



Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 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)

Applicant: Juno Pharmaceuticals

Date of MSAC consideration: MSAC 72nd Meeting, 28-29 March 2018

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, [visit the MSAC website](#)

1. Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing of blue-light rigid cystoscopy (BLC) with hexaminolevulinate (HAL) as an adjunct to white light rigid cystoscopy (WLC) for the diagnosis, treatment and management of non-muscle invasive bladder cancer (NMIBC) was received from Juno Pharmaceuticals by the Department of Health.

BLC with HAL has been developed to better visualise tumours for diagnosis and biopsy. This is intended to enable more complete detection and resection of bladder lesions, to allow better risk stratification and improved detection of recurrence during follow-up.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC supported MBS funding of BLC with HAL as an adjunct to standard WLC, for the diagnosis, treatment and management of NMIBC. MSAC advised there was weak but acceptable evidence of safety, clinical effectiveness and cost-effectiveness with low financial impact.

MSAC advised that the MBS fee should be reflective of the existing WLC service cost with an additional input cost of \$65 for the instillation of HAL. MSAC advised it was not reasonable to include an additional input cost for catheterisation or the cost of the consumable HAL.

MSAC agreed with the advice from the Department that the cost of the HAL component of this service should be met under the National Procedure Banding arrangements.

MSAC advised that this MBS item should be reviewed 12 months post-implementation and requested that the Department write to the Urological Society of Australia and New Zealand (USANZ) for advice on the likely uptake of the service when listed.

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

MSAC noted that the application sought a listing on the MBS for BLC with HAL as an adjunct to rigid WLC for the diagnosis, treatment and management of NMIBC. Cystoscopy is used to visualise the inside of the bladder and urethra to look for abnormalities or to find causes of blockage or bleeding. The standard procedure uses white light; BLC uses an optical imaging agent (HAL) which gets absorbed by cancer cells and causes them to glow pink under blue light, highlighting tumours that may not have been visible using white light alone.

MSAC noted that the five-year recurrence rate for bladder cancer is high (between 31% for low risk and 78% in high risk cases), and noted that incomplete transurethral resection of bladder tumours (TURBT) is a likely contributor to this, with additional tumours found at first post-TUR surveillance in up to 45% of patients.

MSAC noted the two proposed populations considered in the application:

- patients with suspected (new or recurrent) bladder cancer undergoing rigid cystoscopy with or without biopsy and/or resection for the purposes of diagnosis and treatment (population 1); and
- asymptomatic patients with previously diagnosed NMIBC, who are undergoing subsequent follow-up or surveillance with rigid cystoscopy for disease recurrence (population 2).

MSAC noted that the comparator for BLC with HAL is WLC.

MSAC noted that the evidence presented showed that BLC with HAL + WLC has non-inferior safety versus WLC alone (unless HAL is contraindicated). In the largest study in which comparative safety was assessed (Stenzl et al., 2010: n = 726) the proportion of patients experiencing adverse events was similar for both groups (55.3% BLC with HAL + WLC versus 53.5% WLC only, not significant).

MSAC noted that the evidence base of eight randomised controlled trials (n = 1487) applied to population 1 only and that no studies addressed population 2 (surveillance of asymptomatic patients). MSAC noted that there were significant limitations in the evidence with all included studies at high or unclear risk of bias, high levels of heterogeneity and varying ranges of follow-up (six weeks to 4.5 years).

MSAC noted that six studies provided evidence of reasonable diagnostic performance, all of which had high or unclear risk of bias. Evidence showed:

- BLC with HAL was found to have higher sensitivity than WLC alone in six studies and lower specificity in five studies (specificity was the same in one study);
- accuracy per lesion:
 - improved sensitivity for BLC with HAL + WLC compared to WLC (more lesions detected; range 0.76 to 0.99 versus 0.46 to 0.88, respectively);
 - slightly lower specificity for BLC with HAL + WLC compared to WLC (more false-positives; range 0.30 to 1.00 versus 0.37 to 1.00, respectively);
- accuracy per patient (two out of six studies):
 - improved sensitivity for BLC with HAL + WLC compared to WLC (0.89 to 0.96 versus 0.73 to 0.79, respectively);
 - similar values for specificity of the two procedures (0.43 to 1.00);
- wide variation in incremental accuracy of between 3 and 230 additional lesions found and between 3 and 104 true positives and 0 to 126 false positives, and that this variation was unexplained.

MSAC considered that the consequences of a false positive result would be limited by histopathology but may result in more extensive resection and/or single dose intravesical chemotherapy. MSAC noted that inflammatory changes (cystitis, previous resection, previous intravesical chemotherapy or Bacille Calmette-Guerin [BCG] instillation) can contribute to false-positive BLC with HAL for 6-12 weeks: 5 of the 8 RCTs excluded patients who had received intravesical chemotherapy or BCG within 6 weeks (1 study) or 3 months (4 studies).

MSAC noted that the use of BLC with HAL + WLC was reported to change the clinical management in approximately 20% of patients as a result of better detection of bladder cancer and improved risk stratification (Geavlete B et al 2012; Gkritisios P et al 2014), and considered that this should decrease recurrence rate and reduce progression to muscle invasive bladder cancer.

MSAC noted that the evidence presented for comparative effectiveness showed that BLC with HAL has non-inferior safety and superior effectiveness for rate of recurrence, median time to recurrence and recurrence-free survival but uncertain effectiveness for rate of progression and progression-free survival, relative to WLC. MSAC noted:

- rate of recurrence was consistently lower in all studies with statistically significant reductions seen in five studies (Geavlete B et al 2010; Geavlete B et al 2012; Gkritisios P et al 2014; Hermann G et al 2011; Karaolides T et al 2012);
 - benefit maintained at two years (two studies; Geavlete B et al 2012; Gkritisios P et al 2014);
- recurrence-free survival – statistically significant increase in four of five studies (Dragoescu O et al 2011; Grossman H et al 2012; Hermann G et al 2011; Karaolides T et al 2012);
- time to recurrence – significantly longer in two of three studies, with a median difference of four to seven months (Grossman H et al 2012; Karaolides T et al 2012);
- rate of progression – non-significant reduction at one year in four studies;
- mortality – no improvements at 4.5 years follow-up in one study, underpowered to detect outcome of interest (Grossman H et al 2012);
- residual tumour – increase in additional tumours detected by BLC after resection under WLC, of 8.5% and 49% (two studies; reason for divergence unclear; Geavlete B et al 2012; Hermann G et al 2011).

MSAC noted the omission of a patient-level meta-analysis which demonstrated comparative effectiveness (Burger M et al 2013), with a 24.9% increase in additional T_a or T₁ papillary lesions and an additional 26.7% carcinoma *in situ* lesions (T_{CIS}) detected by BLC with HAL + WLC, and a reduction in recurrence rates at one year compared to WLC alone (risk ratio, 0.76, p = 0.006). MSAC also noted the lower risk of progression for the use of BLC with HAL + WLC found in the meta-analysis included in the Agency for Healthcare Research and Quality Comparative Effectiveness Review No.153 (Chou R et al 2016).

MSAC considered that although there were no studies of the safety or effectiveness of BLC with HAL for follow-up surveillance of asymptomatic patients with NMIBC (population 2), it was highly likely that due to the potential overlap of surveillance and recurrence, there may be some merging of population 2 with population 1 because identifying lesions through surveillance would be of benefit to patients, given the high risk of recurrence.

Based on the evidence of effectiveness, MSAC considered the economic model in which BLC with HAL + WLC is used: (i) to guide resection of NMIBC; and (ii) as part of follow-up surveillance after diagnosis, resection and treatment of NMIBC.

MSAC noted that the base-case incremental cost-effectiveness ratio (ICER) was dominant (incremental cost, -\$4153; incremental effectiveness, 0.12 quality adjusted life years). MSAC noted that incremental effectiveness and cost savings were maintained in a number of sensitivity analyses with the exception of risk of recurrence.

MSAC noted that there were some translation issues associated with the economic model:

- patients with CIS only were excluded from one of the trials (Dragoescu O et al 2011);
- the extrapolation of recurrence- and progression-free survival beyond the study duration of 4.5 years to a lifetime time horizon; and
- utilities were taken from studies of overseas populations, and may not be relevant in the Australian setting but were most likely transferrable.

MSAC agreed, based on the advice provided by ESC and the Department, that the MBS costs should exclude the costs of catheterisation for the instillation of HAL, preparation fees, and the cost of HAL. MSAC noted that the revised financial estimates were based on current MBS utilisation data. The revised financial estimates provided a net cost to the MBS i.e. MBS cost of BLC with HAL minus the MBS cost of WLC, which significantly reduced the costs to the MBS presented in the initial assessment (~\$14 million). MSAC noted that the revised estimates of the cost of extra test positives resulting from the use of BLC with HAL and reduction of recurrence associated with the intervention generated an additional cost of between \$1,870,689 and \$5,333,038. However, MSAC considered that this could be an overestimation, as:

- the utilisation data assumed that all cystoscopy items are claimed for bladder cancer, which was unlikely; and
- 100% uptake of BLC with HAL was assumed; this had not been demonstrated in Scandinavia where uptake after five years was 27%.

MSAC considered that the costs and feasibility of upgrading current systems to BLC with HAL, estimated at ~\$35,000 to \$85,000, might also slow the uptake of the procedure, and that there were additional minor considerations around the degree of training required and associated cost which had not been addressed.

MSAC discussed the impact of low uptake of the service on the availability to consumers, and considered that communications to consumers should address access limitations due to the numbers of providers performing the service.

MSAC considered the advice provided by the Department that as HAL is a consumable it was inappropriate to be included as a component of the MBS fee, and agreed that the cost of HAL would be better accommodated under National Procedure Banding arrangements. MSAC considered that advice should be sought as to the level at which banding will apply, as there had been a decline in the cost of HAL overseas. MSAC advised that the MBS fee should be reflective of the existing WLC service cost with an additional input cost of \$65 for the instillation of HAL. MSAC advised it was not reasonable to include an additional input cost for catheterisation as it is a routine part of the procedure and is currently very rarely co-claimed with cystoscopy items.

MSAC considered the applicant's claim that BLC with HAL + WLC is an internationally recognised standard of care, noting that this was not the case in either Europe or the United States (Babjuk M et al 2017; Chang SS et al 2016). MSAC advised that the decision was to accept listing of the item on the MBS based on evidence that BLC with HAL + WLC appears to be safe, clinically effective and cost-effective, and that the financial impact would be low.

MSAC recommended supporting listing for both proposed populations, as identifying lesions through surveillance would be of benefit to patients given the high risk of recurrence.

MSAC advised that this MBS item should be reviewed 12 months following listing and requested that the Department write to the Urological Society of Australia and New Zealand (USANZ) for advice on the likely uptake of the service when listed.

4. Background

MSAC has not previously considered this application.

5. Prerequisites to implementation of any funding advice

Only TGA registered cystoscopic equipment should be used, equipped with necessary filters to allow both standard white light cystoscopy and blue light (wavelength 380-450 nm) fluorescence cystoscopy.

HAL is TGA registered for diagnostic use only.

BLC with HAL must be performed by healthcare professionals trained in cystoscopy (e.g. urologists) and also with experience in blue light imaging as an adjunct to white light imaging. Training options are peer-to-peer interaction and onsite training, the equipment manufacturers and HAL sponsor also offer training options.

6. Proposal for public funding

The proposed MBS item descriptors are summarised in Table 1.

Table 1 Proposed MBS item descriptors

Category: – New item number - Investigative cystoscopic item using blue light with hexaminolevulinate as an adjunct to white light for conduct of biopsy
RIGID CYSTOSCOPY using blue light with hexaminolevulinate as an adjunct to white light, including catheterisation, 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: – New item number - Therapeutic cystoscopic item using blue light with hexaminolevulinate as an adjunct to white light with concurrent resection of tumour
RIGID CYSTOSCOPY using blue light with hexaminolevulinate as an adjunct to white light, including catheterisation, 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 – New item number - Therapeutic cystoscopic item using blue light with hexaminolevulinate as an adjunct to white light with concurrent resection of tumour
RIGID CYSTOSCOPY using blue light with hexaminolevulinate as an adjunct to white light, including catheterisation, 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% = \$172.40 85% = \$195.40
Category: – New item number - Investigative cystoscopic item using blue light with hexaminolevulinate as an adjunct to white light for routine scheduled (follow-up) management
RIGID CYSTOSCOPY using blue light with hexaminolevulinate as an adjunct to white light, including catheterisation, 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

7. Summary of Public Consultation Feedback/Consumer Issues

One response was received from an organisation to the targeted consultation survey. The response noted that the proposed service will provide a more accurate identification of small lesions within the bladder at cystoscopy, which may potentially be missed on white light cystoscopy. Better identification assists pathological classification, potentially reducing recurrences of tumours and allowing appropriate and timely intravesical therapies and treatment of carcinoma *in situ*.

8. Proposed intervention's place in clinical management

There are two proposed patient populations:

Population 1: Patients with suspected bladder cancer who are undergoing rigid cystoscopy with or without biopsy and/or resection.

These patients are those in whom there is a clinical suspicion of bladder cancer, or previous testing (urine cytology and, in some patients, imaging and/or flexible cystoscopy) has raised the suspicion of bladder cancer. They are undergoing rigid cystoscopy during which they may have a biopsy or a resection.

Population 2: Asymptomatic patients with previously diagnosed NMIBC (proven by biopsy or resection), who are undergoing subsequent follow-up or surveillance for disease recurrence with rigid cystoscopy.

BLC with HAL is proposed to be used as an adjunct to WLC, therefore it is used whenever WLC is recommended in the clinical management algorithm.

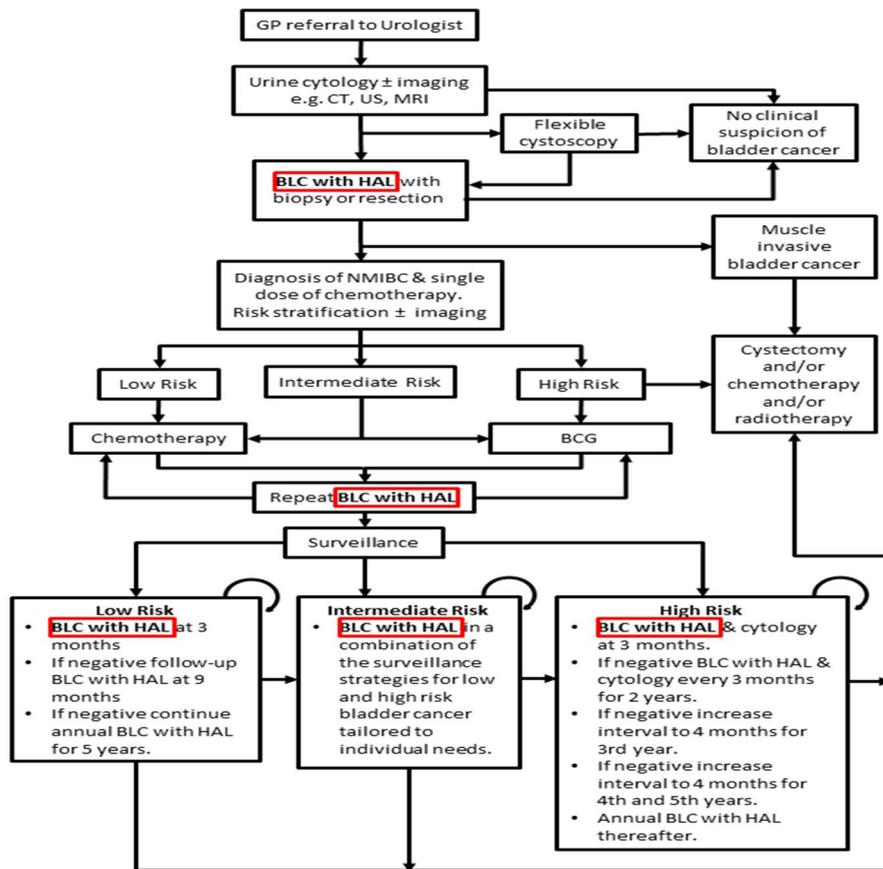


Figure 1 Clinical management algorithm for BLC with HAL relative to current management

9. Comparator

The comparator is standard WLC, which is currently used in the Australian health care system.

The reference standard used to determine the accuracy of BLC with HAL compared to WLC is histopathology.

10. Comparative safety

Similar proportions of patients experienced adverse events in one comparative study (55.3% in the BLC group vs 53.5% in the WLC group). Serious adverse events were also similar in both groups (10.7% vs 8.9% of patients). Adverse events related to HAL instillation occurred in 1.0% to 2.6% of patients with haematuria being the most common.

BLC with HAL appears to have non-inferior safety to WLC alone.

11. Comparative effectiveness

Rate of recurrence

Eight studies found that recurrence rates were lower in the BLC with HAL group than the WLC only group at all follow-up times (except at 3 months in one study).

One applicable study found recurrence rates of 7.2% in the BLC with HAL group compared to 15.8% in the WLC at 3 months (RR=0.46; 95%CI: 0.21, 0.97), 21.6% versus 32.5% at

12 months (RR=0.67; 95%CI: 0.43, 1.02) and 31.2% versus 45.6% at 24 months (RR=0.68; 95%CI: 0.49, 0.95).

Another applicable study reported that the RR of recurrence was 0.84 (95%CI: 0.72, 0.99) at 3 months and 0.91 (95%CI: 0.80, 1.03) at 24 months.

Recurrence-free survival

Four of the five studies that reported recurrence-free survival found a statistically significant increase in recurrence-free survival in the BLC with HAL group compared to the WLC group.

Time to recurrence

Three studies found a longer median time to recurrence; in two this difference was statistically significant. The difference in median time to recurrence ranged from 4 to 7 months.

Rate of progression

Four studies reported on the rate of progression and all found a non-statistically significant reduction in the progression rates in the BLC with HAL group compared to the WLC group at one year.

One highly applicable study found progression rates of 2.4% and 4.4% in the BLC with HAL group and WLC group respectively (RR=0.55; 95%CI: 0.13, 2.24) at one year and 4.0% versus 7.0% T 2 years (RR= 0.57; 95%CI: 0.19, 1.69).

Progression-free survival

One study found that progression-free survival was marginally significantly improved with BLC with HAL (p=0.05).

Mortality

One study found that mortality was not significantly different between the BLC with HAL and WLC groups up to 4.5 years, but was considered to be underpowered for this outcome.

Residual tumour

BLC with HAL detected residual tumour in 49% of patients in one study and 8.5% of patients in another.

On the basis of the included evidence, it is suggested that, relative to the comparator, the intervention has non-inferior safety and superior effectiveness for rate of recurrence, median time to recurrence and recurrence-free survival. Moreover, it is suggested that the intervention has uncertain effectiveness for rate of progression and progression-free survival. No conclusion can be made about mortality due to the studies not being powered to detect this outcome. There is evidence from two studies that BLC with HAL is likely to result in less residual tumour after TURBT; however the true magnitude of this is uncertain.

Effectiveness from linked evidence

Accuracy

Evidence for the comparative and incremental accuracy of BLC with HAL as an adjunct to WLC relative to WLC alone comes from two level III-2 studies and four level III-3 studies. On the basis of this evidence, it is proposed that BLC with HAL as an adjunct to WLC is more sensitive on a per-lesion basis in detecting bladder cancer than WLC alone but less specific. On a per person basis the evidence is less robust but does suggest that BLC with

HAL is more sensitive than WLC. There is no change in the specificity on a per-patient basis when WLC with HAL is added to WLC.

With regards to incremental accuracy, the evidence suggests that BLC with HAL will detect more cancers and this will result in more biopsies or resection of healthy tissue.

Comparative accuracy

BLC with HAL was found to have a higher sensitivity than WLC alone in six studies and a lower specificity in five studies (specificity was the same in one study).

The most applicable study found the sensitivity of BLC with HAL was 0.93 (95%CI: 0.91, 0.95) compared to 0.76 (95%CI: 0.73, 0.80) in WLC and specificity was 0.74 (95%CI: 0.71, 0.77) and 0.87 (95%CI: 0.85, 0.89) respectively.

Two studies show that BLC with HAL is more sensitive to detecting bladder cancer *per person* but just as specific as WLC alone: the most reliable and applicable study reported sensitivity to be 0.96 (95%CI: 0.85, 0.99) for BLC with HAL versus 0.73 (95%CI: 0.58, 0.85) for WLC; specificity was 0.43 (95%CI: 0.10, 0.82) for both BLC and WLC.

Incremental accuracy

The incremental accuracy was highly variable with between 3 and 230 additional lesions detected by BLC with HAL with between 3 and 104 true positives and 0 to 126 false positives.

The most applicable study with the largest sample size found that for every additional true positive there was approximately another false positive detected.

Therapeutic efficacy and effectiveness (change in management and health benefit from change in management)

Based on the evidence provided in the Contracted Assessment Report, the use of BLC with HAL as an adjunct to WLC will change the clinical management in approximately 20% of patients. This is due to categorising patients in a higher risk group which results in their receiving more appropriate treatment which, it is suggested, improves clinical outcomes.

Clinical Claim

It is proposed that BLC with HAL has non-inferior safety and superior effectiveness and diagnostic accuracy to WLC. It is proposed that BLC with HAL as an adjunct to WLC will result in improved detection and more complete resection of bladder lesions leading to more accurate risk stratification and thus more appropriate treatment and management post-operatively. This, in turn, may lead to reduced rates of recurrence, longer times to recurrence, reduced rates of progression and longer times to progression to muscle invasive disease. In addition, surgery may be avoided due to more accurate diagnosis and more complete resection. Moreover, there may be improved progression-free survival and overall survival due to more appropriate entry into the clinical management pathway (e.g. earlier if diagnosis is more accurate) and more appropriate management (e.g. more appropriate treatment regimens due to better risk stratification).

12. Economic evaluation

A cost utility analysis was undertaken for the economic evaluation of BLC with HAL as an adjunct to WLC for population 1 - patients with suspected bladder cancer who are undergoing rigid cystoscopy with or without biopsy and/or resection. A summary of the economic evaluation is shown in Table 2.

Table 2 Summary of the economic evaluation

Population	Patients where there is a clinical suspicion of bladder cancer, or previous testing – cytology and, in some patients, imaging and/or flexible cystoscopy – has raised the suspicion of bladder cancer
Perspective	Australian government
Comparator	Standard white light cystoscopy
Type of economic evaluation	Cost utility analysis
Primary sources of evidence	Palou et al. (2015), Grossman et al. (2012), Mowatt et al. (2010)
Time horizon	Life time
Outcomes	Quality Adjusted Life Years (QALYs)
Methods used to generate results	Decision tree followed by Markov cohort model
Health states	Non-muscle invasive (low risk); Non-muscle invasive (intermediate risk); Non-muscle invasive (high risk); Non-muscle invasive recurrence (low risk); Non-muscle invasive recurrence (intermediate risk); Non-muscle invasive recurrence (high risk); No tumour recurrence (non-muscle invasive - low risk) – surveillance; No tumour recurrence (non-muscle invasive - intermediate risk) – surveillance; No tumour recurrence (non-muscle invasive - high risk) – surveillance; Muscle invasive; No tumour recurrence (muscle invasive); Non metastatic muscle invasive recurrence; Metastatic muscle invasive recurrence; Tumour related death; Natural death
Cycle length	3 months
Discount rate	5%
Software packages used	TreeAge Pro® 2017 R2.0

The overall costs and outcomes, and incremental costs and outcomes as calculated for the test and comparator in the model, and with the base case assumptions, are shown in Table 3.

Table 3 Base case incremental costs effectiveness ratio

BASE CASE	Cost	Incremental cost	Effectiveness (QALYs)	Incremental effectiveness
BLC+WLC	\$63,536	(\$4,153)	7.29	0.12
WLC	\$67,689		7.17	

Abbreviations: ICER = Incremental Cost Effectiveness Ratio; QALY = quality adjusted life year; WLC = white-light cystoscopy; BLC = blue-light cystoscopy.

The sensitivity analysis found that when diagnostic accuracy values, male/female gender, disease severity at diagnosis and age at diagnosis are modified, BLC with HAL remains dominant. The economic model was sensitive to variations in the relative risk of recurrence of BLC with HAL as an adjunct to WLC compared to WLC alone.

13. Financial/budgetary impacts

An epidemiological approach was used to estimate the financial implications of the introduction of BLC with HAL as an adjunct to WLC.

The financial implications to the MBS resulting from the proposed listing of BLC with HAL as an adjunct to WLC are summarised in Table 4.

Table 4 Total costs to the MBS associated with BLC with HAL as an adjunct to WLC

<i>Population</i>	<i>2018</i>	<i>2019</i>	<i>2020</i>	<i>2021</i>	<i>2022</i>
Annual cost, initial BLC with HAL in patients with suspected bladder cancer	\$8,332,820	\$8,455,859	\$8,563,518	\$8,677,330	\$8,792,679
Total annual cost, 1 st year after presentation, all patients	\$26,485,522	\$26,875,706	\$27,215,474	\$27,578,912	\$27,948,268
Annual cost all NMIBC, 1 st year surveillance	\$6,885,203.	\$7,040,506.	\$7,198,105	\$7,355,579	\$7,512,326
Total annual cost, incident and prevalent cases	\$ 33,370,726	\$33,916,212	\$34,413,580	\$34,934,493	\$35,460,595

The cost of BLC using the weighted average of the MBS items based on 2016 utilisation, adding the cost of HAL, catheterisation item cost, and preparation cost is \$1,390.51 per patient.

Updated financial costs were provided by the assessment group using the average costs per person of BLC and WLC and taking a market-based approach as recommended in the Critique and by the Applicant. Based on these estimates the net cost to the MBS could be an additional cost of between \$1,870,689 and \$5,333,038 assuming a 100% uptake of the BLC technology (Table 5). There is considerable uncertainty in these figures which may, in fact, include a cost neutral result.

Table 5 MBS costs adjusted for extra positive tests and reduction of recurrence associated with BLC with HAL as an adjunct to WLC

Assumption	Cost to MBS
Distribution of extra test results same as utilisation distribution	\$5,333,038.35
All of the extra positive tests involve biopsy only	\$1,870,689.66

Using uptake rates supplied by the Applicant of the Scandinavian experience, the associated additional costs for each year after introduction are estimated in Table 6.

Table 6 Additional cost estimates based on uptake data supplied by the Applicant

Year	1	2	3	4	5
% uptake	2%	8%	13%	21%	27%
Additional cost*	\$106,660.77	\$426,643.07	\$693,294.99	\$1,119,938.05	\$1,439,920.35
Additional cost†	\$37,413.79	\$149,655.17	\$243,189.66	\$392,844.83	\$505,086.21

* assuming the extra positive tests are distributed as per the utilisation cohort from July 2016 to June 2017

† assuming that the extra positive tests involve biopsy only

14. Key issues from ESC for MSAC

This submission is a new application to support the listing on the Medicare Benefits Schedule (MBS) of blue light cystoscopy (BLC) with hexaminolevulinate (HAL). This service would be used as an adjunct to rigid white light cystoscopy (WLC) for the diagnosis, treatment and management of non-muscle invasive bladder cancer (NMIBC).

ESC noted that there are two proposed populations considered in this application. The populations are:

- patients with suspected (new *or* recurrent) bladder cancer undergoing rigid cystoscopy with or without biopsy and/or resection for the purposes of diagnosis and treatment (population 1); and
- asymptomatic patients with *previously diagnosed* NMIBC, who are undergoing subsequent follow-up or surveillance with rigid cystoscopy for disease recurrence (population 2). ESC noted the pre-test probability of disease is higher in this population.

ESC queried the inclusion of both suspected *new* and suspected *recurrent* cases in population 1, but noted that only one study was restricted to suspected new NMIBC cases (O'Brien T et al 2013); the remaining studies were mixed or unspecified populations.

ESC noted that the current joint guidelines of the American Urological Association and the Society of Urologic Oncology (Chang S et al 2016) recommend the use of BLC with HAL (BLC with HAL) for routine surveillance of NMIBC following transurethral resection of the bladder. The European Association of Urology guidelines (Babjuk M et al 2017) recommended its use (i) after intravesical treatment (at 3 or 6 months) in patients with carcinoma *in situ* (CIS, Grade C recommendation); and (ii) in patients with positive cytology and no visible tumour in the bladder (Grade B recommendation) – such patients (with positive cytology) are not considered truly “asymptomatic”.

ESC noted that there were no studies of the safety or effectiveness of BLC with HAL for follow-up surveillance of *asymptomatic* patients with NMIBC (population 2), the population in which high utilisation would be expected.

ESC noted that there were significant limitations in the evidence base with all included studies at high or unclear risk of bias, with high levels of heterogeneity.

ESC noted that BLC with HAL + WLC has non-inferior safety versus WLC alone (unless HAL is contraindicated). In the most comprehensive study (Stenzl et al. 2010), the proportion of patients experiencing adverse events was similar for both groups (55.3% BLC with HAL + WLC versus 53.5% WLC only).

ESC noted that the populations included in the diagnostic accuracy trials were not homogenous; some studies included only patients with suspected NMIBC (initial cancer only) and/or recurrence; other studies included routine follow-up patients.

ESC noted that six studies provided evidence of diagnostic performance, all of which had high or unclear risk of bias. Evidence showed:

- BLC with HAL had higher sensitivity than WLC alone in six studies and lower specificity in five studies (specificity was the same in one study);
- *accuracy per lesion*:
 - improved sensitivity for BLC with HAL + WLC compared to WLC (more lesions detected: range 0.76 to 0.99 versus 0.46 to 0.88, respectively);
 - slightly lower specificity for BLC with HAL + WLC compared to WLC (more false-positives: range 0.30 to 1.00 versus 0.37 to 1.00, respectively);
- *accuracy per patient* (two out of six studies):
 - improved sensitivity for BLC with HAL + WLC compared to WLC (0.89 to 0.96 versus 0.73 to 0.79, respectively);

- similar values for specificity of the two procedures (0.43 to 1.00);
- wide variation in incremental accuracy of between 3 and 230 additional lesions found and between 3 and 104 true positives and 0 to 126 false positives, and that this variation that was unexplained.

ESC noted that the use of BLC with HAL as an adjunct to WLC was reported to change the clinical management in approximately 20% of patients. This information was derived from two of the RCTs that demonstrated a statistically significant reduction in recurrence (Geavlete B et al 2012; Gkritisios P et al 2014).

ESC noted that relative to the comparator, BLC with HAL has non-inferior safety and superior effectiveness for rate of recurrence, median time to recurrence and recurrence-free survival but uncertain effectiveness for rate of progression and progression-free survival. ESC noted that of eight studies providing evidence for comparative effectiveness for BLC with HAL compared to the comparator:

- rate of recurrence was consistently lower in all studies with statistically significant reductions seen in five studies (Geavlete B et al 2010; Geavlete B et al 2012; Gkritisios P et al 2014; Hermann G et al 2011; Karaolides T et al 2012);
 - benefit maintained at two years (two studies; Geavlete B et al 2012; Gkritisios P et al 2014);
- recurrence-free survival – statistically significant increase in four of five studies (Dragoescu O et al 2011; Grossman H et al 2012; Hermann G et al 2011; Karaolides T et al 2012);
- time to recurrence – significantly longer in two of three studies, with a median difference of four to seven months (Grossman H et al 2012; Karaolides T et al 2012);
- rate of progression – non-significant reduction at one year in four studies;
- mortality – no improvements at 4.5 years follow-up in one study, underpowered to detect outcome of interest (Grossman H et al 2012);
- residual tumour – increase in additional tumours detected by BLC after resection under WLC, of 8.5% and 49% (two studies; reason for divergence unclear; Geavlete B et al 2012; Hermann G et al 2011).

ESC noted the omission of a patient-level meta-analysis which demonstrated comparative effectiveness (Burger M et al 2013), with a 24.9% increase in additional papillary lesions and an additional 26.7% CIS lesions detected by BLC with HAL + WLC, and a reduction in recurrence rates at one year compared to WLC alone. ESC also noted that in contrast to the results presented in the assessment, the use of BLC with HAL in conjunction with WLC was associated with a lower risk of progression in a meta-analysis included in the Agency for Healthcare Research and Quality Comparative Effectiveness Review No.153 (Chou R et al 2016).

ESC noted that the economic model had undergone extensive revision, including the addition of HAL as a resource cost, following feedback by the critique that had identified differences between the model and the literature, and had queried the ability of the model to assess the cost-effectiveness of BLC with HAL versus WLC.

ESC noted that the base-case incremental cost-effectiveness ratio (ICER) was dominant over WLC alone. ESC noted that sensitivity analyses showed that the intervention was dominant for all other inputs with the exception of risk of recurrence. ON the other hand, the incremental cost and QALY components of the ICERs were not provided, and ESC considered that the reporting of the incremental cost and incremental benefit components of

the ICER is necessary in order to determine whether costs or outcomes are the main drivers of the ICER.

ESC noted the variable lengths of follow-up in the included studies, which ranged from 6 weeks to 4.5 years. ESC considered that the extrapolation of recurrence- and progression-free survival beyond the study duration of 4.5 years was a key translation issue for the economic model. ESC noted that the risk of recurrence extrapolated to a 20 year time line is the same regardless of whether a patient has a low, intermediate or high risk NMIBC.

ESC also considered that the application of utilities and probabilities for recurrence, progression and mortality included in the model presented a translation issue, as no discussion had been provided as to the source of the utilities or the relevance to an Australian population. In the source of the utilities, patients with NMIBC, confirmed by histopathology, are assumed to be at low, intermediate or high risk of progression, but no discussion is provided as to the applicability of these risk allocations to Australian clinical practice.

ESC also noted that patients with CIS only were excluded from one of the trials (Dragoescu O et al 2011), and that this may present a minor translation issue in terms of the applicability of the data in the model, since patients with CIS account for only 2.9% of all presentations of NMIBC.

ESC noted that the applicant had highlighted an omission in the clinical algorithm, whereby for a substantial proportion of low-risk patients for whom there is no clinical suspicion of recurrence, follow-up may be in the outpatient setting using flexible cystoscopy. ESC agreed that this was not proposed in the agreed PICO presented to PASC, and should not be included in the model.

ESC noted that despite the revisions to the model, and the consequent dominance of the intervention in the sensitivity analyses performed regarding accuracy and comparative effectiveness inputs, the financial estimates had not been revised. ESC noted that the financial implications are considerable when the cost of HAL is included in the MBS fee, rising from approximately \$14 million to between \$33.37 million and \$35.46 million over five years, based on the usage estimates provided.

Aside from the exclusion of the cost of HAL, ESC noted there were several additional factors requiring consideration that had been omitted from the financial estimates in the contracted assessment, being:

- additional costs and feasibility issues with upgrading current systems to enable the procedure to be performed;
- associated costs and needs of training for the procedure to be undertaken;
- the impact of the procedure on operating theatre workflows; and
- possible restrictions on use to minimise the false positive rate associated with the procedure (e.g., exclusion of patients within 6-12 weeks of intravesical chemotherapy or Bacille Calmette-Guerin [BCG]).

ESC noted that these factors would result in the considerable underestimation of health system costs associated with the use of BLC with HAL. ESC noted that in light of this, the financial estimates in the contracted assessment should be redone.

ESC also queried the appropriateness of the fee structure, given that WLC will always be used in conjunction with the procedure and should be costed as such (BLC with HAL as an adjunct to WLC).

ESC noted that the applicant has proposed the MBS item codes should reflect the existing cost structure for the WLC item, plus the addition of costs for initial catheterisation for instillation of visualisation agent (based on MBS item 36800; fee \$27.60), plus the cost of instillation of the visualisation agent (based on MBS item 13948; fee \$62.25), plus the cost of HAL (\$775), resulting in a fee for the intervention in the range of \$1031.58 to \$1556.28.

ESC queried the inclusion of the cost of \$62.25 for instillation of the visualisation agent and queried whether this claim was valid as this process is an integral part of the overall procedure.

ESC queried the proposed unit cost of HAL (\$775), noting that this is the commercial cost (price to the wholesaler) and no information had been provided as to how this cost is derived.

ESC discussed the cost and reimbursement of HAL, noting that HAL does not meet the criteria for listing on either the Pharmaceutical Benefits Scheme (PBS) or the Prostheses List, and that HAL should not be a component of the MBS (as it is a consumable). ESC also considered that the inclusion of HAL in an MBS fee may have the effect of setting a floor price. ESC noted advice from the Department of Health that as BLC with HAL is an in-hospital procedure, funding may be possible under the National Procedure Banding (NPB) arrangements

ESC noted that under the NPB arrangements, WLC services are categorised as Band 1 (MBS item 36812) and Band 2 (MBS items 36836 and 36840). ESC noted that as the direct cost range for these bands is not high enough to include the cost of HAL, the new BLC with HAL items would need to be allocated higher theatre bands appropriate to cover the additional cost of HAL. ESC noted that under this arrangement the theatre costs for BLC with HAL would have a higher benefit than the comparator WLC procedure and the additional payment could provide cost coverage of HAL.

ESC considered that new technologies such as narrow-band imaging may have an impact on the uptake of this service and future use, but that no data were available.

ESC noted that as false positives can occur (due to high-grade dysplasia [a premalignant condition], or inflammation from prior transurethral resection of bladder lesions, intravesical BCG, intravesical chemotherapy or infection), restrictions to the item descriptor should be considered to minimise the rate of false positives. However, ESC noted that the consequences of a false positive result, revealed by histopathology, were likely to be limited to more extensive resection and/or a single dose of intravesical chemotherapy.

ESC considered that given this intervention is requested for two populations (diagnosis and treatment), it may have been more appropriate to present separate clinical management algorithms for the different target populations, as suggested in the critique.

ESC noted that the algorithm does not account for contraindications for the use of HAL.

ESC noted that the method of reimbursement of HAL may have an impact on equity for patients if HAL is an out-of-pocket expense. Additional equity issues for consumers include access barriers to services due to the requirement for upgraded procedures, especially for rural/remote or uninsured patients or those with no access to private sector services.

ESC Key ISSUES	ESC ADVICE
Item descriptor	Query restrictions to reduce FP rate
Proposed fee	<p>ESC queried the inclusion of the cost of \$62.25 for instillation of the visualisation agent and the proposed unit cost of HAL (\$775).</p> <p>HAL does not meet the criteria for listing on either the Pharmaceutical Benefits Scheme (PBS) or the Prosthesis List, and that HAL should not be a component of the MBS (as it is a consumable). ESC noted that BLC with HAL is an in-hospital procedure, funding may be possible under the National Procedure Banding (NPB) arrangements</p>
Reimbursement for HAL	may have an impact on equity for patients if HAL is an out-of-pocket expense
'Hidden' costs	<p>Upgrading systems for BLC</p> <p>Training in BLC</p> <p>Impact on OT workflow</p>
Population	<p>Query 2 populations: suspected NEW bladder cancer, suspected RECURRENT bladder cancer; however, only 1 study (O'Brien et al, 2013) was restricted to suspected NEW NMIBC</p> <p>No evidence of effectiveness of BLC for surveillance of asymptomatic patients (population 2)</p>
Deviance from PICO	Query model use of flexible cystoscopy for surveillance of low-risk patients – not proposed in agreed PICO
Economic evaluation	<p>Query appropriateness of economic model</p> <p>Role of new technologies</p> <p>False positives</p> <p>Sensitivity analyses</p>

15. Other significant factors

Nil

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

Juno Pharmaceuticals welcomes MSAC's decision to support the funding of Blue Light Cystoscopy (BLC) with hexaminolevulinate (HAL) as an adjunct to standard White Light Cystoscopy (WLC), for the diagnosis, treatment and management of NMIBC. However, Juno is concerned over the lack of clarity on the path for public reimbursement of the

hexaminolevulinate. The recommendation has been made to pursue reimbursement of HAL via the National Procedure Banding arrangements which we will do.

17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website:
[visit the MSAC website](#)