



Australian Government

Department of Health

Application 1460:

Blue-Light Cystoscopy with Hexaminolevulinate as an adjunct to Standard White Light Cystoscopy, for the Diagnosis, Treatment and Management of Non-Muscle Invasive Bladder Cancer (NMIBC)

PICO Confirmation

Summary of PICO/PPICO criteria to define the question(s) to be addressed in an Assessment Report to the Medical Services Advisory Committee (MSAC)

Patients with confirmed or suspected bladder cancer

Component	Description
Patients	Patients with confirmed or suspected bladder cancer undergoing rigid cystoscopy.
Prior tests (for investigative medical services only)	Urine cytology (proportion of patients) Imaging (proportion of patients) Flexible cystoscopy (proportion of patients)
Intervention	Blue-light cystoscopy/Photodynamic diagnosis (PDD) with hexaminolevulinate, as an adjunct to white-light cystoscopy
Comparator	Standard white light rigid cystoscopy alone
Outcomes	<p><u>Efficacy/effectiveness</u></p> <ul style="list-style-type: none"> • Sensitivity/Specificity/positive predictive value/negative predictive value/ROC area under the curve (AUC) • Recurrence rates • Time to recurrence • Changes to management (e.g. surgeries avoided, post-operative treatment regimens) • Degree of resection (e.g. amount of residual tumour not resected) • Disease progression • Health-related quality of life • Risk stratification • Progression-free survival • Overall survival <p><u>Safety</u></p> <ul style="list-style-type: none"> • Frequency of adverse reactions (classified by System Organ Class) • Patient reported adverse reactions <p><u>Cost-effectiveness</u></p> <ul style="list-style-type: none"> • Cost per life year gained • Cost per QALY gained <p><u>Healthcare resources</u></p> <ul style="list-style-type: none"> • Cost of hexaminolevulinate • Cost of cystoscopy • Cost to adapt specialised equipment (if required) • Costs associated with clinical management changes e.g. changes in post-operative management, surgeries avoided, changes in need for tests used after cystoscopy for cancer staging (e.g. CT or MRI). <p><u>Total Australian Government Healthcare costs</u></p>

Component	Description
	<ul style="list-style-type: none"> • Total Cost to the Medical Benefits Schedule (MBS) • Total Cost to the Pharmaceutical Benefits Scheme (PBS) • Total Cost to other healthcare services

Patients with prior resected non-muscle invasive bladder cancer

Component	Description
Patients	Patients with prior resected non-muscle invasive bladder cancer, who are undergoing post-operative follow-up or surveillance for disease recurrence with rigid cystoscopy.
Prior tests (for investigative medical services only)	Urine cytology (proportion of patients) Imaging (proportion of patients) Flexible cystoscopy (proportion of patients) Rigid cystoscopy with resection
Intervention	Blue-light cystoscopy/Photodynamic diagnosis (PDD) with hexaminolevulinate, as an adjunct to white-light cystoscopy
Comparator	Standard white light rigid cystoscopy
Outcomes	<p><u>Efficacy/effectiveness</u></p> <ul style="list-style-type: none"> • Sensitivity/specificity/positive predictive value/negative predictive value/ROC area under the curve (AUC) • Recurrence rates • Time to recurrence • Changes to management (e.g. surgeries avoided, post-operative treatment regimens) • Degree of resection (e.g. amount of residual tumour not resected) • Disease progression • Health-related quality of life • Risk stratification • Progression-free survival • Overall survival <p><u>Safety</u></p> <ul style="list-style-type: none"> • Frequency of adverse reactions (classified by System Organ Class) • Patient reported adverse reactions <p><u>Cost-effectiveness</u></p> <ul style="list-style-type: none"> • Cost per life year gained • Cost per QALY gained <p><u>Healthcare resources</u></p> <ul style="list-style-type: none"> • Cost of hexaminolevulinate • Cost of cystoscopy • Cost to adapt specialised equipment (if required)

Component	Description
	<ul style="list-style-type: none"> • Costs associated with clinical management changes e.g. changes in post-operative management, surgeries avoided, changes in need for tests used after cystoscopy for cancer staging (e.g. CT or MRI). <p><u>Total Australian Government Healthcare costs</u></p> <ul style="list-style-type: none"> • Total Cost to the Medical Benefits Schedule (MBS) • Total Cost to the Pharmaceutical Benefits Scheme (PBS) • Total Cost to other healthcare services

Population

The intervention is proposed in Australia for the use in patients undergoing rigid cystoscopy (in an operating theatre under general anaesthetic) for the purposes of diagnosis and management of bladder cancer.

Bladder cancer is a relatively common disease with high morbidity if left untreated. Bladder cancer occurs most commonly in patients over 50 years of age and is more common in men. Smoking is the most important risk factor for bladder cancer. Other risk factors include having a family history of or gene mutations linked to bladder cancer; occupational exposure to certain chemicals used in processing paint, dye, metal and petroleum products; certain chemotherapy drugs, drinking contaminated well water; and chronic urinary tract infections.

Urothelial tumours are staged according to the 2002 TNM Classification system. Tumours staged as Ta, T1 or carcinoma in situ (CIS) are collectively grouped as non-muscle invasive bladder cancer (NMIBC) but are heterogeneous with very different prognoses. Accordingly, patients are continuously stratified into low, intermediate, and high risk groups in order to determine management strategies which differ significantly between the two categories of tumour and risk typologies.

In patients with bladder cancer, about 70% present initially as non-muscle-invasive bladder tumours and the remainder as muscle-invasive tumours.

The incidence and mortality rates of bladder cancer in Australia closely parallel those of other developed countries. Bladder cancer is the 13th most common cancer leading to death in Australia.

Bladder cancer is the most common malignancy of the urinary tract. In 2011, there were 1,806 new cases of bladder cancer in men and 598 in women in Australia. The age standardised rates (ASR) were 16.2 per 100,000 persons in men and 4.3 per 100,000 persons in women. The incidence of bladder cancer is increasing and these rates are expected to rise annually, with an estimated 2,170 new cases in men, and 705 new cases in women in 2014 (CancerAustralia, 2011)

Two patient populations are considered:

1. Patients with suspected bladder cancer undergoing rigid cystoscopy.

These patients are those where previous testing (cytology and, in some patients, imaging and/or flexible cystoscopy) has indicated or there is a clinical suspicion of bladder cancer. They are undergoing rigid cystoscopy where they will either have a biopsy or a resection.

2. Patients with prior resected non-muscle invasive bladder cancer, who are undergoing post-operative follow-up or surveillance for disease recurrence with rigid cystoscopy.

These patients have had prior confirmed and resected non-muscle invasive bladder cancer. They are undergoing post-operative follow-up or surveillance for disease recurrence with rigid cystoscopy.

Rationale

Currently in the Australian healthcare system, rigid cystoscopy is conducted using standard white-light for diagnosis of bladder cancer, resection of bladder cancer, post-operative follow-up after bladder cancer resection, and surveillance for recurrence of bladder cancer. As the intervention proposed is a replacement, the population presenting for this procedure will be the same as it is currently in the Australian health care system.

Bladder cancer commonly presents with intermittent or persistent microscopic or macroscopic haematuria. Other symptoms can include frequency of urination, urgency and dysuria. Typically, patients first present to their General Practitioner who would refer them to a specialist urologist for further investigation.

Prior tests

There is no standard or routine screening test for bladder cancer. Cystoscopy, imaging studies and urine cytology are used to investigate suspected bladder cancer.

After referral to a specialist urologist the patient will first have urine cytology. A positive or atypical cytology may indicate the presence of urothelial carcinoma and will be further investigated. Patients who are deemed high risk but with negative cytology also require further evaluation, such as imaging, as a negative result does not preclude bladder cancer.

Imaging is used to examine the renal parenchyma and upper tract urothelium. Three phase computerised tomography (CT) urography is typically first-line as the delayed contrast phase outlines the renal collecting system, ureters and bladder. Lymphadenopathy and tumour size can also be determined. Magnetic resonance imaging (MRI) is second-line, and is usually reserved for patients with contrast allergy, when detailed examination of the pelvic soft tissues is required, or in pregnancy. Renal impairment limits the use of contrast in both modalities. Ultrasonography is sometimes used in low risk patients but provides little detail about the urothelium.

Asymptomatic patients with large muscle-invasive tumours or patients with bone pain or bony lesions on CT scan may undergo a nuclear whole body bone scan to assess the skeleton for bony metastases. Positron emission tomography is a second-line investigation which may be used to characterise lesions found on CT or bone scan

Flexible cystoscopy: Patients with negative cytology and imaging may undergo further investigation with white light cystoscopy using a flexible or rigid cystoscope. Where abnormal findings are detected under flexible cystoscopy, patients will then need to proceed to a second cystoscopy with a rigid cystoscope under general anaesthetic where a biopsy or transurethral resection will be performed, if necessary.

For most other patients presenting with macroscopic haematuria, painful urination or urgency, imaging studies are undertaken.

Patients with radiological evidence of a bladder lesion or positive cytology proceed to rigid cystoscopy under general anaesthesia for a transurethral resection (TUR) in papillary tumours, or

multiple bladder biopsies in CIS. A prior flexible cystoscopy in these patients is unnecessary and inappropriate.

Intervention

The intervention is blue-light cystoscopy with hexaminolevulinate (Hexvix®) as an adjunct to white light visualisation for the diagnosis, treatment and management of bladder cancer. Hexvix® is an optical imaging agent for use in blue light cystoscopy.

Each vial of powder contains 85 mg hexaminolevulinate (as hexaminolevulinate hydrochloride). After reconstitution in 50 ml of solvent, 1 ml of the solution contains 1.7 mg hexaminolevulinate which corresponds to an 8 mmol/l solution of hexaminolevulinate.

50 ml of 8 mmol/l reconstituted solution is instilled into the bladder through a catheter. The patient should retain the fluid for approximately 60 minutes.

Following evacuation of the bladder, the cystoscopic examination in blue light should start within approximately 60 minutes. The cystoscopic examination should not be performed more than 3 hours after Hexvix is instilled in the bladder. If the retention time in the bladder is considerably shorter than one hour, examination should start no earlier than after 60 minutes.

The entire bladder should be examined and mapped under both white first and then blue light before any surgical measures are initiated. The mapping with blue light is similar to a standard white light cystoscopy.

Diagnosis and treatment

Detection and biopsies of all mapped lesions should normally be taken under white light and then under blue light.

Investigations are undertaken to facilitate histological classification based on the architecture and degree of differentiation of the tumour. Low and high grade papillary urothelial carcinoma (UC) and carcinoma in situ (CIS) are considered true malignancies. Of urothelial bladder tumours, 90% to 95% are urothelial carcinoma, usually papillary and multifocal, while squamous cell carcinoma accounts for 5% and adenocarcinoma accounts for 2%.

The reference standard is the histopathological examination of biopsied tissue.

Post-operative follow-up/Surveillance/Management

Post procedural management requires surveillance for recurrence, at scheduled intervals determined according to stage and risk profiling resulting from biopsy or resection. For patients where the cystoscopy was performed under both blue light and white light, it is envisaged that follow-up cystoscopies will also utilise blue light and white light visualisation. The expected management post-operatively is outlined below.

After macroscopic tumour removal, patients with high grade non-muscle-invasive bladder cancer and CIS undergo intravesical immunotherapy with Bacillus Calmette-Guerin (BCG), to further prevent or delay recurrences. Weekly instillations are given for 6 weeks once the bladder has healed. All

patients will be given a single immediate instillation of postoperative intravesical chemotherapy following TUR.

Cystoscopy is repeated 6 weeks after the final instillation.

Adjuvant BCG treatment is not recommended for low grade non-muscle-invasive bladder cancer as these tumours respond poorly. Aside from immediate postoperative instillations of chemotherapy, patients with recurrent low grade tumours can be treated with a course of intravesical mitomycin C.

Patients with non-muscle-invasive bladder cancer require follow up with repeat imaging and cystoscopy. Frequency depends on the predicted recurrence and progression rates for the particular tumour.

- Low risk: Patients deemed to be low risk will have a repeat rigid cystoscopy at 3 months. If this is negative then patients should be followed up with cystoscopy at 9 months. If this is negative then patients should continue annual cystoscopy for 5 years.
- High risk: Patients deemed to be high risk will have a repeat rigid cystoscopy and cytology at 3 months. If both cystoscopy and cytology is negative then patients should be followed up with every 3 months for 2 years, then every 4 months for the 3rd year, then every 4 months for 4th and 5th years and an annual cystoscopy thereafter.
- Intermediate risk: Patients deemed to be intermediate risk go through a combination of the surveillance strategies for low and high risk bladder cancer tailored to individual needs.

Rationale

This proposed service includes a registered trademark compound (Hexvix®) with characteristics that distinguish it from any other health technologies.

Blue light cystoscopy with hexaminolevulinate (Hexvix®) as an adjunct to white light is not currently funded for any service for any indication.

Once in contact with the bladder mucosa Hexvix® penetrates rapidly proliferating cells, selectively leading to the accumulation of fluorescent compounds within the tumour. An hour after instillation a sufficient number of these compounds have accumulated making the bladder cancer glow red under blue light illumination, clearly differentiating cancer cells from healthy cells in a manner proposed as superior to white light imaging alone.

It is anticipated that blue light cystoscopy with hexaminolevulinate (Hexvix®) as an adjunct to white light is unlikely to completely replace all current rigid cystoscopies. However, it's proposed that the improved detection and resection of bladder cancer will mean some patients experience more intensive treatment and surveillance than if they had undergone cystoscopic diagnosis and treatment with white light alone.

Comparator

The comparator is standard white light rigid cystoscopy, which is currently used in the Australian health care system.

Rationale

The clinical claim is that blue-light cystoscopy as an adjunct to white-light cystoscopy is superior to white-light cystoscopy for clinical effectiveness and non-inferior in terms of safety.

Outcomes

Patient relevant

It is proposed that the intervention will lead to a more complete detection and resection of bladder lesions. This then allows for better risk stratification and thus a more appropriate, effective and individualized assignment of post-operative treatment regimen. This may result in reduced recurrence, less time to recurrence, reduced progression and reduced progression to muscle invasive disease.

Other outcomes that may be relevant to patients are:

- Health-related quality of life
- Freedom from symptoms of disease
- Surgeries avoided due to improved resection of bladder cancer.

The safety claim is that blue-light cystoscopy as an adjunct to white-light cystoscopy is non-inferior to white-light cystoscopy for safety

Healthcare system

In terms of the services, the elements of the post procedural clinical pathway remain the same for the health system overall. However more accurate diagnosis, treatment and management plans may result in patients entering the clinical management pathway at more appropriate times (e.g. earlier if initial diagnosis is accurately picked up early) and being managed more appropriately (e.g. different treatment regimens based more upon accurate risk stratification). This may result in savings to the health system as fewer procedures are needed due to better detection rates and more complete resection of bladder cancers coupled with more accurate risk stratification, lower progression rates, longer time to progression and lower rates of recurrence.

Some of the cystoscopic equipment that is currently used in Australian hospitals may require an upgrade to allow the additional use of blue light as well as white light imaging.

Blue light cystoscopy with hexaminolevulinat (Hexvix®) must be performed by healthcare professionals trained in cystoscopy (e.g. urologist) and also with experience in blue light imaging as an adjunct to white light imaging. As for most surgical techniques, peer-to-peer interaction and on-site training is the generally accepted method to master new techniques or changes to existing established procedures. Many urologists with overseas experience will have experience using blue

light imaging as an adjunct to white light when conducting cystoscopy. The equipment manufacturers and Hexvix® sponsor also offer training options.

Rationale

The evidence provided in the application report the following results.

Detection

- The results of the Ta/T1 detection primary endpoint analyses demonstrate that blue light cystoscopy with hexaminolevulinate (Hexvix®) was able to detect more Ta or T1 tumours than white light cystoscopy alone. (Hermann, Mogensen, Carlsson, Marcussen, & Duun, 2011) (Fradet et al., 2007; Jocham et al., 2005; Schmidbauer et al., 2004)
- The detection of patients with CIS was improved when blue light cystoscopy with hexaminolevulinate (Hexvix®) was used. Across the five phase 3 studies, more of the patients would not have had their CIS detected if blue light cystoscopy with hexaminolevulinate (Hexvix®) had not been used (Hermann, Mogensen, Carlsson, Marcussen, & Duun, 2011) (Fradet et al., 2007; Jocham et al., 2005; Schmidbauer et al., 2004)

Recurrence

- The proportion of patients with tumour recurrence was lower in the blue light cystoscopy with hexaminolevulinate (Hexvix®) group compared with the white light cystoscopy group for both ITT and PP population analyses (Stenzl et al., 2010).
- Long-term follow up of recurrence of up to six years after blue light cystoscopy with hexaminolevulinate (Hexvix®) documents a median time to recurrence significantly longer in patients in the blue light cystoscopy with hexaminolevulinate (Hexvix®) group compared with the white light group (Grossman et al., 2012).

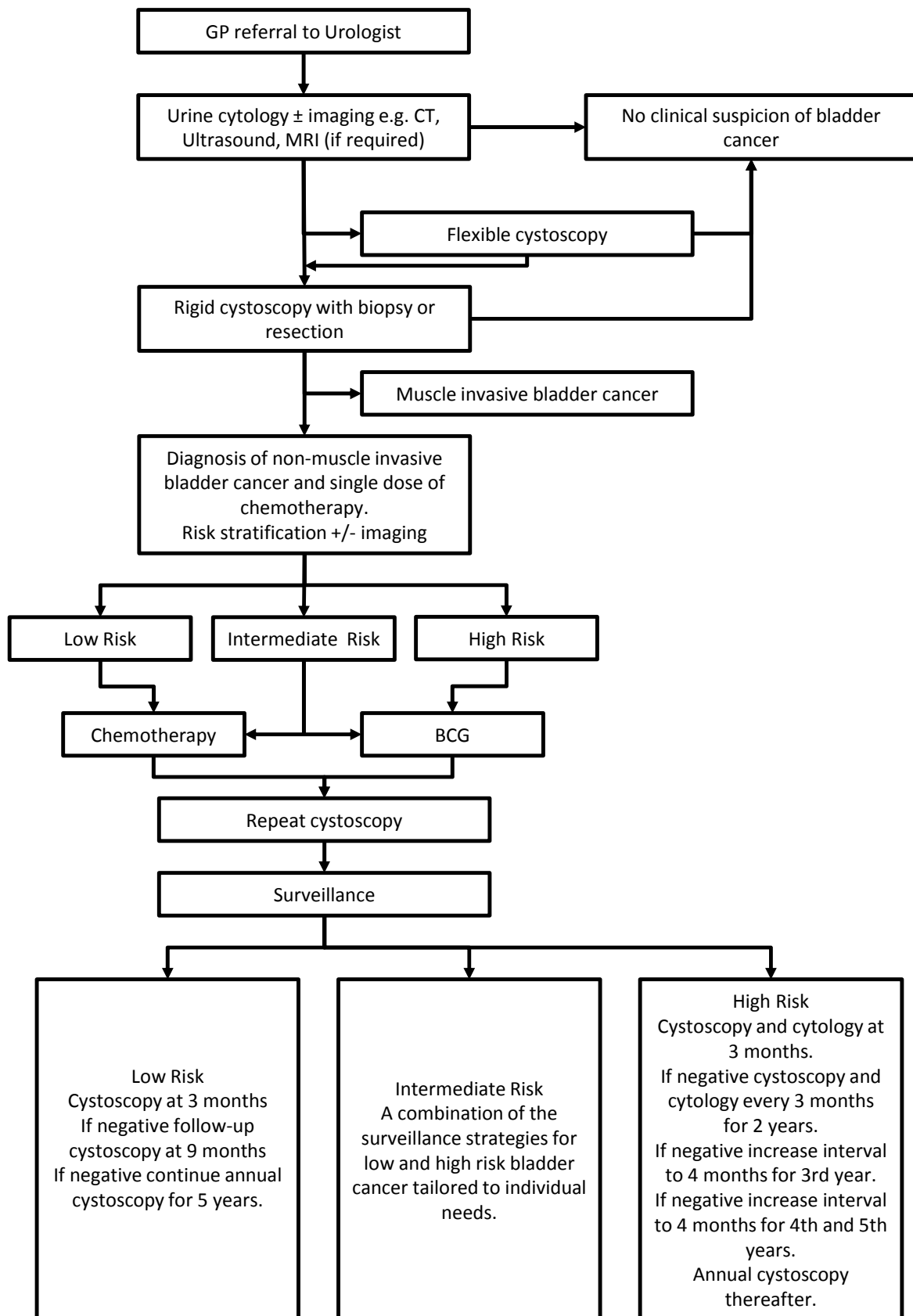
Sensitivity and Specificity

- In general, false-positive detection rates for blue light cystoscopy with hexaminolevulinate (Hexvix®) and white light cystoscopy were comparable within the individual studies, with rates for blue light cystoscopy with hexaminolevulinate (Hexvix®) only slightly higher than the rates for white light cystoscopy (Hermann, Mogensen, Carlsson, Marcussen, & Duun, 2011) (Fradet et al., 2007; Jocham et al., 2005; Schmidbauer et al., 2004).

Current clinical management algorithm for identified population

As the intervention is proposed as a replacement the clinical management algorithm is the same for both current management and proposed management.

Proposed clinical management algorithm for identified population



Proposed economic evaluation

The clinical claim is that blue-light cystoscopy as an adjunct to white-light cystoscopy is non-inferior in safety and superior in clinical effectiveness to standard white-light cystoscopy. According to the *Technical Guidelines for preparing assessment reports for the Medical Services Advisory Committee: Investigative* the required economic analysis is therefore a cost-utility or a cost-effectiveness analysis.

Proposed item descriptor

Category: 36836 – Investigative cystoscopic item for conduct of biopsy

CYSTOSCOPY, with biopsy of bladder, not being a service associated with a service to which item 36812, 36830, 36840, 36845, 36848, 36854, 37203, 37206 or 37215 applies (anaesthesia).

Fee: \$229.85 Benefit: 75% = \$172.40 85% = \$195.40

Category: 36840 – Therapeutic cystoscopic item with concurrent resection of tumour

CYSTOSCOPY, with resection, diathermy or visual laser destruction of bladder tumour or other lesion of the bladder, not being a service to which item 36845 applies (anaesthesia).

Fee: \$323.20 Benefit: 75% = \$242.40 85% = \$274.75

Category: 36845 – Therapeutic cystoscopic item with concurrent resection of tumour

CYSTOSCOPY, with diathermy, resection or visual laser destruction of multiple tumours in more than 2 quadrants of the bladder or solitary tumour greater than 2cm in diameter (anaesthesia).

Fee: \$691.40 Benefit: 75% = \$518.55 85% = \$611.90

Category: 36812 – Investigative cystoscopic item for routine scheduled (follow-up) management

CYSTOSCOPY with urethroscopy with or without urethral dilatation, not being a service associated with any other urological endoscopic procedure on the lower urinary tract except a service to which item 37327 applies (anaesthesia).

Fee: \$166.70 Benefit: 75% = \$125.05 85% = \$141.70

References

- CancerAustralia. (2011). Bladder cancer (C67). *Incidence and mortality of bladder cancer*.
- Fradet, Y., Grossman, H. B., Gomella, L., Lerner, S., Cookson, M., Albala, D., & Droller, M. J. (2007). A comparison of hexaminolevulinate fluorescence cystoscopy and white light cystoscopy for the detection of carcinoma in situ in patients with bladder cancer: a phase III, multicenter study. *J Urol*, *178*(1), 68-73; discussion 73. doi:10.1016/j.juro.2007.03.028
- Grossman, H. B., Stenzl, A., Fradet, Y., Mynderse, L. A., Kriegmair, M., Witjes, J. A., . . . Burger, M. (2012). Long-term decrease in bladder cancer recurrence with hexaminolevulinate enabled fluorescence cystoscopy. *J Urol*, *188*(1), 58-62. doi:10.1016/j.juro.2012.03.007
- Hermann, G. G., Mogensen, K., Carlsson, S., Marcussen, N., & Duun, S. (2011). Fluorescence-guided transurethral resection of bladder tumours reduces bladder tumour recurrence due to less residual tumour tissue in Ta/T1 patients: a randomized two-centre study. *BJU Int*, *108*(8 Pt 2), E297-303. doi:10.1111/j.1464-410X.2011.10090.x
- Jocham, D., Witjes, F., Wagner, S., Zeylemaker, B., van Moorselaar, J., Grimm, M. O., . . . Kurth, K. H. (2005). Improved detection and treatment of bladder cancer using hexaminolevulinate imaging: a prospective, phase III multicenter study. *J Urol*, *174*(3), 862-866; discussion 866. doi:10.1097/01.ju.0000169257.19841.2a
- Schmidbauer, J., Witjes, F., Schmeller, N., Donat, R., Susani, M., & Marberger, M. (2004). Improved detection of urothelial carcinoma in situ with hexaminolevulinate fluorescence cystoscopy. *J Urol*, *171*(1), 135-138. doi:10.1097/01.ju.0000100480.70769.0e
- Stenzl, A., Burger, M., Fradet, Y., Mynderse, L. A., Soloway, M. S., Witjes, J. A., . . . Grossman, H. B. (2010). Hexaminolevulinate-guided fluorescence cystoscopy reduces recurrence in patients with non-muscle invasive bladder cancer. *J Urol*, *184*(5), 1907-1913. doi:10.1016/j.juro.2010.06.148