Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1439 – Intravesical instillation of sodium hyaluronate (1.6%) & sodium chondroitin sulphate (2.0%) for painful bladder syndrome /interstitial cystitis and recurrent urinary tract infection and radiation induced cystitis

Applicant: **Juno Pharmaceuticals Pty Ltd**

Date of MSAC consideration: **MSAC 70th Meeting, 27 July 2017**

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 a new Medicare Benefits Schedule (MBS) listing for the intravesical instillation of sodium hyaluronate (HA, 1.6%) & sodium chondroitin sulphate (CS, 2.0%) into the bladder as a glycosaminoglycan (GAG) layer replacement therapy, for patients with painful bladder syndrome (PBS)/interstitial cystitis (IC), patients with recurrent urinary tract infections (rUTIs) and patients with radiation-induced cystitis, was received by the Department of Health from Juno Pharmaceuticals Pty Ltd.

2. MSAC's advice to the Minister

MSAC agreed that painful bladder syndrome/interstitial cystitis (PBS/IC), recurrent urinary tract infections (rUTIs) and radiation induced cystitis (RIC) can be debilitating conditions and there is a place for instillation of sodium hyaluronate and sodium chondroitin sulphate (hereafter HA-CS) in some patients. However, MSAC was unable to support the MBS listing of a service for HA-CS instillation due to limitations in the evidence base and considerable uncertainty around clinical effectiveness and cost-effectiveness.

MSAC was also concerned that the listing of the service could result in considerable out-of-pocket expenses for consumers because there is no clear mechanism for subsidising the cost of the pre-filled syringe containing the HA-CS solution.

MSAC advised that stronger evidence would be required before listing could be reconsidered and suggested randomised clinical trials of HA-CS instillation in well-defined patient populations were feasible.

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

MSAC noted the application to list a service for the bladder instillation of sodium hyaluronate and sodium chondroitin sulphate (hereafter HA-CS). MSAC noted that the

clinical claim was that the HA-CS solution can restore the glycosaminoglycan (GAG) layer of the bladder. Damage to the GAG layer can lead to bladder dysfunction including pain, frequent urination and chronic inflammation.

MSAC noted that the service involves an in/out (intermittent) urinary catheter inserted into the bladder to allow the infusion of the HA-CS solution. The patient is asked to hold the solution in the bladder for as long as possible (preferably more than 30 minutes) before emptying their bladder as normal.

MSAC noted that the application covered three indications, all of which could be debilitating. These were patients with:

- painful bladder syndrome/interstitial cystitis (PBS/IC);
- recurrent urinary tract infections (rUTIs); or
- radiation induced cystitis (RIC) that persists for more than three months after radiation.

MSAC noted that the patient population for the PBS/IC indication were patients whose condition remains chronic despite first line treatment (conservative management, multimodal pain management and oral medication).

MSAC noted that the comparator for the PBS/IC population was dimethyl sulfoxide (DMSO). However, MSAC noted that DMSO is not PBS listed or TGA registered for this indication and its clinical effectiveness and cost-effectiveness for the treatment of PBS/IC has not been established in the Australian setting.

In addition, MSAC noted that it was unclear how frequently DMSO was being used to treat PBS/IC. TGA data indicated that DMSO is only provided 80–100 times per year through the Special Access Scheme (SAS). However, MSAC noted the applicant's statement that pharmacists often make up DMSO instillations for clinicians without the need to access it through the SAS. MSAC noted that the lack of information on how often DMSO instillations were being used to treat PBS/IC introduced further uncertainty into deliberations.

Bearing this in mind, MSAC noted that the evidence base to support the use of HA-CS in the PBS/IC population relied upon a single, open label randomised controlled trial (n = 110; Cevigni M et al 2016) in which HA-CS or DMSO was instilled weekly for 13 weeks. MSAC noted HA-CS appeared to have superior safety to DMSO with the risk of adverse events in the HA-CS arm (15%) being half that in the DMSO arm (31%).

MSAC noted that while both HA-CS and DMSO instillations significantly improved pain levels at 6 months when compared with baseline in the PBS/IC population, there was no statistically significant difference in the mean pain intensity reduction between the two treatment groups (mean difference -8.8; 95% confidence interval [CI] -20.8 to 3.19, p = 0.15). MSAC noted that there was a trend towards improved quality of life with HA-CS compared with DMSO (EQ-5D unadjusted mean difference of 0.08; 95% CI -0.16 to 0.32) but again the difference was not statistically significant.

MSAC was unconvinced that use of HA-CS instillation would be cost-effective in the PBS/IC population. MSAC noted that the non-significant difference in quality of life drove the economic model and this introduced considerable uncertainty as to the model's reliability. MSAC noted that further uncertainty was introduced into the model because the cost-effectiveness of DMSO has not been established. MSAC queried whether the price of $117 for DMSO used in the model was too high. MSAC noted that given the uncertainties inherent in the model, a cost minimisation approach would have been informative.

MSAC noted that it had been estimated that approximately 12,000 patients with PBS/IC would undergo HA-CS treatment in 2022 at an MBS cost of $8.8 million. MSAC queried these estimates noting that they did not account for treatment in the public hospital system and relied upon an assumption that 90% of eligible patients would be willing to undergo HA-CS instillation despite its invasive nature.

MSAC noted that it was possible that HA-CS had superior safety when compared with DMSO but too much uncertainty remained around the effectiveness and cost-effectiveness of HA-CS, particularly as DMSO itself has not been evaluated for safety, effectiveness and cost-effectiveness. As a result, MSAC was unable to support MBS listing of the service for PBS/IC.

MSAC noted that the rUTI population included patients with uncomplicated recurrent urinary tract infections (UTIs) where damage to the GAG layer was suspected. MSAC noted that the comparators in this population are prophylactic antibiotics and on-demand antibiotics.

MSAC noted that the evidence base to support the use of HA-CS in the rUTI population was based upon two, very small randomised controlled trials. In one study, 57 women received instillations of HA-CS or placebo (saline) — this trial was used as a proxy for on-demand antibiotic use (Damiano R et al 2011). After a year of follow-up, the women in the HA-CS group had a mean of 3.5 fewer UTIs than the placebo group. In the other open label study, 28 women received either prophylactic antibiotics or HA-CS instillation — over a year, the women in the HA-CS group had a mean of 1.3 fewer UTIs than the prophylactic antibiotics group (DeVita D & Giordano S 2012). MSAC noted that HA-CS instillation and antibiotics had similar safety although this was based upon small patient numbers.

MSAC agreed that the cost-effectiveness of HA-CS instillation compared with on-demand or prophylactic antibiotics was not acceptable. MSAC noted that HA-CS instillation would cost $3,637 over five years for a gain of 4.05 QALYs compared with $1,212 and 4.02 QALYs for antibiotics on-demand, resulting in an incremental cost-effectiveness ratio (ICER) of $79,718 per QALY. MSAC noted HA-CS instillation would cost $2,801 over five years for a gain of 4.03 QALYs compared with $1,208 and 4.02 QALYs for prophylactic antibiotics, resulting in an ICER of $154,678 per QALY.

MSAC acknowledged that use of HA-CS instillation to treat rUTIs instead of antibiotics may have benefits with regards to antibiotic resistance but noted this could not be quantified and incorporated into the economic model.

MSAC noted that HA-CS appeared to reduce the number of UTIs when compared with on-demand or prophylactic antibiotics although this was based upon small patient numbers. However, MSAC was unable to support the MBS listing of the service for rUTIs due to unacceptable cost-effectiveness.

MSAC noted that the evidence base for the RIC population relied upon one small uncontrolled cohort study (n = 30; Gacci M et al 2016). MSAC noted that this very poor quality evidence meant that it was not possible to evaluate the safety, effectiveness or cost-effectiveness of HA-CS instillation in the RIC population. As a result, MSAC was unable to support MBS funding for RIC.

In addition, MSAC suggested that the estimated number of RIC patients undergoing the procedure was too high and did not reflect the precautions taken during radiotherapy treatment to minimise irradiation of the bladder.

MSAC noted that the applicant had argued that HA-CS instillation would cure most patients in all three indications and that this benefit had not been reflected in the economic modelling. However, MSAC noted that no evidence to support this claim had been provided for any indication.

MSAC noted that the number of instillations for each indication was unclear. The studies used to support the use of HA-CS in different indications varied with regards to the number of instillations undertaken (9–13) and duration of treatment (2–6 months). MSAC noted that this introduced further uncertainty into the financial estimates for all three indications. MSAC noted that the applicant was amenable to including a maximum number of instillations in the item descriptor(s).

MSAC queried the inclusion of costs for sedation during use of an intermittent catheter, and the selection of diazepam (PBS item 3162K) as the choice of sedative, in the cost components of the proposed MBS fee for undertaking HA-CS instillation for each indication.

MSAC noted that it was possible that GPs, nurses or specialists could perform the service. MSAC was concerned that the pre-filled syringe containing the HA-CS solution was unlikely to be listed on the Prostheses List, which is for surgically implanted prostheses, human tissue items and other medical devices, as instillation of the solution is undertaken is most likely to be performed as an outpatient procedure. MSAC also noted that the technology was listed as a device on the Australian Register of Therapeutic Goods (ARTG) and so the syringe would not be eligible for PBS listing. MSAC noted that as the price of each syringe was ~$215–235, and the protocols for use indicated that six or more instillations were required to manage each indication, this would result in considerable out-of-pocket expenses for patients.

Overall, MSAC noted that the evidence presented for the use of HA-CS in all three indications was not sufficient to support the requested listings. MSAC noted that:

- it was possible that HA-CS was non-inferior to the comparator of DMSO in patients with PBS/IC but was unable to support the MBS listing of the service due to considerable uncertainty as to the effectiveness and cost-effectiveness of HA-CS, particularly given DMSO itself has never been evaluated for safety, effectiveness and cost-effectiveness in an Australian setting.
- HA-CS appeared to reduce the number of urinary tract infections (UTIs) when compared with on-demand or prophylactic antibiotics but was unable to support the MBS listing of the service for rUTIs due to unacceptable cost-effectiveness.
- the evidence base for RIC was of very poor quality and so the safety, effectiveness or cost-effectiveness of HA-CS instillation in this population was unable to be evaluated.

MSAC noted that stronger evidence would be required before listing could be reconsidered. MSAC noted that the conditions are not uncommon and further clinical trials of HA-CS instillation in well-defined patient populations are feasible.

4. Background

MSAC has not previously considered this application.

5. Prerequisites to implementation of any funding advice

The iAluRil® Procedure pack and Prefill pack are registered on the Australian Register of Therapeutic Goods (ARTG) as shown in Table 1.

Table 1 iAluRil listed on the ARTG

ARTG no.	Product no.	Product description	Product category	Sponsor
233622	44670, Bladder instillation, barrier	iAluRil Procedure pack consisting of a clear plastic pre-filled syringe containing a sterile aqueous solution of hyaluronic acid sodium salt (1.6%), sodium chondroitin sulphate (2%) and calcium chloride administered as a bladder instillation via connection to a catheter using the leur lock adaptor included in the pack.	Medical Device Class III	Juno Pharmaceuticals Pty Ltd
230280	44670 Bladder instillation, barrier	iAluRil Prefill consisting of clear plastic pre-filled syringe containing a sterile aqueous solution of hyaluronic acid sodium salt (1.6%), sodium chondroitin sulphate (2%) and calcium chloride administered as a bladder instillation via a catheter.	Medical Device Class III	Juno Pharmaceuticals Pty Ltd

Source: Therapeutic Goods Administration, accessed 02 February 2017 TGA.gov.au

An application to include the HA-CS irrigation system on the Prostheses List was submitted.

6. Proposal for public funding

The proposed MBS item descriptors are in Table 2, Table 3 and Table 4.

Table 2 Proposed MBS item descriptor for PBS/IC

Category 3 – THERAPEUTIC PROCEDURES
MBS ##### Male or female patients, diagnosed with Painful Bladder Syndrome / Interstitial Cystitis (PBS/IC), whose condition remains chronic despite the application of conservative management, multimodal pain management and oral medication. - Consider further limiting to females only due to applicability of evidence - Consider including a maximum number of instillations per course of treatment Fee: $65.75 Benefit: 75% = $49.32 85% = $55.89

Abbreviations: MBS; Medicare Benefits Schedule

Table 3 Proposed MBS item descriptor for rUTI

Category – THERAPEUTIC PROCEDURES
MBS ##### Female patients diagnosed with recurrent urinary tract infection (UTI), which is defined as a minimum of two infections in the previous six-month period, or three infections in the previous 12-months, and where damage to the GAG layer is suspected. - Consider limiting to "uncomplicated" UTIs due to applicability of evidence - Consider including a maximum number of instillations per course of treatment Fee: $65.75 Benefit: 75% = $49.32 85% = $55.89

Abbreviations: MBS; Medicare Benefits Schedule

Table 4 Proposed MBS item descriptor for RIC

Category – THERAPEUTIC PROCEDURES
MBS ##### Male or female patients with lower urinary tract symptoms three months post-radiation therapy, whose condition remains significant after standard conservative/1st line drug therapy. - Consider limiting to acute (second line) or late (last line) radiation-induced cystitis. - Consider limiting to men with prostate cancer due to applicability of evidence - Consider including a maximum number of instillations per course of treatment Fee: $65.75 Benefit: 75% = $49.32 85% = $55.89

Abbreviations: MBS; Medicare Benefits Schedule

The proposed fee of $65.75 for the service is based on time taken, the degree of difficulty and the expertise required to perform the procedure. The proposed fee is based on costs of consumables, concomitant medications and professional time. The overall fee of $65.75 is greater than the fee for MBS item 36800 (catheterisation of the bladder where no other

procedure is performed; $27.60) and slightly less than the fee for MBS item 11921 (bladder washout test for localisation of urinary infection not including bacterial counts for organisms in specimens), $75.05.

The MBS fee does not include the HA-CS solution which would be reimbursed through the Prostheses List in the in hospital setting if approved.

7. Summary of Public Consultation Feedback/Consumer Issues

No public consultation feedback was received.

8. Proposed intervention's place in clinical management

The target population includes patients with the following conditions:

1. Patients with painful bladder syndrome (PBS)/interstitial cystitis (IC)
2. Patients with recurrent urinary tract infections (rUTIs)
3. Patients with radiation-induced cystitis (RIC).

HA-CS therapy is indicated to re-establish the GAG layers of the urothelial vesical tissue in cases in which their loss can cause frequent and recurring problems such as PBS, interstitial cystitis IC, rUTIs, cystitis as a result of Bacillus Calmette-Guerin therapy, or cystitis resulting from chemical and radiation therapy.

HA-CS therapy is also indicated in the cases where the loss of the GAG layers is associated with forms of chronic inflammation, in which their composition and integrity appear compromised in different ways.

HA-CS therapy is instilled into the bladder and held for as long as possible (30 + mins). As an out-patient procedure, the service can be provided by nurses, GPs or specialists.

In the pre-MSAC response, the applicant stated that it does not believe this product would be administered by a GP and considered it unlikely that the service would be delivered in a community setting, given that catheterisation and instillation requires a very specific set of skills not normally mastered or used by a GP.

<u>Painful Bladder Syndrome (PBS)/Interstitial Cystitis (IC)</u>
Currently, treatment strategies for PBS/IC after diagnosis should proceed from conservative ones to more invasive therapies. Following diagnosis, patients are initially encouraged to attempt conservative approaches to patient management. If these less invasive approaches to patient management are unsuccessful, a range of treatments with variable effectiveness are available.

Oral medications such as tricyclic antidepressants (TCAs) and sodium pentosan polysulfate are frequently used. Bladder instillation therapy with a range of agents including dimethyl sulfoxide (DMSO) is used in patients with refractory disease.

The clinical management algorithm for the treatment of PBS/IC will remain largely unchanged if intravesical instillation with HA-CS is listed on the MBS. The only difference between the current and proposed algorithms is the inclusion of the intravesical instillation of HA-CS as an alternative to bladder instillation with DMSO.

<u>Recurrent urinary tract infection (rUTI)</u>
Initial treatment for uncomplicated rUTIs may include "conservative" measures such as the use of spermicide, post-coital voiding and cranberry products. However, the evidence to

support the efficacy of these measures is generally poor (Dason, 2011). Thus, the mainstay of rUTI prevention remains the use of longer-term (3-6 months) low dose antibiotic prophylaxis, post-coital antibiotics and patient-initiated antibiotics guided by symptoms. HA-CS instillation will be used as an alternative to these strategies.

Radiation-induced cystitis (RIC)
First line conservative management of radiation cystitis can involve a range of measures including anticholinergics, analgesics, IV hydration and bladder irrigation. Patients who fail to respond to conservative therapies have a range of second line treatment options; however, most are supported by poor quality evidence. These include systemic treatments, hyperbaric oxygen therapy, interventional procedures such as surgery and laser, and intravesical treatments. Given the lack of evidence to support each of these interventions, the order in which they should be administered is unclear. Consistent with the Final Protocol, the application models the use of HA-CS instillation of radiation-induced cystitis after all other first and second line treatments have failed. However, it should be noted that the applicability of the comparator ("no treatment") may be at odds with the PICO-defined population, which is second line positioning of HA-CS.

9. Comparator

Painful Bladder Syndrome (PBS)/Interstitial Cystitis (IC)
Bladder instillation with HA-CS will be provided as an alternative to bladder instillation using DMSO, and to be utilised before more serious invasive interventions such as surgery or neuromodulation. In the case of DMSO, it is claimed that HA-CS is as effective (non-inferior comparative effectiveness) to DMSO with fewer side effects (superior comparative safety). However, Medicare utilisation data suggest that the service used to administer DMSO (MBS item 11921; bladder washout test) is very infrequently used. DMSO does also not appear on the ARTG, and has been supplied in the past through the TGA special access scheme (SAS). If DMSO is rarely used in Australia, it is possible that other comparators should be considered.

In the pre-MSAC response, the applicant noted that whilst DMSO is not formally listed on the ARTG, the formulation is readily available in Australia and DMSO is not, nor need to be supplied under the Special Access Scheme. Confirmation was provided from the Director of Pharmacy at Monash Medical Centre, that DMSO instillations are being made up by the pharmacy and that this is not via the TGA's SAS scheme. Arrangements for supply differ across various public and private settings and accurately capturing the extent of use from available datasets is problematic, but the absence of reliable data do not indicate an absence of use. The applicant therefore contends that DMSO remains the appropriate comparator, as per the agreed and approved Final Protocol.

Recurrent urinary tract infection (rUTI)
It is intended that the proposed service will be eligible to patients who meet the NPS definition of rUTIs, and will be used in place of the chronic use of oral antibiotics to prevent rUTIs. Several strategies can be used, all of which are relevant comparators in this Assessment Report (Hutton et al., 2014):

- Continuous prophylaxis
- Post-coital antibiotics
- Intermittent patient-initiated treatment

Radiation-induced cystitis (RIC)
Bladder instillation is to be used as a course of three months post-radiation therapy, after all other first and second line treatments have failed (e.g. anticholinergic agents, hyperbaric

therapy, other bladder instillations/irrigations such as alum), and before surgery to remove the bladder. As noted previously, this positioning is at odds with the proposed indication, "in patients whose condition remains significant after standard conservative/first line drug therapy".

It is claimed that treatment with HA-CS in this setting is more appropriate than no treatment or bladder removal surgery to treat/reduce the lower urinary tract symptoms (LUTS) of urgency, frequency and nocturia. In this group of patients, the comparator is therefore no treatment.

For patients with PBS/IC, the delivery of HA-CS is likely to be identical to that of DMSO, i.e. the product is likely to be administered by a nurse, GP or specialist, in an outpatient setting. For patients with rUTI, the main comparator is antibiotic prophylaxis or patient-initiated treatment. Treatment with antibiotics is less resource intensive than treatment with HA-CS, as it involves fewer medical visits and may be prescribed by any general practitioner. For patients with RIC, the main comparator is standard care/no treatment. Therefore, all procedures associated with the administration of HA-CS occur in addition to existing management strategies.

10. Comparative safety

For patients with PBS/IC, patients treated with DMSO experienced approximately twice the rate of AEs as patients treated with HA-CS instillation (RR 0.49 [95% CI 0.23, 1.01]; p=0.05). There was also a statistically significant reduction in the rate of treatment-related AEs and discontinuations for lack of efficacy with HA-CS instillation. These results suggest that HA-CS is superior to DMSO in terms of safety; however, this conclusion is based on an open-label study design and small patient numbers.

In patients with rUTI, HA-CS is non-inferior to antibiotics in terms of safety; however, this conclusion is based on small patient numbers.

In patients with RIC, bladder instillation therapy was well tolerated; however, this conclusion is based on non-comparative evidence and small patient numbers.

11. Comparative effectiveness

For patients with PBS/IC, a significant reduction in pain intensity based on a visual-analogue scale (VAS) was observed at 6 months in both treatment groups versus baseline ($p<0.0001$) in the intention-to-treat (ITT) population. Patients treated with HA-CS reported a greater mean VAS reduction compared with those treated with DMSO at 6 months (-39.2 ± 29.1 vs. -30.4 ± 30.5, respectively), however, the between-group difference was not statistically significant (-8.8; 95% CI -20.8, 3.19; p=0.15).

The changes from baseline in both study arms were clinically important; however, the difference between study arms did not meet the minimum clinically important difference (MCID) threshold of a 30-point reduction.
In terms of utility values, the EQ-5D results suggested a small non-significant benefit (unadjusted mean difference=0.08; 95% CI -0.16, 0.32), in favour of HA-CS at 6 months. On this basis, it is reasonable to assume that HA-CS instillation is at least non-inferior to DMSO instillation in terms of clinical efficacy, with a trend towards improved clinical efficacy. This conclusion is based on moderate quality clinical evidence.

In patients with rUTI, the decrease in UTI rate per patient per year at the end of the study (12 months) was significantly greater in the HA-CS group compared to placebo, with a mean difference of 3.5 episodes per year (95% CI -4.0, -3.1; p<0.00001). Where antibiotic prophylaxis was the main comparator, there was a smaller mean difference between the HA-CS and the control group, with a mean difference of 1.3 episodes per year (95% CI -2.3, -0.3; p=0.01).

Overall, the results suggest that HA-CS instillation is superior to antibiotic prophylaxis and patient-initiated therapy in terms of clinical efficacy. This conclusion is based on high quality studies but with small patient numbers.

In patients with RIC, HA-CS instillation significantly reduced overall LUTS and bother as measured by the Interstitial Cystitis Problem Index (ICPI)/ Interstitial Cystitis Symptom Index (ICSI) questionnaire (P < 0.001 and P = 0.006). As this was an uncontrolled study, it is not possible to determine whether a change in symptoms would have occurred in the absence of the HA-CS intervention.

Clinical Claim
On the basis of the evidence profile, the following clinical claims can be made:

In patients with PBS/IC:
- HA-CS is superior to DMSO in terms of safety;
- HA-CS is non-inferior to DMSO in terms of clinical efficacy, with a trend towards improved efficacy; and
- These claims are based on moderate quality evidence.

In patients with rUTI:
- HA-CS is non-inferior to antibiotics in terms of safety;
- HA-CS instillation is superior to antibiotic prophylaxis and patient-initiated therapy in terms of clinical efficacy; and
- These claims are based on high quality evidence, although in a small number of patients.

In patients with RIC:
- It is not possible to evaluate safety and efficacy based on the available evidence.

12. Economic evaluation

Three economic evaluations were presented. Given HA-CS is potentially superior on either effectiveness or safety parameters in the PBS/IC and rUTI setting, a cost-utility analysis (CUA) was presented for each of these populations. Despite the poor quality evidence a simple CUA was also presented in the RIC population.

The economic evaluations were trial-based, in that they model the direct health outcomes and associated quality of life benefits observed over the duration of trial follow-up. These benefits are then extrapolated beyond follow-up, where appropriate, over a clinically relevant time horizon. During extrapolation, the benefits applied to each treatment arm return to the observed baseline values, unless treatment is continuing. In the latter scenario, the treatment benefits observed at the final follow-up visit of the relevant trial are assumed to persist as long as treatment is ongoing.

The incremental cost-effectiveness and outcomes for intravesical instillation of HA-CS in each proposed MBS population, relative each of the nominated comparators is presented in **Table** 5 and in each population is at Table 6.

Table 5: Incremental cost-effectiveness of intravesical instillation of HA-CS versus DMSO in PBS/IC - Base case - 13 weeks treatment, convergence of effect at 12 months

	Cost	Incremental cost	Effectiveness (QALYs)	Incremental effectiveness	ICER
HA-CS	$3,758		0.4901		
DMSO	$2,484	$1,274	0.4610	0.0291	$43,790

ICER = Incremental Cost-Effectiveness Ratio
Key assumptions of the economic evaluation are that the observed mean difference in clinical effect between treatment arms at Month 6 in Cervigni et al (2016) persists over the remaining 6 months modelled duration, converging to baseline in each treatment arm over this period.

Table 6: Incremental cost-effectiveness of intravesical instillation of HA-CS in each patient population

	Cost	Incremental cost	Effectiveness (QALYs)	Incremental effectiveness	ICER
PBS/IC [a]					
HA-CS	$3,758		0.4901		
DMSO	$2,484	$1,274	0.4610	0.0291	$43,790
rUTI [b]					
Comparator: Antibiotic on demand (standard care)					
HA-CS	$3,637		4.0476		
Antibiotics	$1,212	$2,425	4.0172	0.0304	$79,718
Comparator: Prophylactic antibiotic therapy					
HA-CS	$2,801		4.0310		
Antibiotics	$1,208	$1,593	4.0207	0.0103	$154,678
RIC					
HA-CS	$2,113		0.1439		
No therapy	$0.00	$2,113	0.0000	0.1439	$14,679

a Key assumption of the economic evaluation for PBS/IC are that the observed mean difference in clinical effect between treatment arms at Month 6 in Cervigni et al (2016) persists over the remaining 6 months modelled duration, converging to baseline in each treatment arm over this period.
b Key assumptions in this economic evaluation in rUTI are that the treatment effect (change in UTI/patient/year) persists over the 5 year modelled time horizon, with the rate of UTI in each treatment arm converging to baseline rate starting from the end of trial follow-up (6 months)

In the pre-MSAC response, the applicant expressed concerns around several of the assumptions in the economic evaluation, such as duration, intensity of therapy, likely continuation of a treatment effect beyond this, the (variable) time horizons and cost inputs.

13. Financial/budgetary impacts

An epidemiological approach has been used to estimate the financial implications of the introduction of HA-CS instillation.

The financial implications to the MBS resulting from the proposed listing are summarised in

Table 7: Total costs to the MBS associated with HA-CS instillation

Population	2017	2018	2019	2020	2021	2022
PBS/IC						
Patients	1,104	2,249	4,583	7,004	9,513	12,111
Services	14,349	29,241	59,584	91,051	123,663	157,439
Sub-total cost	$801,940	$1,634,219	$3,329,998	$5,088,606	$6,911,211	$8,798,872
rUTI						
Patients	579	1,178	2,400	3,666	4,974	6,327
Services	3,471	7,071	14,401	21,993	29,847	37,960
Sub-total cost	$193,997	$395,173	$804,849	$1,229,142	$1,668,065	$2,121,469
Radiation-induced cystitis						
Patients	90	184	375	573	778	990
Services	632	1,287	2,623	4,008	5,444	6,931
Sub-total cost	$35,302	$71,939	$146,588	$224,003	$304,234	$387,330
All indications						
Total patients	1,773	3,612	7,358	11,242	15,265	19,427
Total services	18,452	37,599	76,608	117,052	158,953	202,329
Total cost	$1,031,239	$2,101,331	$4,281,435	$6,541,751	$8,883,511	$11,307,671

In the pre-MSAC response, the applicant stated that the likely utilisation of HA-CS in clinical practice and the associated financial cost to the MBS is significantly overestimated. The applicant believes that the true maximal potential utilisation of HA-CS in Australia will be less than one third of the estimates presented, with an associated reduction to the likely cost to the MBS.

. The net cost of listing the service, assuming no cost offsets due to DMSO instillation, increase from $1,031,239 in 2017 to $11,307,671 by 2022.

Table 7: Total costs to the MBS associated with HA-CS instillation

Population	2017	2018	2019	2020	2021	2022
PBS/IC						
Patients	1,104	2,249	4,583	7,004	9,513	12,111
Services	14,349	29,241	59,584	91,051	123,663	157,439
Sub-total cost	$801,940	$1,634,219	$3,329,998	$5,088,606	$6,911,211	$8,798,872
rUTI						
Patients	579	1,178	2,400	3,666	4,974	6,327
Services	3,471	7,071	14,401	21,993	29,847	37,960
Sub-total cost	$193,997	$395,173	$804,849	$1,229,142	$1,668,065	$2,121,469
Radiation-induced cystitis						
Patients	90	184	375	573	778	990
Services	632	1,287	2,623	4,008	5,444	6,931
Sub-total cost	$35,302	$71,939	$146,588	$224,003	$304,234	$387,330
All indications						
Total patients	1,773	3,612	7,358	11,242	15,265	19,427
Total services	18,452	37,599	76,608	117,052	158,953	202,329

Population	2017	2018	2019	2020	2021	2022
Total cost	$1,031,239	$2,101,331	$4,281,435	$6,541,751	$8,883,511	$11,307,671

In the pre-MSAC response, the applicant stated that the likely utilisation of HA-CS in clinical practice and the associated financial cost to the MBS is significantly overestimated. The applicant believes that the true maximal potential utilisation of HA-CS in Australia will be less than one third of the estimates presented, with an associated reduction to the likely cost to the MBS.

14. Key issues from ESC for MSAC

ESC noted the application to list a service for the bladder instillation of sodium hyaluronate and sodium chondroitin sulphate (HA-CS) was for three populations:

- painful bladder syndrome/interstitial cystitis (PBS/IC);
- recurrent urinary tract infections (rUTIs); and
- radiation induced cystitis (RIC) that persists for more than three months after radiation.

ESC noted that dimethyl sulfoxide (DMSO) was presented as the comparator for HA-CS instillation in PBS/IC and that the clinical effectiveness and cost-effectiveness of DMSO for the treatment of PBS/IC has not been established in the Australian context, given it is not TGA registered or PBS listed for this indication.

ESC noted the applicant argued that DMSO is an appropriate comparator for treating PBS/IC because it is widely used, however there was little information provided in the application to support this argument. It was noted that access to DMSO is via the TGA Special Access Scheme (SAS).

ESC noted that information on diagnosis and the reason for use are provided to the TGA each time a SAS request is made and suggested approaching the TGA for information on the number of SAS requests for DMSO to treat PBS/IC would be helpful for decision making.

With regards to the PBS/IC population, there was moderate quality evidence that HA-CS instillation has superior safety and non-inferior efficacy when compared to DMSO but that this was based upon one small, open label randomised trial (n = 110).

ESC noted that the economic model for PBS/IC was driven by a non-significant difference in quality of life (EQ-5D unadjusted mean difference of 0.08; 95% CI -0.16 to 0.32 in favour of HA-CS instillation) and that inclusion of this non-significant difference in the model is problematic and introduces considerable uncertainty into the reliability of the economic model for PBS/IC.

With regards to the rUTI population, ESC noted that there was high quality evidence that HA-CS instillation had non-inferior safety and superior efficacy when compared to prophylactic antibiotics or self-initiated antibiotics based upon two small randomised trials (n = 85).

ESC was uncertain as to the acceptability of HA-CS instillation in the rUTI population given the greater burden imposed by multiple catheterisations to complete the course of HA-CS treatment in comparison with taking antibiotics.

ESC indicated that use of self-initiated antibiotics as a comparator in the economic model for rUTIs was more likely to reflect usual Australian clinical practice than prophylactic antibiotic and that the incremental cost-effectiveness ratios (ICERs) for HA-CS instillation compared

with prophylactic antibiotics and self-initiated antibiotics were both at levels that indicated that they were not cost-effective.

ESC noted that:

- the evidence base for RIC was very low quality, relying upon a single cohort study that enrolled 30 patients.
- that as such it was not possible to evaluate the safety and efficacy of HA-CS instillation in this population.
- that RIC occurring within 3–6 months of radiation treatment is generally considered to be acute. ESC noted that late RIC occurs from six months to five years post treatment.

ESC considered that the proposed use of HA-CS instillation in people with RIC three months post-treatment would lead to inappropriate use in people with acute RIC.

ESC also noted that:

- the comparator used in the economic modelling for the RIC population was no treatment.
- it was unclear whether HA-CS instillation would be positioned after failure of first line therapies for RIC or would only be used after all other second line therapies had failed.
- the position of HA-CS instillation in the clinical pathway would impact upon the cost-effectiveness of the service.
- the non-significant EQ-5D result from the PBS/IC trial had also been used to inform the economic model in the RIC population.
- the extrapolation of non-significant results seen in one condition to a completely separate condition was problematic.
- no sensitivity analyses had been carried out in the RIC population.
- there was considerable uncertainty in the economic models for all three indications with regards to the time horizon and the extrapolation of treatment effects.
- that Table 77 summarising the univariate sensitivity analyses in the assessment report was incomplete.

ESC noted that HA-CS instillation treatment is not well-standardised and that the studies used to support its use in different indications used different frequencies and durations of treatment which would impact upon the cost of providing the service.

ESC queried the relative patient numbers provided for the PBS/IC population and the RIC population. They considered that the high uptake rates for the service may not accurately reflect patient preferences given the invasive nature of HA-CS instillation.

ESC noted that while it is possible that the service could be undertaken by GPs or practice nurses this was unlikely to occur due to the cost of consumables. However, GPs were more likely to provide the service if they were in a rural or remote area.

ESC noted that the syringe containing the HA-CS solution for instillation would be considered for listing on the Prostheses List and that the Prostheses List covers items provided as part of hospital or hospital substitute treatment whereas HA-CS instillation is anticipated to be undertaken in an outpatient setting. As such, if the syringe was not listed on the Prostheses List, there may be out of pocket expenses for consumers of $215–235 per syringe per treatment.

It was noted that the item descriptors did not contain a service description.

From a consumer perspective, it was noted that the lack of clarity around the service and its delivery made it difficult to determine whether there would be out of pocket expenses for consumers. ESC also noted that while these conditions had the potential to cause distressing and debilitating symptoms, there was a lack of information on patient outcomes provided.

ESC Key ISSUES	ESC ADVICE
Protocol	Note varying duration and intensities in trials
Provider	Note that although it is possible that the service could be undertaken by GPs or practice nurses this was unlikely to occur due to the cost of consumables. However, GPs were more likely to provide the service if they were in a rural or remote area.
Evidence base	Overall low / small clinical trials
Dimethyl Sulfoxide (DMSO)	Is DMSO appropriate? If used (CUA 2016 guidelines Grade B, recommended in select patients for IC/BPS)
rUTIs	Patient Preference – Antibiotics vs multiple catheterisations. Uncertain as to the acceptability of HA-CS instillation in the rUTI population given the greater burden imposed by multiple catheterisations to complete the course of HA-CS treatment in comparison with taking antibiotics.
RIC	RIC occurring within 3–6 months of radiation treatment is generally considered to be acute. Late RIC occurs from six months to five years post treatment. • over-specified "3 months" vs leakage (delayed presentation) • Acute 3-6 vs Late (>6) • Assessment time horizon - 6m
Descriptors	Proposed descriptors do not contain a service description

15. Other significant factors

Nil

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

Juno note the comments that *"MSAC was also concerned that the listing of the service could result in considerable out-of-pocket expenses for consumers because there is no clear mechanism for subsidising the cost of the pre-filled syringe containing the HA-CS solution."* We strongly believe this to be untrue. The product is registered as a medical device, and Juno advised the department from the very beginning that it would be seeking (and currently is doing so) reimbursement for the HA-CS solution via PLAC - which is a clear mechanism. Additionally, listing this service would actually reduce (not increase) patient out-of-pocket expenses, as the product is already available and being used in Australia, and as there is no appropriate item code, many health care practitioners charge above the standard consultation fee (item number 104/105) to fairly cover their time and expertise to administer this intravesical service. As such, appropriately funding this administration part of the treatment would reduce, not increase patients total cost.

17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website:
visit the MSAC website