performed by a specialist or consultant physician with endoscopic training recognised by The Conjoint Committee for the Recognition of Training in Gastrointestinal Endoscopy (and Medicare Australia is notified of that recognition).

5. Consumer Impact Statement

MSAC agreed that, if capsule endoscopy were not definitive in its diagnosis of small bowel Crohn disease, patients may still need to be considered for histological examination such as could be obtained with double balloon enteroscopy (DBE) before being put on long-term drugs which are both toxic and potentially expensive. However, MSAC agreed that, from a consumer’s perspective, capsule endoscopy would be preferable to DBE on the grounds of comfort and risk.

MSAC further agreed that the number of patients who would be eligible for the proposed indication for capsule endoscopy would be very small. In most patients with isolated small bowel Crohn disease, the disease affects that part of the small bowel which can usually be visualised with ileoscopy at the time of colonoscopy.

MSAC also agreed that any MBS listing of capsule endoscopy in small bowel Crohn disease should not permit monitoring or surveillance of diagnosed patients.

6. Proposed intervention's place in clinical management

Capsule endoscopy will be used to provide an additional diagnostic modality to those currently available to confirm the diagnosis of Crohn disease where there is residual diagnostic doubt. In the clinical flow chart, capsule endoscopy is a replacement test for repeat radiology (Computed Tomography (CT)/CT enterography (CTE) or magnetic resonance imaging (MRI)/ Magnetic Resonance Enterography (MRE)) and a replacement for treating the patient empirically based on a suspicion of Crohn disease which could not be confirmed (ie incremental to prior testing).

MSAC noted that ESC drew attention to the diagnostic pathway in the assessment report indicating that the use of capsule endoscopy may only be of assistance in resolving up to 30% of the residual 5% of Crohn disease diagnoses after the initial battery of investigations, because only 30% would have a convincing diagnosis ruling out Crohn disease and therefore changing clinical management from starting treatment for Crohn disease.

MSAC noted ESC's advice that there would be no change to the clinical management strategy for the remaining 70% of these residual 5% of patients, in whom the diagnosis of Crohn disease would either be confirmed or remain unclear.

7. Other options for MSAC consideration

See Section 4 for options to limit the number and frequency of tests.

8. Comparator to the proposed intervention

The current interventions, as specified by the applicant, are:

- empirical treatment of suspected Crohn disease without further investigations
- MRI/MRE (MRI +/- enterography) (although MRI is not funded by the MBS for this purpose)
- abdomen CT +/- enterography

These comparators are appropriate and are further delineated and then used in the assessment report.

MRI and MRE are currently not funded on the MBS for the purpose of diagnosing small bowel Crohn disease. Expert advice suggests that MRE is likely to cost more than MRI, due to the longer duration and special expertise required to perform the procedure, but no cost information is available for this economic analysis.

The current MBS schedule fee for CT with intravenous contrast medium of upper abdomen and pelvis is \$480.05 (MBS item 56507). The listed 85% benefit is \$408.85. This cost is used for both CT and Computed Tomography Enterography (CTE). The average copayment for CT performed in an outpatient setting is \$25.32. Hence, the average cost of CT/CTE is \$434.17 (\$408.85 to the government and \$25.32 to the patient).

9. Comparative safety

No studies reported comparative safety data of capsule endoscopy against MR, CT or empirical treatment. Safety data for capsule endoscopy for patients with suspected small bowel Crohn disease were reported in 14 studies. The types of studies were as follows:

Study Type	Number
Prospective, consecutive diagnostic accuracy	3
Prospective, consecutive diagnostic yield	1
Prospective, consecutive blinded diagnostic yield	1
Prospective, non-consecutive blinded diagnostic yield	1
Prospective, blinded diagnostic yield	1
Prospective diagnostic yield	4
Retrospective diagnostic accuracy	2
Retrospective case series	1

Two moderate to severe adverse events associated with the use of capsule endoscopy were reported in one study. One patient had severe nausea with vomiting that was treated with anti-nausea medication (1/120, <1%), the other suffered from moderate pain (1/120, <1%). Both events were resolved within 24 hours. Seven other studies reported no adverse events associated with the use of capsule endoscopy for the diagnosis of patients with suspected small bowel Crohn disease. Adverse events are likely to be similar, and occur at similar rates, as those reported for other indications (MSAC 2003).

Data concerning delayed passage or retention of the capsule were reported in 13 of the 14 studies included in the safety assessment. The rate of capsule retention reported in the included studies ranged from 0% to 15%. The simple average of 2% across studies is difficult to interpret given the wide variation without obvious explanation. Most subjects who retained the capsule did not experience any symptoms as a result of the retention. In included studies where the rate of capsule retention and the rate of surgical removal were reported, 7 of 12 subjects who retained a capsule later had surgery at which the capsule was removed.

However, *somewhat paradoxically*, the reported rates of capsule retention were highest in studies that *excluded* patients on the basis of known intestinal obstruction (current or prior) and/or strictures revealed by x-ray as opposed to strictures revealed by other forms of small bowel radiology.

MSAC agreed with ESC advice that it was not clear whether the reason for the surgery in each case was due to the retained capsule or for other reasons. However, if the retention rates are as high as some of the studies indicate, ESC felt there are consequential safety issues with up to between 1 in 6 and 1 in 7 potentially requiring surgical intervention, which are arguably more important than the consequential impacts for comparative costs (see Item 11 below). Reduction of retention by using a dissolvable capsule as a precursor test for blockages might reduce this safety issue, but is not supported by any evidence.

The intervention is considered safe, but may lead to capsule retention in up to 15% of cases.

10. Comparative effectiveness

MSAC noted ESC advice that the current review did not identify any studies comparing the health outcomes of symptomatic patients with suspected but unconfirmed small bowel Crohn disease, assessed with and without capsule endoscopy. In the absence of direct evidence for the effectiveness of capsule endoscopy, evidence for accuracy, change in clinical management and the expected benefit of changes in treatment on health outcomes are presented in order to draw conclusions about the effectiveness of capsule endoscopy using a linked evidence approach.

A special problem is that approval for capsule endoscopy is being sought for those suspected of having Crohn disease who have failed previous testing but the evidence presented is for the whole population including all those patients who might have been suitable for other testing regimens.

The scientific basis of the comparison of the effectiveness and cost-effectiveness of capsule endoscopy with that of ET, MRI/MRE and CT/CTE was a systematic review that yielded 22 studies. A linked analysis was performed that considered:

- the safety of the test – 14 studies (5 accuracy studies, 8 diagnostic yield studies and 1 case series)
- the accuracy of the test – 5 studies of the accuracy of capsule endoscopy including 2 studies of the comparative accuracy of capsule endoscopy versus MRI or MRE
- impact of availability of results from the test on clinical management – no studies identified
- impact of changes in management on patient outcomes – no studies identified and linked evidence case unable to be made.

A search for existing HTA reports and published systematic reviews on the use of capsule endoscopy for the diagnosis of small bowel Crohn disease yielded one HTA report, one meta-analysis and one systematic review after exclusion criteria were applied.

Five included studies provided evidence for a comparison of capsule endoscopy and empirical treatment (Albert et al 2005; Casciani et al 2011; Figueiredo et al 2010; Girelli et al 2007; Tukey et al 2009). In studies using a threshold of at least ≥ 2 ulcers or Crohn disease specific lesions, the sensitivity of capsule endoscopy ranged from 47% (95% CI 22-73%) to 92% (95% CI 62-100%) and the specificity ranged from 89% (95% CI 81-94%) to 100% (95% CI 72-100%). The negative LR ranged from 0.08 to 0.58 (Albert et al 2005; Casciani et al 2011; Girelli et al 2007; Tukey et al 2009). For the threshold of any small bowel ulcers, the sensitivity of capsule endoscopy ranged from 85% (95% CI 58-96%) to 100% (95% CI 72-100%) and the specificity ranged from 74% (95% CI 64-82%) to 92% (95% CI 73-99%). The negative LR ranged from 0 to 0.21 (Casciani et al 2011; Figueiredo et al 2010; Girelli et al 2007; Tukey et al 2009). Overall, most studies had negative LRs < 0.10 , the threshold for providing convincing evidence to exclude disease; however, two studies had negative LRs which were above the negative LR threshold for providing strong evidence for excluding disease < 0.20 . This included the largest and most applicable study which had a negative LR > 0.20 at both endoscopic thresholds.

Two included studies comparing capsule endoscopy and MRI or MRE (Albert et al 2005; Casciani et al 2011) found that capsule endoscopy and MRE have similar comparative accuracy and that capsule endoscopy is more accurate than MRI without enterography. Using a threshold of > 3 small bowel ulcers, the sensitivity of capsule endoscopy versus MRE was 91% (95% CI 57-100%) versus 100% (95% CI 82-100%) and the specificity was 100% (95% CI 87-100%) versus 98% (95% CI 87-100%). Using a threshold of any small bowel ulcers, capsule endoscopy and MRE had similar sensitivity (100% [95% CI 72-100%] versus 100% [95% CI 82-100%]) and specificity (92% [95% CI 73-99%] versus 98% [95% CI 87-100%]). On this basis, capsule endoscopy is considered likely to have at least comparable accuracy to MR.

No studies were included that compared the diagnostic accuracy of capsule endoscopy and CT (with or without enterography).

In the assessment of capsule endoscopy as an incremental test over prior tests, a case for improved patient outcomes using a linked evidence approach depends on three pieces of evidence: (1) evidence that capsule endoscopy accurately excludes disease; (2) evidence that this test result leads to an avoidance of treatment; and (3) evidence that this change in management improves patient outcomes.

A case for improved outcomes could not be established due to the uncertainty that affected each of the three components of a potential linked evidence case.

11. Economic evaluation

The systematic review identified three published economic analyses that explored the costs or cost-effectiveness of imaging strategies, including capsule endoscopy, for diagnosing Crohn disease. However, these could not be used as evidence of cost-effectiveness for the use of capsule endoscopy in Australia since they did not reflect the patient population or clinical pathway under consideration in the Assessment Report. In addition, none of the studies were conducted in Australia and substantial differences between health systems limit the transferability of economic studies. MSAC agreed with ESC advice that these analyses were not relevant to the Australian setting.

Due to the lack of comparative effectiveness data it was also not warranted to perform a cost-effectiveness analysis to estimate the value for money of capsule endoscopy. The approach to the economic evaluation was therefore a presentation of the costs and possible consequences of capsule endoscopy and comparators. A healthcare system perspective was used, which included the cost to the government via the MBS and cost to the patient.

In summary, the average cost of capsule endoscopy to the healthcare system is \$1,924 per test (\$1890.74 to the government and \$32.95 to the patient) when the costs of capsule retention are not taken into account. This increases to \$2,085 per test (\$2,008.42 to the government and \$76.75 to the patient) when a 15% capsule retention rate is assumed but the costs of surgery to remove the retained capsule were not attributed to increased cost for the capsule endoscopy in those cases.

MSAC noted ESC advice that some costs for surgical retrieval of retained capsules should be considered. The average cost of CT/CTE is \$434 per test (\$408.85 to the government and \$25.32 to the patient). MRI/MRE as a diagnostic test for Crohn disease is currently not funded through the MBS.

Although not directly specified in the application, it is implied by the application that the proposed schedule fee be \$1,961.95 which is in line with two existing MBS items. No alternative fees were supplied.

MSAC noted ESC advice that the direct treatment cost of the capsule included in the breakdown of costs from Appendix G (p133) of the 2003 report of capsule endoscopy was approximately 52% of the total schedule fee and questioned whether this remained an accurate reflection of cost as there is now more than one manufacturer of capsule endoscopy in the Australian marketplace. At the time of 2003 report the proposed schedule fee was \$1706.56 (which has been subsequently indexed), \$895.00 of which was attributable to direct treatment costs associated with the disposable capsule, \$292.16 attributable to estimated capital cost per examination and the remaining \$519.39 attributable to the professional fee.

Out-of-pocket contributions for capsule endoscopy are only slightly higher than for CTs performed in outpatient setting (\$32.95 versus \$25.32). Hence, the introduction of capsule endoscopy, replacing CT/CTE, is unlikely to have a significant impact upon the EMSN.

MSAC noted ESC advice that the proposed descriptor for the item would mean that this item would impact on the safety net, and given its potential to be used more than once per year, it would then also affect the extended safety net. This concern was reduced as the statistics of out-of-pocket costs compared to the fees charged indicate that the schedule fee was predominantly the fee being charged to patients.

12. Financial/budgetary impacts

MSAC noted with caution the assumptions in the Assessment Report that estimated utilisation of capsule endoscopy for the diagnosis of small bowel Crohn disease unconfirmed on prior tests lies between 664 and 1,431 per year. However the Advisory Panel estimated that approximately 95% of cases would be diagnosed by prior tests, leaving 5% of incident cases to be diagnosed by capsule endoscopy.

If 5% of these are diagnosed by capsule endoscopy for the indication of small bowel Crohn disease, then the estimated number of patients diagnosed with Crohn disease by capsule endoscopy is approximately 186 per year.

It was assumed for the purposes of the economic evaluation that each patient would undergo one capsule endoscopy per year in an outpatient setting and no capsules would be retained.

Taking the Australian incidence estimate of 17 per 100,000 per year from Wilson et al (2010) (see Assessment Report) and multiplying it by the estimated annual resident population of Australia (21,875,000) as at 30 June 2009 would suggest that the annual number of incident cases of Crohn disease in Australia is approximately 3,719.

The total cost of capsule endoscopy to the MBS is estimated to be between \$1,277,337 and \$2,752,814 per year.

If repeat CT/CTEs are replaced by a capsule endoscopy, the incremental cost to society is estimated to be between \$989,049 and \$2,131,517 per year.

The impact on the MBS is determined by dividing the anticipated number of patients diagnosed with Crohn disease by capsule endoscopy (approximately 186 per year) by the estimated yield of the test (between 13% and 28%) the result lies between 664 and 1,431 per year, the incremental cost to the MBS is therefore estimated to be between \$983,962 and \$2,120,599 per year when capsule endoscopy replaces repeat CT/CTE. There is no expected impact to the Medicare Safety Net.

MSAC noted ESC advice that the cost impact is sensitive to the rate of capsule retention and whether costs of surgery to remove a retained capsule are classified as a consequence of capsule endoscopy. Additionally, the implementation of public funding for capsule endoscopy may lead to a modest increase in utilisation; however, it could also lead to a modest decline in claims for MBS item 11820, capsule endoscopy for OGIB, as a proportion of patients with undiagnosed Crohn disease, affecting the small bowel may present clinically with OGIB. However the exact proportion presenting clinically as OGIB is unclear given that Crohn disease can present with a variety of clinical manifestations depending on the part of, and the extent of, the gastrointestinal tract that is affected.

13. MSAC's key issues

MSAC noted ESC advice that the evidence for the safety of the intervention did not address sufficiently the issue of retention of the capsule.

MSAC noted ESC advice that the assessment indicated that the evidence is not relevant to the proposed population in which it will be used, which is the group of patients who are hardest to diagnose and for which the applicant is indicating capsule endoscopy would assist.

MSAC noted ESC advice that the assessment did not identify any direct studies comparing the health outcomes of patient populations with suspected small bowel Crohn disease assessed with and without capsule endoscopy. ESC pointed to the issue that evidence for accuracy, change in management and the expected benefit of changes in treatment on health outcomes were all achieved using a linked evidence approach.

MSAC agreed with ESC advice that the assessment report provided no basis to conclude that the diagnostic accuracy of capsule endoscopy was superior to the alternative investigations of CT or MRI in any population with suspected Crohn disease. At best, the evidence might support a conclusion of similar diagnostic accuracy across these three investigations if compared as alternatives.

MSAC agreed with ESC advice that, even excluding safety issues, there did not seem to be a basis to justify the extra costs of capsule endoscopy over its comparators. This raises doubts over its cost effectiveness.

MSAC also agreed with ESC that it was plausible that the harms and costs of capsule retention might be reduced by the prior use of a dissolvable capsule but there was no evidence presented to directly support this claim.

MSAC also agreed with ESC concerns about the accuracy of using an x-ray versus abdominal MRI or abdominal CT prior to use of capsule endoscopy to possibly reduce the rate of capsule retention and consequent surgery. The costs of doing more than an x-ray would add to the costs of the whole process. ESC was concerned that this would give a mismatch from the descriptor if small bowel radiology in the descriptor was expected to cover more radiology than x-ray as is indicated by the list of tests described as small bowel radiology.

MSAC noted ESC's concerns that at present, the proposed use of capsule endoscopy could already be captured by the use of the MBS item 11820 used for OGIB.

Safety data for capsule endoscopy for patients with suspected small bowel Crohn disease were reported in 14 studies, but MSAC noted that no studies reported comparative safety data of capsule endoscopy against the nominated alternatives of magnetic resonance imaging (MRI), abdomen computed tomography (CT) or empirical treatment.

MSAC noted that capsule endoscopy is generally considered to be a non-invasive and safe diagnostic test, usually conducted in an outpatient setting, in which the gastrointestinal system is visualised via a camera inside an ingested capsule. Capsule retention is a rare (simple average of 2% across the studies included in the assessment report, up to 15% in one study) but potentially serious complication of capsule endoscopy because it may result in the need for surgical retrieval. Therefore, MSAC considered that the use of capsule endoscopy may result in the need for an invasive procedure. However MSAC also noted that surgery following evidence of capsule retention may not simply be undertaken in order to retrieve the capsule; it may also be to correct the stricture that retained the capsule.

MSAC also noted that, whilst the use of a radio-opaque dissolvable capsule of the same size as the capsule used for endoscopy (the Agile patency[®] capsule) was mentioned in the Applicant's comments on the Evaluation Sub-committee's (ESC) Report as a means of identifying when a capsule might be retained, its ability to reduce retention of the capsule endoscope and thus improve the safety of the capsule endoscope was not addressed in the Assessment Report. MSAC noted that, whilst technical developments of the dissolvable capsule appear to have improved its performance, the dissolvable capsule has not been recommended for routine evaluation of patients prior to capsule endoscopy (expert advice), and is only recommended for patients identified as high risk such as when there is evidence of a stricture either clinically or radiologically prior to capsule endoscopy.

MSAC also noted ESC's concerns about the predictive accuracy of using an x-ray +/- enterography or abdominal MRI +/- enterography or abdominal CT +/- enterography before use of capsule endoscopy to identify strictures in an attempt to reduce the rate of capsule retention and consequent surgery. The costs of these possible strategies would add to the costs of the whole procedure of using the capsule. Given ambiguity in the term 'small bowel radiology' in the proposed MBS item descriptor, any of these strategies might be used before the capsule.

MSAC therefore agreed with ESC's advice that the evidence for the safety of the use of the capsule endoscope for the proposed patient group did not sufficiently address the issue of its retention, the consequences of that retention and the costs of measures to avoid that retention. MSAC also remained uncertain as to the extent to which retention rates would reduce with the use of a dissolvable capsule and other prior tests, particularly for those patients with strictures. Whilst MSAC accepted that the use of a dissolvable capsule as a prior test may reduce risks of harm arising from the use of the device, MSAC did not accept that there was persuasive evidence that the risk of harm due to retention of the capsule endoscope would be abolished.

MSAC agreed that one of the benefits of capsule endoscopy over CT is that it does not involve ionising radiation, and so a potential safety advantage is that minimises the repetition of ionising radiation exposure in patients who will have had prior small bowel radiology. This is particularly important given the relatively young age of most of the patients who would be eligible. MSAC also noted that there would be less discomfort with capsule endoscopy than CT enterography or MRI enterography (CT and MRI alone are not uncomfortable).

MSAC concluded that capsule endoscopy appears safe overall, has a low risk of adverse events such as nausea, vomiting and pain, similar to that observed for its use in other indications, but may lead to capsule retention in up to 15% of cases.

MSAC noted that the current review did not identify any studies comparing the health outcomes of symptomatic patients with suspected but unconfirmed small bowel Crohn disease, assessed with and without capsule endoscopy. In the absence of direct evidence for the effectiveness of capsule endoscopy, evidence for diagnostic accuracy needs to be linked to expected changes in clinical management and consequential improvements in health outcomes in order to draw conclusions about the effectiveness of capsule endoscopy.

MSAC noted that capsule endoscopy might fail to provide a diagnostic result for technical reasons which are unique to the technology, such as battery failure before transition through the small bowel (battery life being a source of competition across capsule endoscopy options), the visual field being obscured due to mucus or intestinal contents, and difficulty in swallowing the 11 mm by 26 mm capsule.

MSAC noted that approval for public funding of capsule endoscopy is being sought for those suspected of having small bowel Crohn disease who have had some previous testing which remains inconclusive. However, the evidence presented to MSAC for diagnostic accuracy is for the whole population with Crohn disease including all those patients who might have been suitable for other testing regimens. MSAC therefore accepted ESC's advice that the evidence of comparative test accuracy is not directly relevant to the proposed population for whom it is proposed, which is the group of patients who are hardest to diagnose and for whom the applicant is indicating capsule endoscopy would assist.

MSAC noted that the Assessment Report found that capsule endoscopy is not highly predictive of the absence of Crohn disease in the largest and most applicable study. Like most other available studies, this study assessed incremental diagnostic yield compared to not conducting capsule endoscopy, which does not distinguish between true positives and false positives. MSAC considered this limitation to be important because of concerns about the implications of false diagnoses. Patients who receive a false positive result may be managed inappropriately and potentially exposed to toxic treatments for Crohn disease that they do not need such as aminosalicylates, corticosteroids, thiopurines and anti-tumour necrosis factor (TNF) agents, some of which are costly and have a risk-benefit profile which means that they should only be used if absolutely indicated. Patients who receive a false negative result would not receive timely and appropriate treatment, and could potentially be subjected to further investigations which carry additional risks.

MSAC noted that, based on only two studies of poor to fair quality, capsule endoscopy is considered likely to have at least similar diagnostic accuracy as MR; but there were no included studies that provided evidence on the comparative diagnostic accuracy of capsule endoscopy and CT. MSAC noted that the reference standard for these studies was diagnosis after further follow-up, which did not necessarily include histology. MSAC considered that a biopsy which enables a histological diagnosis is the gold standard method by which to confirm a diagnosis of Crohn disease.

MSAC therefore accepted ESC's advice that the assessment report provided no basis to conclude that the diagnostic accuracy of capsule endoscopy was superior to the alternative investigations of CT or MRI in any population with suspected Crohn disease. At best, the evidence might support a conclusion of similar diagnostic accuracy across these three investigations if compared as alternatives.

In relation to the capsule endoscopy options available, MSAC noted that, although the application was received from a single proprietary manufacturer, its usual approach is to consider assessments across a 'generic' group of related products because an MBS item usually described a professional service, not a particular brand of technology. MSAC noted that there are other brands of capsule endoscopy technologies available from manufacturers in Japan, Korea and China that were not reported in this assessment. MSAC also noted the Applicant's comments in response to the ESC Report that its brand (PillCam[®]) is used for 95% of the total of capsule endoscopies performed in Australia. However, in the absence of any comparative evidence across the various forms of capsule endoscopy mentioned, MSAC could only assume that all brands available in the Australian market could all be regarded as meeting appropriate technical standards.

In relation to the proposed MBS item descriptor, MSAC expressed concern with the ambiguity of including the phrase “small bowel radiology” as well as colonoscopy and attempted ileoscopy as prerequisite tests which failed to confirm or exclude the diagnosis of small bowel Crohn disease in patients with symptoms and positive inflammatory markers. In particular, small bowel radiology options can be interpreted to involve MRI and/or CT as prerequisites, yet these were presented as alternatives to capsule endoscopy. If these investigations (i.e. CT and MRI small bowel imaging) are not intended to be considered in this way, this ambiguity in defining the prerequisite tests could be addressed by more precise terminology such as “small bowel contrast radiology including small bowel series or enteroclysis but not CT or MRI small bowel imaging”.

MSAC noted the Assessment Report (page ix) suggested that, as capsule endoscopy was being assessed for the diagnosis of small bowel Crohn disease, it should only be used once per patient per lifetime. However, some patients for whom this test is equivocal may undergo repeat testing, and there are sometimes cases of technical failures of the capsule endoscopy in which the patients may require a repeat procedure. The report therefore suggested that any MBS listing should either be restricted to once per year or there should be no restriction on frequency of use.

MSAC noted that the nature of Crohn disease would mean a patient would present with different symptoms over a year depending on whether the condition was flaring up or not, thereby making a diagnosis at one particular point in time from capsule endoscopy even more uncertain. However, neither the diagnostic studies nor the economic evaluation considered the consequences of multiple tests per patient, so there is no basis to consider the comparative effectiveness and cost-effectiveness of any use of capsule endoscopy beyond once per patient per lifetime.

MSAC discussed at length the identification and management of patients likely to be suitable for the proposed use of capsule endoscopy. Firstly, MSAC agreed that, in the absence of histopathology as a standard against which to assess patients with Crohn disease, any ‘positive’ capsule endoscopy finding is not really a confirmed diagnosis, but rather another indication in relation to the likelihood of the disease for the clinician to consider in determining treatment options. MSAC also agreed that, if capsule endoscopy were not definitive in its diagnosis of small bowel Crohn disease, patients may still need to be considered for histological examination such as could be obtained with double balloon enteroscopy (DBE) before being put on long-term drugs which are both toxic and potentially expensive. However, MSAC agreed that, from a consumer’s perspective, capsule endoscopy would be preferable to DBE on the grounds of comfort and risk.

Secondly, MSAC agreed that the number of patients who would be eligible for the proposed indication for capsule endoscopy would be very small. In most patients with isolated small bowel Crohn disease, the disease affects that part of the small bowel which can usually be visualised with ileoscopy at the time of colonoscopy. Most attempted ileoscopies undertaken as part of a colonoscopy procedure are successful (80% with skilled endoscopists). In addition, one of the presenting symptoms in this patient group may be anaemia or obscure gastrointestinal bleeding (OGIB), which would mean that such patients are eligible for capsule endoscopy under the existing MBS item 11820. Moreover, there is a risk of leakage of capsule endoscopy to other gastrointestinal conditions such as irritable bowel syndrome, which is more prevalent and also presents as ‘abdominal pain’ in the same demographic group (predominantly young women) and so capsule endoscopy might be considered to provide reassurance that the patient did not have an underlying inflammatory bowel disease. The proposal to include inflammatory markers as a prerequisite to capsule endoscopy was acknowledged as having an important role in mitigating this risk to some extent.

MSAC concluded that, in this overall context, a clear clinical need remains for confirmatory diagnosis in a residual small number (estimated at 5%) of patients for whom a clinical suspicion of small bowel Crohn disease cannot be excluded. However, even with reference to recent British clinical practice guidelines, MSAC could not specify eligibility criteria that would unambiguously identify patients with “suspected small bowel Crohn disease” suitable for the intention of the proposed MBS listing. In particular, MSAC was unable to identify evidence that would specify the discrete subset/s of patients who should be excluded as ineligible because they have other conditions and therefore are at risk of being tested inappropriately and possibly treated inappropriately if incorrectly diagnosed.

Finally, MSAC agreed that any MBS listing of capsule endoscopy in small bowel Crohn disease should not permit monitoring or surveillance of diagnosed patients.

MSAC noted the average cost to society of capsule endoscopy was estimated as \$1,924 per test when the costs of capsule retention were not taken into account, increasing to \$2,085 per test when a 15% capsule retention rate was assumed. However, MSAC also noted that the costs of surgery to remove the retained capsule were not attributed to capsule endoscopy. The average cost of computed tomography/computed tomography enterography was \$434. MRI/MRE is currently not funded through the MBS as a diagnostic test for small bowel Crohn disease. MSAC also found that even if the capsule retention rate were zero, capsule endoscopy would still be more expensive than the comparator, so this issue was not an important factor in the overall economic evaluation. MSAC concluded from the economic evaluation that there is no basis to estimate the extent of improvements in health outcomes from the proposed use of capsule endoscopy which could be used to justify the estimated increase in costs associated with its use.

MSAC accepted ESC’s advice that the direct treatment cost of the capsule included in the breakdown of costs from Appendix G (p133) of the 2003 report of capsule endoscopy was approximately 52% of the total schedule fee and questioned whether this remained an accurate reflection of cost as there is now more than one manufacturer of capsule endoscopy products in the Australian marketplace and lower prices are being advertised in overseas markets. At the time of the 2003 report, the proposed schedule fee was \$1706.56 (which has been subsequently indexed), \$895.00 of which was attributable to direct treatment costs associated with the disposable capsule, \$292.16 attributable to estimated capital cost per examination and the remaining \$519.39 attributable to the professional fee. MSAC also suggested that economies of scale should be brought to bear in finalising any fee for this proposed new use of capsule endoscopy, including the capital costs of associated reusable equipment (the sensor belt, computer station and software updates) and training costs to view and interpret the recordings.

MSAC noted that the inclusion of the cost of the capsule on the MBS would be an exception to the general rule, as MBS fees are intended to only cover the cost of the professional service. The absence of any mechanism to adjust the capsule component of the fee may produce a windfall gain to the service provider should the actual cost of the capsule decrease over time while the MBS fee (including a component for the capsule endoscope) increases annually through indexation.

MSAC also noted that the device does not meet the inclusion criteria for listing on the Prosthesis List as it does not remain within the body, and so the clinician usually purchases the capsule and incorporates the cost into their fees. MSAC noted the applicant’s comments that the cost of its capsule has not increased since the introduction of funding for OGIB in 2004 (MBS Item 11820) but also noted that, conversely, nor has the applicant advised that the cost has come down in the Australian market during that time.

MSAC noted that the systematic review identified three economic studies that explored the costs or cost-effectiveness of imaging strategies, including capsule endoscopy, for diagnosing Crohn disease. However, these could not be used as evidence of cost-effectiveness for the use of capsule endoscopy in Australia since they did not reflect the patient population or clinical

pathway under consideration in this assessment. In addition, none of the studies was conducted in Australia and substantial differences between health systems limit the transferability of economic studies.

MSAC noted with caution the assumptions in the Assessment Report that with an estimated range of 664 to 1,431 capsule endoscopies per year, the incremental cost to the MBS is estimated to be between \$983,982 and \$2,120,599 per year when capsule endoscopy replaces repeat CT/CTE. MSAC further noted that the implementation of public funding for capsule endoscopy may lead to a change in utilisation rate which will result in a modest increase in use; however, it could also lead to a modest decline in claims for MBS Item 11820, capsule endoscopy for OGIB.

14. Other significant factors

MSAC noted ESC's advice that, at present, much of the proposed use of capsule endoscopy could already be captured by the use of the MBS Item 11820 used for obscure gastrointestinal bleeding (OGIB) and noted this would be an issue for the Department to investigate as part of its usual MBS review procedures.

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

MSAC concluded that capsule endoscopy had *prima facie* clinical utility, but there were substantial deficiencies with the evidence base around comparative safety, accuracy and clinical effectiveness data for capsule endoscopy relative to alternative ways of investigating patients with suspected small bowel Crohn disease. MSAC also observed that it had to assume that the four existing capsule endoscopic technologies are the same, even though it had no evidence to support this assumption.

MSAC considered that the more relevant comparator to capsule endoscopy is computed tomography (CT) of the abdomen (with or without enterography) because it is funded by the MBS for this indication, a purpose newly proposed for capsule endoscopy. Magnetic Resonance Imaging (MRI) of the abdomen (with or without enterography) is not funded by the MBS for this purpose.

MSAC noted the importance of a confirmed diagnosis to avoid wrongly adopting empirical treatment, and noted that other diagnostic options were available, albeit not sufficiently used in current practice to change the overall conclusions of the committee. One of these is double balloon endoscopy (DBE), which has the disadvantages of requiring an inpatient procedure and is a more invasive procedure but the advantage of allowing biopsy which enables histology to support a more conclusive diagnosis. The other is "push endoscopy". Rather than being direct comparators to capsule endoscopy, MSAC considered that these might better be considered as potential downstream investigations before empirical treatment.

MSAC accepted that a very small proportion (5%) of patients with suspected small bowel Crohn disease, after having a range of other procedures, may potentially be diagnosed as having small bowel Crohn disease after capsule endoscopy, and that capsule endoscopy usually is complementary to the use of other tests. MSAC found that currently available evidence does not resolve the place in the management algorithm of the use of empirical treatment, other forms of imaging, and the role of DBE and push endoscopy. MSAC also found considerable uncertainty in relation to the comparative diagnostic accuracy and the comparative effectiveness of capsule endoscopy as measured in health outcomes terms, and in terms of the costs of the use of other diagnostic resources. This included the issues related to the consequences of false positives where patients could potentially receive unnecessary treatment and false negatives, where patients could potentially miss out on treatment that is needed and potentially be subjected to further radiographic investigations which have their own risks.

MSAC also found uncertainty in terms of the evidence for the risk of retention of capsules their retrieval and whether using use of a dissolving capsule and pre testing those patients with possible strictures would lessen concerns about harm without disproportionately increasing costs.

MSAC concluded that capsule endoscopy appears safe, has a low risk of adverse events such as nausea, vomiting and pain, similar to that observed for other indications, but may lead to capsule retention in up to 15% of cases. MSAC also noted that use of a dissolvable patency capsule with associated pre testing is not recommended for routine evaluation of patients prior to capsule endoscopy, but is only proposed for patients identified as high risk such as when there is evidence of a stricture either clinically or radiographically prior to capsule endoscopy.

MSAC determined that the strength of the evidence in relation to claimed improvements in health outcomes for the proposed eligible patients examined using capsule endoscopy was insufficient to support its public funding at a cost of approximately \$2,000 per patient and total cost to the MBS of over \$2 million annually. These uncertainties are exacerbated by a lack of evidence that would allow the reimbursement of the procedure to be confined to the expected very small group of intended patients without risk of leakage to another subset of patients such as young women with abdominal pain who may access the test for reassurance. MSAC agreed that capsule endoscopy should not be used for monitoring and surveillance purposes for patients previously diagnosed with Crohn disease.

MSAC acknowledged that there is a very small group of patients with a clinical need and that patients would prefer a less invasive diagnostic method, but nevertheless could not support the application primarily on the basis of insufficient evidence of acceptable cost-effectiveness. MSAC also identified that robust evidence was needed to identify suitable small bowel Crohn disease patients not already eligible for capsule endoscopy under existing MBS items; clarity on the optimal place of capsule endoscopy in the clinical pathway in relation to the identified alternative diagnostic options (including those which are not currently funded on the MBS); better information on the comparative safety, diagnostic performance, clinical utility and cost-effectiveness in relation to otherwise continuing on to empirical treatment or using the identified alternative diagnostic techniques; estimates of how many and what types of patients this more robust identification of suitable patients would involve; and to know whether it is possible to reduce the costs of some of the components in the proposed MBS fee. Noting that the Assessment Report had been prepared with the input of an Advisory Panel, MSAC considered but rejected the possibility of deferring its conclusion and reconvening the Advisory Panel in order to address these needs in conjunction with the Assessment Group.

16. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to the safety, effectiveness and cost-effectiveness of capsule endoscopy to evaluate suspected small bowel Crohn disease in patients who have had some previous testing which remains inconclusive, MSAC does not support its public funding.

17. Context for decision

This advice was made under the MSAC Terms of Reference.

MSAC is to:

- Advise the Minister for Health and Ageing on medical services that involve new or emerging technologies and procedures and, where relevant, amendment to existing MBS items, in relation to:
 - the strength of evidence in relation to the comparative safety, effectiveness, cost-effectiveness and total cost of the medical service;
 - whether public funding should be supported for the medical service and, if so, the circumstances under which public funding should be supported;

- the proposed Medicare Benefits Schedule (MBS) item descriptor and fee for the where funding through the MBS is supported;
- the circumstances, where there is uncertainty in relation to the clinical or cost-effectiveness of a service, under which interim public funding of a service should be supported for a specified period, during which defined data collections under agreed clinical protocols would be collected to inform a re-assessment of the service by MSAC at the conclusion of that period;
- other matters related to the public funding of health services referred by the Minister.
- Advise the Australian Health Ministers' Advisory Council (AHMAC) on health technology assessments referred under AHMAC arrangements.

MSAC may also establish sub-committees to assist MSAC to effectively undertake its role. MSAC may delegate some of its functions to its Executive sub-committee.

18. Linkages to other documents

MSAC's processes are detailed on the MSAC Website at: www.msac.gov.au.

The MSAC Assessment Report is available at
<http://www.msac.gov.au/internet/msac/publishing.nsf/Content/app1146-1>.