



Australian Government
Department of Health

MEDICAL SERVICES ADVISORY COMMITTEE

Final Protocol

for

Application 1439

***Intravesical instillation of sodium hyaluronate (1.6%)
with sodium chondroitin sulphate (2.0%) for Painful
Bladder Syndrome/Interstitial Cystitis, Recurrent Urinary
Tract Infection and Radiation Induced Cystitis***

Juno Pharmaceuticals Pty Ltd

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Summary of decision analytic protocol

A summary of the PICO and health care resource of the comparisons to be assessed, is outlined below.

Table 1 Population 1: Patients with Painful Bladder Syndrome / Interstitial Cystitis (PBS/IC)

Component	Description
Patients	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.
Prior Tests	A range of prior diagnostic tests may be undertaken to exclude other potential causes of the symptoms: <ul style="list-style-type: none"> • Physical examination • Medical history • Cystoscopy and biopsy • Routine or special bacterial cultures • Flowmetry and ultrasound • Imaging (CT or IVP) • Post-void residual urine volume measurement by ultrasound scanning • Urine cytology • Urodynamics • Prostate specific antigen (PSA) test • Nerve blockage
Intervention	Intravesical instillation of sodium hyaluronate (1.6% - 800 mg/50 mL) and sodium chondroitin sulphate (2% - 1 g /50 mL) (iAluRil®).
Comparator	Bladder instillation therapy using dimethyl sulfoxide (DMSO)
Outcomes	<p><u>Effectiveness/Efficacy</u></p> <p>The primary health outcomes (effect) will be measured in terms of:</p> <ul style="list-style-type: none"> • decrease in bladder/pelvic pain; • decrease in urinary urgency; • decrease in urinary frequency; and • improved health related quality of life <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/cost utility</u></p> <ul style="list-style-type: none"> • Cost per QALY gained <p><u>Health service utilisation</u></p> <ul style="list-style-type: none"> • Cost of instillation (including administration and clinical time) • Cost of consumables • Costs associated with clinical management changes e.g. changes in post-operative management, surgeries avoided, changes in need for drugs and other treatments <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

Table 2 Population 2: Patients with Recurrent Urinary Tract Infections (rUTI)

Component	Description
Patients	Female patients diagnosed with recurrent urinary tract infection (UTI) for which eligibility is counted 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.
Prior Tests	A range of prior diagnostic tests may be undertaken to exclude other potential causes: <ul style="list-style-type: none"> • Physical examination • Medical history • Cystoscopy • Urine cytology (esp. routine bacterial cultures)
Intervention	Intravesical instillation of sodium hyaluronate (1.6% - 800 mg/50 mL) and sodium chondroitin sulphate (2% - 1 g /50 mL) (iAluRil®).
Comparator	Chronic use of oral antibiotic prophylactically or to treat recurrent episodes
Outcomes	<p><u>Effectiveness/Efficacy</u></p> <p>The primary health outcomes (effect) will be measured in terms of:</p> <ul style="list-style-type: none"> • reduction in the rates of urinary tract infections over 12 months (i.e. mean number of UTI per patient per year); • reduction in the use of antibiotics and direct and potential long term social related side effects (e.g. increased resistance); and improved health related quality of life. <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/cost utility</u></p> <ul style="list-style-type: none"> • Cost per life year gained • Cost per QALY gained <p><u>Health service utilisation</u></p> <ul style="list-style-type: none"> • Cost of instillation (including administration and clinical time) • Cost of additional consumables • Costs associated with clinical management changes e.g. changes in post-operative management, surgeries avoided, changes in need for drugs and other treatments <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

Table 3 Population 3: Patients with Radiation induced cystitis

Component	Description
Patients	Male or female patients with lower urinary tract symptoms three months post radiation therapy, whose condition remains significant after standard conservative/1 st line drug therapy.
Prior Tests	A range of prior diagnostic tests may be undertaken to exclude other potential causes: <ul style="list-style-type: none"> • Physical examination and symptom assessment • Medical history • Cystoscopy • Urine cytology Routine or special bacterial cultures • Ultrasound
Intervention	Intravesical instillation of sodium hyaluronate (1.6% - 800 mg/50 mL) and sodium chondroitin sulphate (2% - 1 g /50 mL) (iAluRil®).
Comparator	Standard of care
Outcomes	<p><u>Effectiveness/Efficacy</u> The primary health outcomes (effect) will be measured in terms of:</p> <ul style="list-style-type: none"> • reduction in urinary urgency; • reduction in urinary frequency; • reduction in nocturia; and • improved health related quality of life. <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/cost utility</u></p> <ul style="list-style-type: none"> • Cost per life year gained • Cost per QALY gained <p><u>Health service utilisation</u></p> <ul style="list-style-type: none"> • Cost of instillation • Cost of additional consumables • Costs associated with clinical management changes e.g. changes in post-operative management, surgeries avoided, changes in need for drugs and other treatments <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

1. Title of Application

Intravesical instillation of sodium hyaluronate (1.6%) with sodium chondroitin sulphate (2.0%) for painful bladder syndrome/Interstitial cystitis, recurrent urinary tract infections and radiation induced cystitis.

2. Purpose of application

Request and rationale for application

This application seeks a new MBS Item number for the instillation of iAluRil (sodium hyaluronate (1.6%) with sodium chondroitin sulphate (2.0%)) into the bladder as a glycosaminoglycan (GAG) layer replacement therapy.

Three populations are proposed:

- 1) Patients with Painful Bladder Syndrome (PBS)/Interstitial Cystitis (IC)
- 2) Patients with Recurrent Urinary Tract Infections (rUTIs)
- 3) Patients with Radiation-induced Cystitis

As a service rendered in an outpatient setting, the funding proposed for this service is a fee, payable to the service provider. Currently no MBS item exists to facilitate bladder instillation for treatment of these conditions and would be required in order to ensure equity of access for all patients irrespective of treatment setting.

A concurrent application seeking the inclusion of iAluRil on the Prostheses List will also be submitted in conjunction with this MSAC application.

Registered Indications

Intravesical instillation of sodium hyaluronate (1.6%) and sodium chondroitin sulphate (2.0%) therapy (trade name iAluRil®) is indicated to re-establish the glycosaminoglycan layers (GAGs) of the urothelial vesical tissue in cases in which their loss can cause frequent and recurring problems such as painful bladder syndrome (PBS), interstitial cystitis (IC), treatment and prevent of recurrent urinary tract infection, cystitis as a result of bacillus Calmette Guerin Therapy or chemical and radiation therapy.

iAluRil therapy is also indicated in the cases where the loss of the glycosaminoglycan layers (GAGs) is associated with forms of chronic inflammation, in which their composition and integrity appears compromised in different ways.

3. Population and medical condition eligible for the proposed medical services

Description of medical condition and clinical management

Painful Bladder Syndrome (PBS)/Interstitial Cystitis (IC)

PBS/IC is a spectrum of urological symptoms characterised by pain in the bladder, frequency and urgency, primarily affecting women. It is a chronic debilitating condition characterised by:

- Pelvic/bladder pain (pressure/discomfort)
- Urinary urgency - often persistent even after voiding
- Urinary frequency - with voiding from 10 to 50 times within 24 hours (resulting in nocturia and associated QOL impacts such as sleep deprivation).

Currently, there is no cure and so additional treatments that help minimise and manage these life-debilitating symptoms are important.

A range of treatments may be tried before a patient achieves remission and are usually offered in a step-by-step process to see what works for each individual. These include: hydrodistention, oral drugs, bladder instillations, and surgery (USANZ fact sheet, 2016, Cvach and Rosamilia, 2015)).

The exact pathophysiology of PBS/IC remains incompletely understood nor described, however inflammation, mast cell activation, glycosaminoglycan (GAG) layer defects, urothelial dysfunction, autoimmune mechanisms, infection, alteration in autonomic nerve function, direct injury from noxious components of urine, hypoxia and multiple other mechanisms have all been implicated. It is likely that the pathogenic mechanisms are complex and relative components vary between sufferers.

Injury to the GAG layer, in particular, is understood to represent a common pathogenic step in multiple pathways to PBS/IC and hence GAG layer replacement therapy was developed for treating this condition. Intravesical therapy has the advantage of localising therapy to the bladder, with the establishment of high concentrations of the treating agent, and can minimise some systemic side effects. A recent review on intravesical therapies for PBS/IC was recently completed by Australian urogynaecologists Cvach and Rosamilia, and has been published in *Translational Andrology and Urology* (2015).

iAluRil® (hyaluronic acid 1.6% + chondroitin sulphate 2%) is the first intravesical GAG replacement therapy to combine chondroitin sulphate (CS) - the most abundant of the sulphated GAG molecules located on the bladder wall - with one of the most integral component of the GAG layer, hyaluronic acid (HA), a combination designed to facilitate faster and more effective restoration of the bladder epithelium.

Although curing PBS/IC is not yet possible in many people, the high toll that PBS/IC exacts can be partially mitigated with some therapies once the disease is diagnosed.

Numerous treatment options exist for PBS/IC ranging from those that aim to reduce individual symptoms; anticholinergics to counteract frequency, analgesic drugs to reduce pain, antihistamines to reduce inflammation and antidepressants to address the deteriorating quality of life. Intravesical therapies are indicated if 1st line therapies fail (Cvach and Rosamilia, 2015) and are used to address the underlying cause of the disease state and replenish the deficient bladder lining (GAG layer) or alter the process of neurogenic inflammation and hypersensitivity.

Despite the requirement for a number of existing treatments delivery via bladder instillation, there is currently no MBS Item number for bladder instillations.

Recurrent Urinary Tract Infections (rUTIs)

Recurrent urinary tract infections are a common condition with one in three women experiencing at least one episode within their lifetime, compared to one in 20 for men. Between 25% and 35% of initial urinary tract infection (UTI) episodes will be followed by a recurrence within 3-6 months. It is estimated that 10% of these patients will have a further recurrence. Failure to identify the underlying cause and successfully treat UTIs can lead to more serious consequences such as kidney damage and renal failure, as well as adversely affecting patients' quality of life.

An intact GAG layer has been postulated to be essential in protecting bladder epithelial cells from injury by toxic components of urine and there is evidence that it also prevents adhesion of bacteria to the bladder epithelium. Damage to the GAG layer can therefore result in the exposure of epithelial cells, which can lead to an increase in bacterial adherence and infection.

Besides life-style and behavioural modifications, all approaches to dealing with rUTIs are based on treating the infection once it has taken hold, or the prophylactic use of antibiotics to prevent flare-ups.

Until recently, there has been no treatment available to actually address the underlying pathology and prevent rUTIs.

For the first time with a GAG layer replacement therapy, a good quality randomised placebo controlled trial has been published. This shows that treatment with combined high concentration hyaluronic acid and chondroitin sulphate (iAluRil®) resulted in a significant rate of reduction in recurrent urinary tract infections, which consequently led to a significant improvement in patients' quality of life.

Currently there is no MBS item code for bladder instillations to treat rUTIs.

Radiation-induced Cystitis

The urinary bladder can be irradiated intentionally for the treatment of bladder cancer or incidentally for the treatment of other pelvic malignancies. Manifestations of radiation cystitis can range from minor, temporary, irritative voiding symptoms and painless, microscopic haematuria to more severe complications, such as nocturia, gross haematuria; non-functional bladder and persistent incontinence.

It has been hypothesized that many post-radiation lower-urinary tract symptoms (LUTS) - including nocturnal voiding frequency (nocturia) - could be caused by the damage, disruption and, consequently, discontinuation of the glycosaminoglycan (GAG) layer of the bladder mucosa. Therefore, GAG replenishment therapy by instillation of hyaluronic acid (HA) with or without chondroitin sulphate (CS) has been suggested as a viable treatment option to treat post-radiation LUTS

Many patients respond well to current forms of treatment however there are those who many months post radiation still suffer symptoms.

Currently there is no MBS Item number for bladder instillations to treat post-radiation induced cystitis patients still suffering symptoms many months post radiation.

Description of the proposed patient population

Painful Bladder Syndrome / Interstitial Cystitis (PBS/IC)

Whilst the term PBS/IC is used interchangeably, the International Continence Society (2004) defines PBS/IC in the following way:

- PBS: complaint of suprapubic pain related to bladder filling accompanied by other symptoms such as frequency in the absence of proven urinary infection or other pathology.
- IC is reserved for those with typical cystoscopic findings (not further specified) which may include Hunners ulcers and glomerulations.

It should be noted that some, such as the European Society for the Study of Interstitial Cystitis (ESSIC), have also suggested to call this disease Bladder Pain Syndrome (BPS) (van de Merwe *et al*, 2008).

PBS/IC can develop at any age, with the onset for most patients around the age of 40, however it can occur at a much earlier age. Nine out of ten sufferers are women.

The symptoms of PBS/IC can remain misunderstood for several years, and may gain in severity as time passes before a sudden deterioration brings the disease sharply into focus. The disease pathway almost always starts with an increase in the frequency of urination, accompanied by pain on bladder filling leading to a desire to void.

Due to the multi-factorial nature of the disease state, PBS/IC can be notoriously hard to diagnose correctly. For example, the UK National Institute of Diabetes and Digestive and Kidney Diseases criteria have in the past been shown to miss 60% of patients by being both highly specific and overly restrictive (Hanno *et al*, 1999).

As such, when diagnosing patients, it is important to consider aspects like patient history, physical examination, differential diagnosis (e.g. eliminating other disease like urinary tract infections, overactive bladder, endometriosis and bladder carcinoma).

Urine analysis (to eliminate other causes like urinary tract infections) and cystoscopy under anaesthetic is deemed to be an important diagnostic tool in PBS/IC. Cystoscopy allows for direct examination of bladder tissue to highlight inflammation and ulceration of the tissues. Performed under general anaesthetic or epidural, and often accompanied by hydrodistention, or cystoscopy.

Diagnosis of painful bladder syndrome/interstitial cystitis is a stepwise process designed to exclude all other reasonable or possible causes for the irritation and discomfort. Patients undergo tests and procedures dependent upon initial symptoms, presentation and medical history. Other possible causes that must be ruled out include: carcinoma, infestation, radiation, obstructions, urine retention issues, nerve entrapment, pelvic floor muscle issues, endometriosis or candidiasis.

Thus a patient presenting with PBS/IC would be likely to have increased frequency, pain, urgency, fatigue and incontinence in the absence of other possible causes for the condition, as noted above.

It is envisaged that patients with diagnosed PBS/IC will have failed first line treatment and become appropriate for intravesical treatment. They will predominantly be female, aged over 40 years of age and under the care of a urologist or uro-gynaecologist.

Recurrent urinary tract infection (rUTI)

NPS MedicineWise (2016), define a urinary tract infection (UTI) as recurrent as follows:

- Women: those who have experienced two or more symptomatic infections of the urinary tract in six months, or three or more in a one year period.
- Men: recurrent is considered to be more than one episode.

Although overall, men experience UTIs much less commonly than women, if they do contract a UTI they have a higher likelihood of it being a complicated infection and of recurrence.

Recurrent infections occur either as:

- relapse of a previously treated infection, or
- re-infection.

If a recurrence occurs within two weeks of a previous episode, it is classified as a relapse.

The symptoms of recurrent UTIs in women, are often the same as previous episodes and therefore patients can often correctly self-diagnose.

This patient population can be summarised as patients with defined recurrent urinary tract infection where damage to the GAG layer is suspected. They will predominantly be female, over 18 years of age, have previously received antibiotics as treatment or as prophylaxis and will be under the care of a urologist, urogynaecologist or gynaecologist.

Radiation induced cystitis

Radiation induced cystitis can be defined as lower urinary tract symptoms (LUTS) occurring post radiation to the pelvic region. Patients frequently report dysuria, urgency, frequency, nocturia, or pelvic pain and can have a negative impact on quality of life (QoL), including vitality or social and physical performance. (Gacci *et al*, 2016)

Radiation cystitis is a recognised complication of pelvic radiotherapy. Incidence of radiation cystitis ranges from 23 to 80% and the incidence of severe haematuria ranges from 5 to 8%. High quality data on management strategies for radiation cystitis is sparse. Treatment modalities are sub-classified into systemic therapies, intravesical therapies, hyperbaric oxygen and interventional procedures. Short-term cure rates range from 76 to 95% for hyperbaric oxygen therapy and interventional procedures. Ultimately, most patients require multimodal treatment for curative purposes. (Browne *et al*. 2015)

Patients can be described as diagnosed with radiation-induced cystitis caused by radiation to the pelvis that has failed to return to baseline three months after radiation despite multiple treatment modalities, which may or may not include hyperbaric therapy. They are deemed suitable for intravesical therapy (i.e. where damage to the GAG layer is suspected to play a role) and will be under the care of an urologist or radiation oncologist.

Summary of the evidence for the population

Painful Bladder Syndrome / Interstitial Cystitis (PBS/IC)

A prospective study by Gilberti *et al* (2013) verified the efficacy and safety of intravesical treatment combining sodium hyaluronate (HA and Chondroitin sulphate (CS) in patients with PBS/IC.

Table 4 Gilberti *et al* (2013)

Citation	Giberti C, Gallo F, Cortese P, Schenone M. Combined intravesical sodium hyaluronate/chondroitin sulfate therapy for interstitial cystitis/bladder pain syndrome: a prospective study. <i>Ther Adv Urol.</i> 2013 Aug;5(4):175-9.
Objectives	The aim of this study was to verify the efficacy and safety of intravesical treatment combining sodium hyaluronate (HA) and chondroitin sulfate (CS) in patients with interstitial cystitis/bladder pain syndrome (IC/BPS).
Methods	Between February 2010 and May 2011, 20 consecutive women with IC/BPS were treated with intravesical instillations containing sodium HA (1.6%; 800 mg/50 ml) and sodium CS (2%; 1 g/50 ml) weekly for the first month, biweekly for the second month, and then monthly for at least 3 months. Before and after treatment, all patients filled in the Interstitial Cystitis Symptom Index and Problem Index (ICSI/ICPI), the Patient Health Questionnaire 9 and the Pelvic Pain and Urgency/Frequency Patient Symptom Scale (PUF). Treatment efficacy was assessed by comparing the pre- and post-treatment mean scores of the three questionnaires using Student's t test (p value <0.05 was considered significant).
Results	Statistically significant mean decreases in ICSI (from 13.0 to 9.3; p = 0.0003), ICPI (from 11.35 to 8.85; p = 0.0078) and PUF (from 20.0 to 15.75; p = 0.0007) questionnaire scores were seen. No cases of side effects or complications were observed. The mean follow-up was 5 months.
Conclusions	Despite the limitations of this study, the outcomes confirmed the role of combination therapy with HA and CS as a safe and effective option for the treatment of IC/BPS. Further randomized controlled studies with a higher number of patients and a longer follow-up period are needed to confirm these results.

The objective results of mid-term intravesical instillation of hyaluronic acid and chondroitin sulphate on urinary symptoms and bladder pain in 22 women diagnosed with PBS/IC were assessed by Porru *et al* (2012).

Table 5 Porru *et al* (2012)

Citation	Porru D, Leva F, Parmigiani A, Barletta D, Choussos D, Gardella B, Daccò MD, Nappi RE, Allegri M, Tinelli C, Bianchi CM, Spinillo A, Rovereto B. Impact of intravesical hyaluronic acid and chondroitin sulfate on bladder pain syndrome/interstitial cystitis. <i>Int. Urogynecol J.</i> 2012 Sep;23(9):1193-9.
Introduction with hypothesis	Intravesical instillations of hyaluronic acid (HA) and chondroitin sulfate (CS) may lead to regeneration of the damaged glycosaminoglycan layer in interstitial cystitis/bladder pain syndrome (IC/BPS).
Methods	Twenty-two patients with IC/BPS received intravesical instillations (40 ml) of sodium HA 1.6% and CS 2.0% in 0.9% saline solution (IALURIL, IBSA) once weekly for 8 weeks, then once every 2 weeks for the next 6 months.
Results	The score for urgency was reduced from 6.5 to 3.6 (p = 0.0001), with a reduction in pain scores from an average of 5.6 to 3.2 (p = 0.0001). The average urine volume increased from 129.7 to 162 ml (p < 0.0001), with a reduction in the number of voids in 24 h, from 14 to 11.6 (p < 0.0001). The IC Symptom and Problem Index decreased from 25.7 to 20.3 (p < 0.0001), and the Pain Urgency Frequency score, from 18.7 to 12.8 (p < 0.0001).
Conclusions	The treatment appeared to be effective and well tolerated in IC/BPS in this initial experience.

Cervigni *et al* (2016) conducted a randomised, open-label, multicentre study of the efficacy and safety of intravesical hyaluronic acid and chondroitin sulfate versus dimethyl sulfoxide in women with bladder pain syndrome/interstitial cystitis.

Table 6 Cervigni et al (2016)

Citation	Cervigni M, Sommariva M, Porru D, Ostaro E, Tenaglia R, Giammò A, Pappagallo G.A Randomized, Open-Label, Multicentre Study Of Efficacy And Safety Of Intravesical Hyaluronic Acid And Chondroitin Sulfate (Ha 1.6% And CS 2%) Vs. Dimethyl Sulfoxide (DMSO 50%) In Women With Bladder Pain Syndrome/Interstitial Cystitis (PBS/IC). <i>Neurological Urodynamics</i> 2016, 9999: 1-9
Hypothesis/ Aims of Study	This study compared the efficacy, safety, and costs of intravesical HA/CS (iAluRil®, IBSA) to dimethyl sulfoxide (DMSO, RIMSO® Bioniche).
Methods	This was a phase III, randomized, controlled study. An open-label design was adopted due to the garlic-like taste of DMSO after intravesical administration, which would have been impossible to mask. The study enrolled female patients aged 18 years or more with a diagnosis of BPS/IC unresponsive to first line non-invasive treatments (e.g., oral drugs considered to be a standard treatment for BPS/IC, such as antidepressants, antiepileptics, antihistaminics, cyclosporine-A, pentosan polysulfate) or at first observation. A total of 110 women with a mean age of 50.2 were randomized to receive thirteen weekly instillations (3 months) of HA (1.6%)/CS (2.0%) or 50% DMSO were given with a 2:1 allocation ratio (HA/CS:DMSO). Patients were evaluated at 3 (end-of-treatment) and 6 months. Primary endpoint was reduction in pain intensity at 6 months by visual analogue scale (VAS) versus baseline. Secondary efficacy measurements were quality of life and economic analyses.
Results	A total of 88 patients were evaluated of whom 61 had HA/CS and 27 had DMSO 22 patients, 15 (20.3%) in the HA/CS group and 7 (19.4%) in the DMSO group, withdrew before the end of the study). <ul style="list-style-type: none"> • A significant reduction in pain intensity was observed at 6 months in both treatment groups versus baseline (P < 0.0001) in the ITT population • A significant reduction in pain intensity at 6 months in favour of HA/CS in the PP population was observed with a mean VAS reduction of 44.77 versus 28.89, p = 0.0186 • There were significantly fewer treatment-related adverse events for HA/CS versus DMSO (1.4% versus 22.2%, p = .001).
Conclusions	This trial provides further support to previous data showing sustained improvement in symptoms following treatment of BPS/IC with HA/CS, in addition to subjective improvement in the quality of life and a more favourable safety profile compared with DMSO.

Recurrent urinary tract infections (rUTI)

In a multi-centre study carried out by Torella *et al* (2013), demonstrated iAluRil intravesical therapy is an effective therapeutic approach to prevent episodes of recurrent urinary tract infections.

Table 7 Multi-centre study by Torella et al (2013)

Citation	Torella M, Schettino MT, Salvatore S, Serati M, De Franciscis P, Colacurci N. Intravesical therapy in recurrent cystitis: a multi-center experience. <i>J Infect Chemother.</i> 2013 Oct;19(5):920-5. Epub 2013 May 7.
Hypothesis/ Aims of Study	Approximately 20-30% of women suffer from recurrent cystitis. Recently, the problem of bacterial internalization, especially by <i>Escherichia coli</i> , has been significantly emerging as the main cause of recurrent episodes. It is believed that such a process is favoured by damage to the urothelial mucous membrane. Concerning this, intravesical therapy with hyaluronic acid alone or in association with chondroitin sulfate was shown to improve urothelium thickness and reduction of bacterial load in the urine. The aim of the study was to assess whether intravesical therapy with hyaluronic acid (HA) and chondroitin sulfate (CS) is more effective than antibiotic therapy in reducing episodes and symptoms of recurrent urinary tract infections.
Methods	We compared the number of recurring episodes in three groups of patients affected by recurrent urinary tract infections assigned to three different therapeutic regimens: the first group was treated only with HA and CS, the second group with HA and CS associated with fosfomycin, and the third group was treated only with fosfomycin (F). We assessed the number of recurrent episodes for each patient that occurred during a 6- to 12-month follow-up.
Results	The results showed 72.7% of patients in the HA-CS group, 75% in the fosfomycin + HA-CS group,

Citation	Torella M, Schettino MT, Salvatore S, Serati M, De Franciscis P, Colacurci N. Intravesical therapy in recurrent cystitis: a multi-center experience. J Infect Chemother. 2013 Oct;19(5):920-5. Epub 2013 May 7.
	and only 30.4% in the fosfomycin group were event free at follow-up. The results were analyzed using the Fisher's exact test.
Conclusions	In conclusion, intravesical therapy with hyaluronic acid and chondroitin sulfate is an effective therapeutic approach to treat and prevent episodes of recurrent cystitis.

Based on a placebo controlled randomised trial by Damiano *et al* (2011), iAluRil intravesical instillations significantly reduced recurrent urinary tract infection rate without severe side effects while improving symptoms and QoL.

Table 8 Damiano et al (2011)

Citation	Damiano R, Quarto G, Bava I, Ucciero G, De Domenico R, Palumbo MI, Autorino R. Prevention of recurrent urinary tract infections by intravesical administration of hyaluronic acid and chondroitin sulphate: a placebo-controlled randomised trial. Eur Urol. 2011 Apr;59(4):645-51 Epub 2011 Jan 18. Erratum in Eur Urol. 2011 Jul;60(1):193.
Hypothesis/ Aims of Study	Urinary tract infection (UTI) is a prevalent condition in women during their lifetime with a high rate of recurrence within 3-6 months. Our aim was to investigate the efficacy and tolerability of the intravesical administration of combined hyaluronic acid (HA) and chondroitin sulphate (CS) in female patients with a history of recurrent UTI.
Methods	We conducted a prospective, randomised, double-blind, placebo-controlled study comparing the intravesical instillation of HA-CS with placebo in women with recurrent UTI. Participants were randomised to receive 50 ml of sterile sodium HA 1.6% and CS 2.0% solution (IALURIL®) weekly for 4 wk and then monthly for 5 mo. The primary end point of the study was defined as the mean number of UTI per patient per year. Participants were evaluated addressing UTI status/urinary symptoms and with a general health-related quality-of-life (QoL) questionnaire at baseline and after 3, 6, 9, and 12 mo.
Results	In the intention-to-treat analysis, 57 women were randomly allocated to HA-CS (n=28) or placebo (n=29). The UTI rate per patient per year at the end of the study (12 mo) (mean±SD: -86.6%±47.6 vs -9.6%±24.6; mean difference: 77%; 95% confidence interval, 72.3-80.8; p=0.0002) and the mean time to UTI recurrence (52.7±33.4 vs 185.2±78.7 d; p<0.001) were significantly reduced after treatment with HACS compared with placebo. Overall urinary symptoms and QoL measured by questionnaires significantly improved compared with placebo (Pelvic Pain and Urgency/Frequency questionnaire symptom score: 14.53±4.32 vs 9.88±6.77; p=0.004; SF-36 QoL score: 78.6±6.44 vs 53.1±4.72; p<0.001). No serious adverse event was reported.
Conclusions	Compared with placebo, HA-CS intravesical instillations significantly reduced UTI rate without severe side effects while improving symptoms and QoL over a 12-mo period in patients with recurrent UTI.

In a retrospective cohort multicentre study involving 7 European centres, clinical data and outcomes of patients who had undergone instillations of iAluril as a prophylaxis against rUTIs was collected demonstrating iAluril improves symptoms and quality of life in this patient group.

Table 9 clinical data and outcomes of patients who had undergone instillations of iAluril as a prophylaxis against rUTIs

Citation	Cicione A, Cantiello F, Ucciero G, Salonia A, Torella M, De Sio M, Autorino R, Carbone A, Romancik M, Tomaskin R, Damiano R. Intravesical treatment with highly-concentrated hyaluronic acid and chondroitin sulphate in patients with recurrent urinary tract infections: Results from a multicentre survey. Can Urol Assoc J 2014;8(9-10):e721-7.
Hypothesis/ Aims of Study	We assess the effectiveness of intravesical instillation of hyaluronic acid (HA) and chondroitin sulphate (CS) as a non-antibiotic treatment option for prophylaxis of recurrent urinary tract infections (UTIs) in female patients.
Methods	This was a retrospective cohort study involving 7 European institutions. We included patients with recurrent UTIs who received intravesical instillations of iAluRil (IBSA International) (50 mL HA 1.6% and CS 2% solution) between January 2010 and March 2012. Medication schedule,

Citation	Cicione A, Cantiello F, Ucciero G, Salonia A, Torella M, De Sio M, Autorino R, Carbone A, Romancik M, Tomaskin R, Damiano R. Intravesical treatment with highly-concentrated hyaluronic acid and chondroitin sulphate in patients with recurrent urinary tract infections: Results from a multicentre survey. <i>Can Urol Assoc J</i> 2014;8(9-10):e721-7.
	length of follow-up, recurrence infection time, number of UTIs/patients/year, patient quality of life, subjective symptoms score, and treatment emergent side effects were recorded and analyzed.
Results	In total, 157 women (mean age: 54.2 ± 4.1 years) were included in the analysis. All patients had at least 12 months follow-up. After 4 weekly and 5 monthly HACS bladder instillations, UTI episodes decreased from 4.13 ± 1.14 to 0.44 ± 0.50 (p = 0.01) at 12 months, while recurrent UTI time prolonged from 94.8 ± 25.1 days to 178.4 ± 37.3 days (p = 0.01) at 12 months. An improvement in symptoms and quality of life was achieved. A medium-depth pain after medication instillation was the most reported side effect. Regression model analysis showed significant risk factors in developing new UTI episodes: being more than 50 years old and having more than 4 UTI episodes per year (OR 3.41; CI 95%; 1.51-7.71, p = 0.003 and OR 3.31; CI 95% 1.51-7.22; p = 0.003, respectively). Retrospective design and lack of a control group represent two main limitations of the study.
Conclusions	Restoring glycosaminoglycans bladder layer therapy is a promising non-antibiotic therapy to prevent recurrent UTIs.

In a randomised study by De Vita *et al* (2013) iAluRil intravesical therapy was shown to significantly reduced cystitis recurrence, mean UTI recurrence time, and PUF total score.

Table 10 De Vita *et al* (2013)

Citation	De Vita D, Giordano S. Effectiveness of intravesical hyaluronic acid/chondroitin sulfate in recurrent bacterial cystitis: a randomized study. <i>Int Urogynecol J.</i> 2012 Dec;23(12):1707-13.
Hypothesis/Aims of Study	The glycosaminoglycan hyaluronic acid (HA) protects the urothelium; damage may increase bacterial adherence and infection risk. This study evaluated the effect of intravesical HA in recurrent bacterial cystitis (RBC).
Methods	Women with RBC were randomized to intravesical HA 800 mg and chondroitin sulfate (CS) 1 g (IALURIL, IBSA) in 50 mL of saline solution once weekly for 4 weeks then once every 2 weeks twice more (group 1) or long term antibiotic prophylaxis using sulfamethoxazole 200 mg and trimethoprim 40 mg once weekly for 6 weeks (group 2; control). Evaluations included: cystitis recurrence at 2 and 12 months; subjective pain symptoms (visual analog scale [VAS]); 3 day voiding; sexual function; quality of life (King's Health Questionnaire [KHQ]); frequency symptoms/frequency symptoms (PUF symptom scale); and maximum cystometric capacity (MCC). Means ± standard deviations were reported, with Mann-Whitney test for between-group comparison (significance P < .05).
Results	Of 28 women (mean age 60 ± 13 y) randomized, 26 completed follow-up (mean follow-up 11.5 mo). Group 1 showed a significant improvement in all evaluations; cystitis recurrence (1 ± 1.2 versus 2.3 ± 1.4, P = .02); 3-day voiding (mean 17.8 ± 3.5 vs 24.2 ± 8.3, P = .04); symptom VAS (1.6 ± 0.8 vs 7.8 ± 1.6, P < .001); PUF score (11.2 ± 2.7 vs 19.6 ± 2.2, P < .001), KHQ score (18.4 ± 7.2 vs 47.3 ± 13.6, P < .001), and MCC (380 ± 78 vs 229 ± 51 mL, P < .001) vs group 2 at 12 mo. No adverse effects were recorded.
Conclusions	Intravesical HA and CS in combination significantly reduced cystitis recurrence and improved urinary symptoms, quality of life, and cystometric capacity in RBC patients at 12 mo follow-up versus antibiotic prophylaxis. Study limitations include a small sample and relatively short follow-up.

De Vita *et al* (2013) also conducted a meta-analysis showing HA-CS in combination significantly reduced cystitis recurrence, mean UTI recurrence time, and PUF.

Table 11 De Vita *et al* (2013)

Citation	De Vita D1, Antell H, Giordano S. Effectiveness of intravesical hyaluronic acid with or without chondroitin sulfate for recurrent bacterial cystitis in adult women: a meta-analysis. <i>Int Urogynecol J.</i> 2013 Apr;24(4):545-52.
Hypothesis/Aims of	Glycosaminoglycan hyaluronic acid (HA) and chondroitin sulphate (CS) protect the urothelium. Damage to the urothelium may increase bacterial adherence and infection risk. This meta-

Citation	De Vita D1, Antell H, Giordano S. Effectiveness of intravesical hyaluronic acid with or without chondroitin sulfate for recurrent bacterial cystitis in adult women: a meta-analysis. <i>Int Urogynecol J.</i> 2013 Apr;24(4):545-52.
Study	analysis evaluated the effect of intravesical HA and HA and CS (HA-CS) combination therapy in recurrent bacterial cystitis (RBC) in adult women.
Methods	A systematic literature search was performed. Primary outcomes were urinary tract infection (UTI) rate per patient-year, and UTI recurrence time (days). Secondary outcomes were 3-day voids and Pelvic Pain and Urgency/Frequency (PUF) symptom scale total score.
Results	Four studies involving a total of 143 patients were retrieved and assessed in this analysis. Two were randomized, and two were nonrandomized. A significantly decreased UTI rate per patient-year [mean difference (MD) -3.41, 95 % confidence interval (CI) -4.33 to -2.49, $p < 0.00001$] was found. Similarly, pooled analysis showed a significantly longer mean UTI recurrence time (days) using either HA or HA-CS therapy (MD 187.35, 95 % CI 94.33-280.37, $p < 0.0001$). Two studies using HA and HA-CS therapy reported outcomes on 3-day voids, which were not significantly improved after therapy (MD -3.59, 95 % CI -8.43-1.25, $p = 0.15$), but a significantly better PUF total score (MD -7.17, 95 % CI -9.86 to -4.48, $p < 0.00001$) was detected in HA-CS groups.
Conclusions	Intravesical HA and HA-CS in combination significantly reduced cystitis recurrence, mean UTI recurrence time, and PUF total score. Study limitations include the small number of patients and possible bias. Further studies are needed to validate this promising treatment modality.

Radiation Induced Cystitis

A prospective study by Gacci *et al* (2016) demonstrated that bladder instillation therapy with hyaluronic acid and chondroitin sulphate improves symptoms of post radiation cystitis.

Table 12 Gacci et al (2016)

Citation	Gacci M. et al. Bladder instillation therapy with hyaluronic acid and chondroitin sulfate improves symptoms of post-radiation cystitis: prospective pilot study. <i>Clin. Genitourin. Cancer.</i> 2016 Feb 8. [Epub ahead of print]
Hypothesis/ Aims of Study	After radiotherapy (RT) for prostate cancer (PCa), several patients reported lower urinary tract symptoms (LUTS) due to damage and discontinuation of the glycosaminoglycan layer of the bladder. Instillation of hyaluronic acid and chondroitin sulfate (HA-CS) represents replenishment therapy of the glycosaminoglycan layer. The aim of the study is to evaluate the efficacy and safety of HA-CS in men with symptomatic cystitis after RT for PCa.
Methods	Eighty consecutive men were treated with RT for PCa; 30 of these (37.5%) reported clinically relevant LUTS and associated bother as measured by the Interstitial Cystitis Symptom Index and Problem Index (ICSI/ICPI) Questionnaire 3 months after RT. Symptomatic patients received instillation therapy with HA-CS weekly for the first month and then at weeks 6, 8, and 12. All patients completed the ICSI/ICPI questionnaire before and after RT and at the end of HA-CS treatment.
Results	HA-CS significantly reduced post-radiation LUTS ($P < 0.001$) and bother ($P=0.006$). Age, Gleason score, and radiation dose were the main determinants of worsening of LUTS after radiation (ICSI score baseline vs. post-radiation: $P=0.047$, 0.043 , and 0.023). In multivariate analysis, only age influenced LUTS worsening after RT ($P=0.01$). Age, radiation dose, and radiation toxicity were related to recovery of LUTS (ICSI score post-radiation vs. post HA-CS $P=0.041$, $P=0.050$, and $P=0.046$). In multivariate analysis, no factor was statistically significant.
Conclusions	A remarkable worsening of symptoms and bother was observed after RT. HA-CS instillation is a safe treatment and resulted in an improvement of LUTS irrespective of age and clinical features, with full recovery of urinary bother.

Expected Utilisation

PBS/IC

PBS/IC		Reference
Australian population	24,000,000	ABS population clock (2016)
Estimated prevalence	2% - 17.3%	Davis et al, 2015
Prevalence meeting diagnostic criteria	0.10%	Payne et al, 2007
Estimated prevalence	24,000	-
Estimated diagnosed	30%	Data on file - discussions with key opinion leaders
Estimated patients eligible for iAluRil %	99%	Data on file - discussions with key opinion leaders
Patients eligible number	7,128	-
Estimate patients willing for iAluRil bladder instillation	90%	Data on file - discussions with key opinion leaders
Estimated patients private insurance	47%	APRA (2015)
Estimated private patients seeking help	60%	
Total eligible population	3,028	

rUTIs

rUTIS		
Australian population	24,000,000	ABS population clock (2016)
Incidence of UTI	1.14%	Chung et al (2014)
UTI incidence pa	272,727	
Meeting rUTI criteria (2+/6 months)	25% -35%	Ronald A et al (2002); Foxman B et al (2000); Bassi et al (2011)
rUTI rate median	30%	
Ongoing/chronic rUTIs	10%	Ronald A et al (2002); Foxman B et al (2000); Bassi et al (2011)
Estimated patients eligible for iAluRil %	85%	Data on file - discussions with key opinion leaders
Patients eligible number	6,955	
Estimate patients willing for iAluRil bladder instillation	20%	Data on file - discussions with key opinion leaders
Estimated patients private insurance	47%	APRA (2015)
Estimated patients in private setting	60%	
Total eligible population	835	

Radiation induced cystitis

Radiation induced cystitis		
Australian population	24,000,000	ABS population clock (2016)
Rate of pelvic radiation	26,000	Data on file
Incidence of radiation induced cystitis	23%-80%	Brown et al(2015)
Incidence median	52%	
Short term cure rates	76%-95%	Brown et al(2015)
Short term cure rate median	86%	
Chronic rates (+2 months)	15%	
Estimated patients eligible for iAluRil %	99%	Data on file - discussions with key opinion leaders
Patients eligible number	1,922	
Estimate patients willing for iAluRil bladder instillation	95%	Data on file - discussions with key opinion leaders
Estimated patients private insurance	47%	APRA (2015)
Estimated patients in private setting	47%	
Total eligible population	862	

4. Intervention – proposed medical service

The Product

iAluRil® is a sterile solution of sodium hyaluronate (1.6 % - 800 mg/50 mL) and sodium chondroitin sulphate (2 % - 1 g /50 mL) for intravesical instillation.

The urothelium is covered by a layer of polyanionic molecules mainly made up of glycosaminoglycans (GAGs). This is a class of aminosugars which form an impermeable, protective and neutralizing barrier against the toxic and irritating substances present in urine (e.g. bacteria, microcrystals, proteins, ionic and non-ionic residue etc.), preventing them from being reabsorbed at systemic level.

Of the GAGs that form this barrier, chondroitin sulphate and hyaluronic acid play a central role in its functioning.

Qualitative and quantitative variations at various levels of the two GAGs deactivate the barrier effect, causing a series of conditions which can foster the onset of cystitis's of various kinds (e.g. interstitial cystitis, recurring cystitis's caused by infections, cystitis's induced by antitumoral agents, cystitis's induced by radiation, traumatic cystitis's).

iAluRil is a balanced association of sodium hyaluronate, chondroitin sulphate and calcium chloride, can be functionally integrated into the barrier thanks to the action of the calcium chloride, re-establishing its protective function (Approved Australian product information, July 2014).

The procedure

After the patient has urinated spontaneously, the bladder is emptied of all traces of urine by inserting a suitable sterile catheter through the external urethral meatus and wait for the full leakage of urine collected in the bladder (use of an 8 Ch catheter is recommended during this stage);

- The plunger rod is screwed into the pre-filled syringe until it is perfectly in place.
- The Luer-Lock Adapter is mounted on the top of the pre-filled syringe and applied on the sterile catheter previously placed in the bladder.
- The iAluRil solution contained in the syringe is gently instilled into the bladder through the catheter.
- The iAluRil solution is held in the bladder for as long as possible (minimum time recommended: 30 minutes) then voided into any toilet (no specific discharge requirements necessary as the product is non-toxic).

The patient is able to walk around and continue normal daily function after instillation of the iAluRil and no specific clinical care is required after instillation.

Dosage regimen and duration

The TGA approved dosing regimen is as follows:

- One instillation a week the first month
- One instillation every two weeks the second month
- In the following months, one instillation a month until the stable remission of the symptoms.

Replenishment of the GAG layer occurs gradually and is therefore not immediate. It is important the patient receives the full course of at least 7 instillations to achieve maximum bladder wall healing effect. Stable remission of symptoms is normally seen around 6 - 8 weeks. As such duration is expected to be a minimum of 12 weeks as per TGA approved indication (i.e. week, 1, 2, 3, 4, 6, 8 and 12)

For PBS/IC it is standard clinical practice for patients to receive the full recommended course of therapy (i.e. in this instance 7 doses over 12 weeks) to determine whether a satisfactory response has been achieved. At this stage, a review is completed to determine whether further instillations are necessary or appropriate.

For rUTIs, patients would initially receive full recommended course of therapy (i.e. in this instance 7 doses over 12 weeks) and then once monthly for 1 month (i.e. total of 8 doses). The requirement for further instillations would then be reviewed on an ongoing/recurrence basis - this watch and wait is standard clinical practice for this patient group.

For post-radiation cystitis, treatment will be as per the TGA approved indications for an initial treatment course (and in line with the key clinical evidence) being 7 instillations over 12 weeks, on the following schedule - week, 1, 2, 3, 4, 6, 8 and 12.

Treatment delivery

- Frequency of use: Re-treatment could be considered appropriate upon recurrence or deterioration of symptoms if a maintenance regimen has not been implemented.
- Duration of use: After 8 weeks should no significant reduction in symptoms be seen, treatment would be stopped.
- Clinical setting: Administration will be performed in the specialist consulting rooms, in private hospitals and aged care facilities – places where urethral catheterization can competently take place by trained personnel.
- Pre-procedure patient preparation: Minimal – light sedation for some patients.
- Personnel performing the procedure; Urologist, uro-gynaecologists, gynaecologists, urology nurses (under supervision), and other clinical practitioners trained in urothelial catheterisation.
- Additional equipment or product required for performing the procedure: 8Ch catheter, sterile swab for cleaning urethral opening, anaesthetic gel for catheter insertion, jar for excess urine collection).
- Additional training required before medical staff can administer the product: Nil.

This service is not for investigative purposes.

This service includes the use of a registered trademarked device, iAluRil®. This product contains sterile solution of sodium hyaluronate (1.6% - 800 mg/50 mL) and sodium chondroitin sulphate (2% - 1 g/50 mL). Delivery as a 50 mL pre-filled syringe for intravesical instillation.

Proposed Setting

The proposed setting for the delivery of this service is outpatient settings such as clinics or consulting rooms. The product can also be used in a hospital in-patient setting.

Details of the delivery of this service include:

- The procedure is to be performed by qualified personnel under controlled and sterile conditions.
- The procedure can be performed in clinic/surgery rooms by a trained nurse, general practitioner or urologist, or in a hospital setting by adequately trained staff.
- The intended treatment duration is 12 weeks (7 instillations) or longer depending on the severity of symptoms and chance of remission.
- iAluRil is instilled directly into the bladder using a thin tube (in/out catheter) that is passed through the urethra into the bladder. Note: An in/out catheter is used rather than an indwelling catheter.

5. Co-dependent information

Not applicable.

6. Comparator – clinical claim for the proposed medical service

Painful Bladder Syndrome / Interstitial Cystitis (PBS/IC)

This service will be provided as an alternative to bladder instillation using either dimethyl sulfoxide (DMSO), and to be utilised before more serious invasive interventions such as surgery or neuromodulation.

In the case of DMSO, it is claimed that iAluRil is as effective (non-inferior) to DMSO with fewer side effects.

Recurrent urinary tract infection (rUTI)

It is intended that this service will be eligible to provide once the patient has met the NPS defined criteria of recurrent UTIs, and is to be used in place of the chronic use of oral antibiotics to prevent (not to treat) rUTIs.

It is claimed that iAluRil is more effective than antibiotics in the medium to long-term prevention of rUTIs (superior effect) and offers a treatment that is at least as safe (i.e. no-inferior) with the benefit of reducing antibiotic induced resistance in society. This was demonstrated in a study by Torella et al (2013) previously mentioned.

The comparator antibiotic in this study was fosfomycin, an antibiotic not registered in Australia but available under SAS. However, the key point to note is that by the way iAluRil works, it changes the bladder pathology to help prevent rUTIs. This contrasts with antibiotics which are used to treat infections once they have reoccurred or keeping them (when they work) subclinical.

De Vita 2012 shows Intravesical HA and CS in combination significantly reduced cystitis recurrence and improved urinary symptoms, quality of life, and cystometric capacity in recurrent bacterial cystitis patients at 12-month follow-up versus antibiotic prophylaxis using sulfamethoxazole 200 mg and trimethoprim 40 mg.

Long-term prophylaxis and use of recommended antibiotics has two significant issues:

- Facilitating the development within the community of antibiotic resistant organisms, and which goes against good antimicrobial stewardship philosophies;
- A range of side effects ranging from digestive issues to more significant injuries. For example, the antibiotics listed below and recommended for treating/preventing rUTIs long term commonly cause the problems noted:
 - Cephalexin - diarrhoea, dizziness, tiredness, headache, stomach upset, abdominal pain, joint pain, vaginal itching or discharge, nausea/vomiting, itching/swelling, and rash, and
 - Trimethoprim+sulphamethoxazole - severe itching, rash, sun-sensitivity.

Radiation induced cystitis

This therapy 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.

It is claimed, that treatment with iAluRil 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.

The efficacy in reducing these symptoms is demonstrated in the study by Gacci *et al* (2016) where iAluRil significantly reduced post-radiation LUTS ($P < 0.001$) in patients who suffered from post-radiation cystitis, three months after radiation therapy.

7. Expected health outcomes relating to the medical service

Expected patient relevant health outcomes

Painful Bladder Syndrome / Interstitial Cystitis (PBS/IC)

The primary health outcomes (effect) when the proposed therapy is used for PBS/IC will be measured in terms of:

- decrease in bladder/pelvic pain;
- decrease in urinary urgency;
- decrease in urinary frequency; and
- improved health related quality of life.

Recurrent urinary tract infection (rUTI)

The primary health outcomes (effect) when the proposed therapy is used for rUTIs will be measured in terms of:

- reduction in the rates of urinary tract infections over 12 months (i.e. mean number of UTI per patient per year);
- reduction in the use of antibiotics and direct and potential long term social related side effects (e.g. increased resistance); and improved health related quality of life.

Radiation induced cystitis

The primary health outcomes (effect) when the proposed therapy is used in radiation induced cystitis will be measured in terms of:

- reduction in urinary urgency;
- reduction in urinary frequency;
- reduction in nocturia; and
- improved health related quality of life.

Potential risks identified

Irrespective of use, the potential risk to the patients in receiving iAluRil includes the following:

- medium depth pelvic pain felt immediately following each instillation
- UTI (likely associated with repeat catheterisation)
- Urinary storage symptoms (muscular hypertone induced by pain).

Of note, according to post-marketing experience, urinary storage symptoms (increased frequency and urgency) have been recorded with very rare frequency.

Type of economic evaluation.

The economic evaluation will be a cost-effectiveness / cost-utility analysis.

8. Fee for the proposed medical service

As a service rendered in an outpatient setting, the type of funding proposed for this service is a fee, payable to the service provider. It is intended that an application seeking the inclusion of iAluRil on the Prostheses List will also be submitted.

As with all new MBS Items, the proposed fee for this service will be based on the time taken, the degree of difficulty and the expertise required to perform the service and will be in line with the MBS fee for 'similar' services.

The proposed service fee will accommodate the following:

Professional Time

- Treating physician or urology nurse: total estimated at 20 minutes (which includes initial patient discussion (5 minutes), preparation of materials (10 minutes), and instillation (5 minutes)).

Due to the anxiety and pain sometimes associated with these conditions and the area of catheterisation, some patients may also require a pre-instillation admission of a light oral sedative (30 mins prior), adding to the total patient engagement time.

Consumables

- IAluRil (at this point in time) per instillation ranges between \$215 - \$235 depending upon pharmacy markup.
- In/out catheter <\$10
- Latex/rubber gloves <\$1
- Chlorhexidine solution (prep solution) <\$1
- Container for residual urine collection <\$1
- Sterile drapes < \$5

Concomittant medications

- Anaesthetic gel (KY gel or lignocaine syringe) <\$2
- Light oral sedative <\$1

Relevant peri-procedure costs

- NA.

It is anticipated that the MBS scheduled fee will be greater than:

MBS item 36800

BLADDER, catheterisation of, where no other procedure is performed Fee:

\$27.60 Benefit: 75% = \$20.70 85% = \$23.50

and 'similar to':

MBS Item 11921

BLADDER WASHOUT TEST for localisation of urinary infection not including bacterial counts for organisms in specimens

Fee: \$75.05 Benefit: 75% = \$56.30 85% = \$63.80

9. Clinical Management Algorithm - clinical place for the proposed intervention

Painful Bladder Syndrome / Interstitial Cystitis (PBS/IC)

Existing clinical practice

Treatment strategies after diagnosis should proceed from conservative ones to more invasive therapies as outlined below.

Diagnosis

- Bladder hydrodistension.

Conservative approaches

- Diet changes: avoid food that triggers symptoms (eg. spicy foods, alcohol, caffeine).
- Altering the concentration or volume of urine, whether by fluid restriction or additional hydration.
- Pelvic floor muscle relaxation / avoid pelvic floor strengthening exercises.
- Bladder retraining with urge suppression.
- Manual physical therapy (trigger point release by physiotherapist).

Application of

hypersensitivity

Up Strategies to manage flare

Multimodal pain management

- May involve medications, stress management or manual therapy.
- A pain specialist is usually involved.
- It is difficult to predict which pain medication is most effective; this may require a trial of different medications.

Oral medications

- Tricyclic antidepressants - Some examples are amitriptyline, imipramine. Side effects are fatigue, drowsiness, weight gain, dry mouth (a third of patients cannot tolerate this).
- Sodium pentosan polysulfate (Elmiron) - Acts by aiding the repair of defects in the bladder mucosa. A course of three to six months is needed to demonstrate an effect. At a dose of 100mg three times a day, it is well tolerated and has few side effects.

Bladder hydrodistention

- Whilst sometimes undertaken as part of diagnosis, it can also relieve symptoms in about half of patients. Weeks or months of relief may follow, and the procedure can be repeated if successful.

Bladder instillation therapy

- Multiple therapies are usually required. This route of administration provides high drug concentrations in the bladder and avoids systemic side effects. Long term remission is achievable in a few patients, but most will relapse eventually and need more treatments. Examples of these medications that are currently used in Australia are dimethyl sulfoxide (DMSO), Clorpactin, heparin (sometimes mixed with DMSO). Steroids mixed with DMSO and BCG, an agent used to stimulate the bladder's immune system.

Surgery

When all else fails, and particularly when the patient has a progressive condition where they are losing bladder volume, surgery can be considered. Types of surgery include

- Sacral neuromodulation. Electrodes are implanted in the lower back which block nerves that transmit pain from the bladder. This procedure should be carried out in specialist centres.
- Urinary diversion (ileal conduit). This operation allows urine to by-pass the bladder and be collected in a bag on the outside of the abdominal wall. Despite the body image issues created by this option, many patients value the freedom it gives them because they do not have to worry about proximity to a toilet. Over time some people who have had this operation may suffer deterioration of their kidneys.
- Bladder reconstruction. Part or all of the bladder is removed and then reconstructed from a segment of the bowel. This expands the capacity of the bladder but pain may persist.
- Bladder removal (cystectomy). Very occasionally, when pain persists despite urinary diversion, the bladder may be removed. Even still pain can persist.

Please refer to the copy of the American Urological Association treatment algorithm for interstitial cystitis provided at the end of this document. (AUA, 2016)

Proposed clinical practice

- The proposed clinical management algorithm is the same as the current clinical management algorithm except for the inclusion of the intravesical instillation of sodium hyaluronate with sodium chondroitin sulphate (iAluRil) as an alternative to the currently used bladder instillations of dimethyl sulfoxide (DMSO).

Treatment algorithm for Recurrent Urinary Tract Infection (rUTI)

Existing clinical practice

Investigations

- Clinicians should confirm the diagnosis and look for a cause in adults with recurrent urinary tract infections. Risk factors include sexual activity (including anal intercourse), contraceptive devices (such as intrauterine devices), hormonal deficiency in postmenopausal women, diabetes, foreign objects (including bladder calculi), secretory type of certain blood groups and urinary tract obstruction (including benign prostatic hyperplasia or pelvic organ prolapse). Recurrent infections can be due to bacterial persistence or re-infections. It is important to have an adequate course of antibiotics and repeat urine microscopy, culture and susceptibility tests after treatment is completed to ensure clearance of the organism. Consider an ultrasound of the urinary tract to exclude structural abnormality and document complete bladder emptying. Therapeutic strategies include low-dose antibiotic prophylaxis and patient-initiated antibiotics guided by symptoms, although this should be only undertaken following comprehensive assessment as long-term antibiotics should preferably be avoided.

Individualised treatment programmes

- Clinician prescribed antibiotics as occurs.
- “Self-start antibiotics”- starting antibiotics at home AFTER taking a urine specimen (MSU) to confirm infection.
- Preventive antibiotics- a longer course of low dose antibiotics to help eradicate troublesome urinary tract bacteria which can help break the cycle of recurrent urinary tract infection.

Proposed clinical practice

- The proposed clinical management algorithm is the same as the current clinical management algorithm except for the inclusion of the intravesical instillation of sodium hyaluronate with sodium chondroitin sulphate (iAluRil) as an alternative to the currently used antibiotics

Investigations

- Clinicians should confirm the diagnosis and look for a cause in adults with recurrent urinary tract infections. Risk factors include sexual activity (including anal intercourse), contraceptive devices (such as intrauterine devices), hormonal deficiency in postmenopausal women, diabetes, foreign objects (including bladder calculi), secretory type of certain blood groups⁷ and urinary tract obstruction (including benign prostatic hyperplasia or pelvic organ prolapse). Recurrent infections can be due to bacterial persistence or re-infections. It is important to have an adequate course of antibiotics and repeat urine microscopy, culture and susceptibility tests after treatment is completed to ensure clearance of the organism. Consider an ultrasound of the urinary tract to exclude structural abnormality and document complete bladder emptying. Therapeutic strategies include low-dose antibiotic prophylaxis and patient-initiated antibiotics guided by symptoms, although this should be only undertaken following comprehensive assessment as long-term antibiotics should preferably be avoided.

Bladder instillation therapy

- Intravesical instillation of sodium hyaluronate with sodium chondroitin sulphate (iAluRil)

Individualised treatment programmes

- “Self-start antibiotics”- starting antibiotics at home AFTER taking a urine specimen (MSU) to confirm infection.
- Preventive antibiotics - a longer course of low dose antibiotics to help eradicate troublesome urinary tract bacteria which can help break the cycle of recurrent urinary tract infection.

Treatment algorithm for Radiation Induced Cystitis (generalised)

Existing clinical practice

The paucity of high quality evidence in the form of randomized control trials makes development of meaningful evidence based treatment algorithms difficult and include the following:

- Systemic treatments such as TCDO/WF10, flavoxate hydrochloride, cranberry juice, conjugated oestrogen

- Intravesical treatments such as botulinum toxin A, Hyaluronic acid +/-chondroitin sulphate, formalin, polydeoxyribonucleotides, early placental extract, DMSO, clorpectin, early placental extract.
- Hyperbaric oxygen
- Interventional procedures such as surgery and laser.

Specifically, the treatment of radiation-induced cystitis is currently essentially symptomatic, consisting of trying to control the episodes of haematuria, then additional oral medication to reduce pain and urinary urgency and frequency.

Treatment of Radiation Induced Haematuria (specifically)

- Initial management includes intravenous fluid replacement, blood transfusion if indicated and transurethral catheterization with bladder washout and irrigation.
- Oral or parenteral agents that can be used to control haematuria include conjugated estrogens and pentosan polysulfate.

Cystoscopy with laser fulguration or electrocoagulation of bleeding points is sometimes effective. Several treatments of varying specificity have been proposed in order to decrease the episodes of haematuria. The treatments most frequently used are intravesical instillations of formalin, prostaglandins, silver nitrate or alum with an efficacy on symptoms of about 70%.

Another more recent treatment option is hyperbaric oxygen therapy, which allows better tissue diffusion of oxygen, improving neo-angiogenesis by increasing the vascular density of irradiated tissues. Hyperbaric oxygen therapy involves the administration of 100% oxygen at higher than atmospheric pressure for 1-2 hours, 30-50 times. The reported success rate for radiation cystitis varies from 60% - 92%. This technique is effective in about 80-90% of cases with a lasting effect. It allows objective improvement of the bladder mucosa.

In severe cases of persistent haematuria, more aggressive treatment options include selective embolization or ligation of the internal iliac arteries. Surgical options include urinary diversion by percutaneous nephrostomy or intestinal conductivity with or without cystectomy.

Treatment of pain and urgency/frequency

- Oral medications – Solifenacin, Oxybutynin, Mirabegron, Tolterodine
- Oral analgesic including Paracetamol and Codeine

All the above treat the symptoms, not the cause.

GAG layer restoration therapy of sodium pentosane polysulfate (oral) may also be considered however this requires a course of three to six months to demonstrate an effect.

Bladder instillation of lidocaine.

Proposed clinical practice

The proposed clinical management algorithm is the same as the current clinical management algorithm except for the inclusion of the intravesical instillation of sodium hyaluronate with sodium chondroitin sulphate (iAluRil) should the patients have an inadequate response to the oral medications for treating pain, urgency, frequency and nocturia, or should treatments primarily directed at treating haematuria (e.g. hyperbaric oxygen) also have had an inadequate secondary response.

10. Proposed Questions for Public Funding

Usage

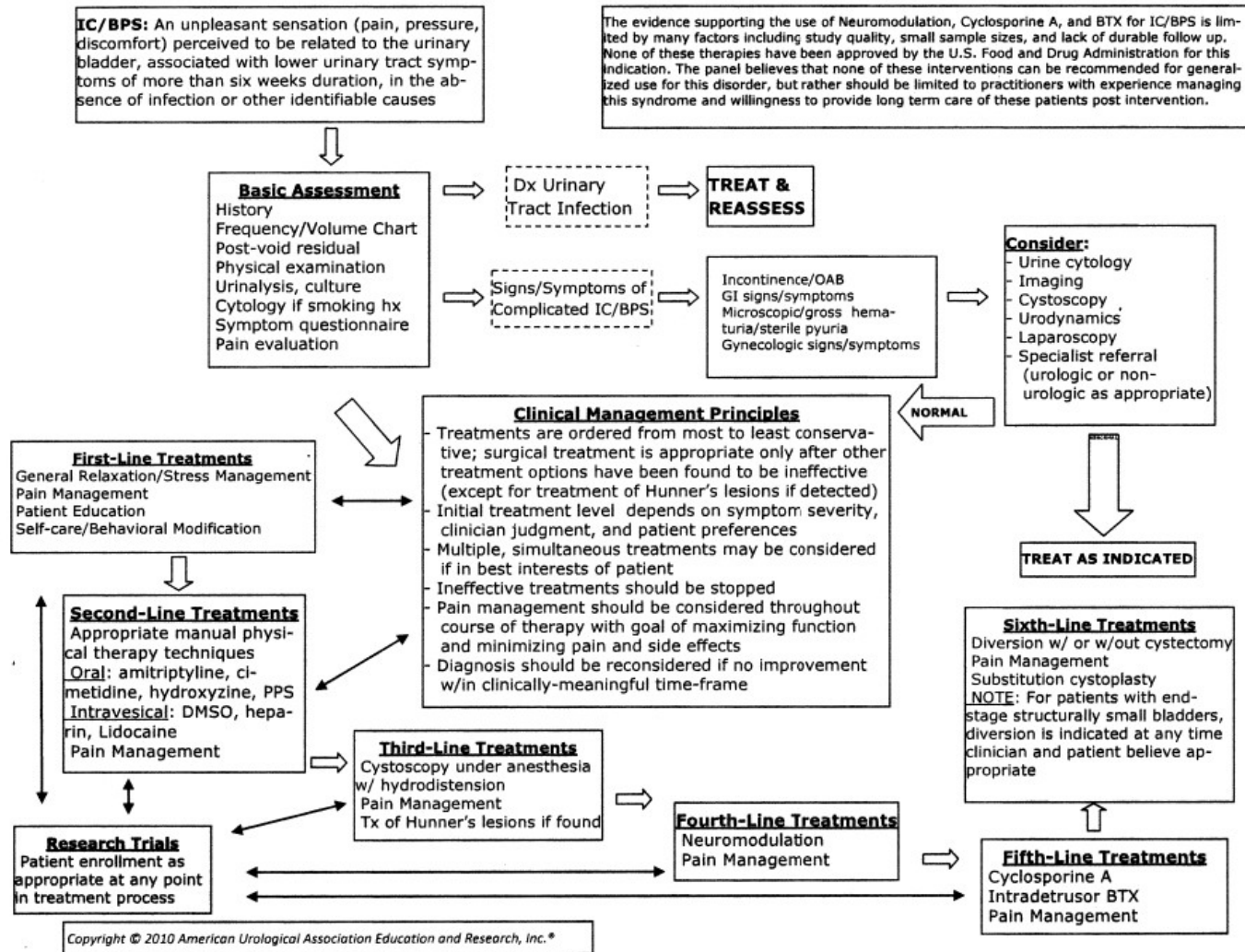
1. What proportion of patients would be eligible for the proposed treatment?
2. What proportions of patients would have conditions meeting the clinical/diagnostic definitions for PBS/IC, rUTI and radiation induced cystitis?
3. What proportions of patients would use the alternative comparison therapy (to be specified)?
4. What proportions of patients would meet the eligibility criteria for receiving the proposed service?

Efficacy

5. What is the efficacy of iAluRil instillation compared to each comparator for PBS/IC, rUTI and radiation induced cystitis?
6. How translatable are the results of the evaluation of the clinical studies to the context of the requested listing in Australia?
7. What is the evidence for sustained efficacy relative to the comparator?
8. What is the evidence for short-term and long-term safety profiles of iAluRil instillation relative to each comparator for PBS/IC, rUTI and radiation induced cystitis?

Resource utilisation

9. What is the resource utilisation associated with the use of iAluRil, including peri-procedure period, relative to the comparators for PBS/IC, rUTI and radiation induced cystitis?
10. What is the cost effectiveness of iAluRil, compared to the comparators for PBS/IC, rUTI and radiation induced cystitis.



33

Figure 1 - American Urological Association treatment algorithm for interstitial cystitis (AUA, 2016)

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