North Staffordshire and Stoke-on-Trent Area Prescribing Committee

Medicine Review Summary

iAluril® bladder irrigation (sodium hyaluronate 800mg, chondroitin 1g in 50ml water with calcium chloride 440mg)

Verdict:	
Formulary inclusion:	Not approved by the Area Prescribing Committee (APC) for inclusion in the North Staffordshire Joint Formulary
Formulary category:	Grey – not suitable for inclusion in the North Staffordshire Joint Formulary.
Prescribing restrictions	Non- formulary
Reason for not including in the North Staffordshire Joint Formulary:	This medication has been reviewed by the New Medicines Committee and the Area Prescribing Committee and found not to be suitable for inclusion in the Joint Formulary due to inadequate or weak evidence for efficacy. Prescribers can consider this medication where formulary alternatives are unsuitable, ineffective or not tolerated.
Link to formulary:	Primary care: http://www.northstaffordshirejointformulary.nhs.uk/ Secondary care: http://uhns/clinicians/clinical-guidance/clinical-guidelines/prescribing-formularies/
Link to medicine review summary:	Primary care: https://www.stokeccg.nhs.uk/stoke-governance/policies/medicines-optimisation/formulary-review-and-verdict-sheets Secondary care: Trust Intranet→ Clinicians→ Support services → Pharmacy → Joint Formulary Related Documentation → North Staffordshire & Stoke-on-Trent Area Prescribing Committee Medicine Review Summary Verdict Sheets
Link to full review:	Primary care: https://www.stokeccg.nhs.uk/stoke-governance/policies/medicines-optimisation/formulary-review-and-verdict-sheets Secondary care: Trust Intranet→ Clinicians → Support Services → Pharmacy → Joint Formulary Related Documentation → New Medicine Committee (NMC) Medicines Reviews

Review summary:

Formulary application:

An application to include iAluril® bladder instillation in the North Staffordshire Joint Formulary was presented to the New Medicines Committee on 02/10/2019. Ms Mistry-Pain, consultant urologist at UHNM, attended the NMC meeting to support the application. The application is also supported by Mr Anurag Golash, consultant urologist at UHNM.

Licensed indications:

iAluril® is a bladder instillation indicated for the temporary replenishment of the glycosaminoglycan (GAG) layer in the following bladder conditions; interstitial cystitis , painful bladder syndrome (PBS), cystitis caused by recurrent UTIs, and chemical, trauma or radiation induced cystitis. Replacement of the GAG layer results in symptomatic relief through regulation of the permeability of the bladder wall, containment of the inflammatory response, and

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supporting wound healing.

Dosing:

The licensed dosage is administration once weekly for the first month, followed by one instillation every two weeks for the second month. In the following months, one instillation a month should be

given until symptoms resolve to the satisfaction of both the clinician and patient.

The urology team at UHNM are proposing the following dosage regimens

PAINFUL BLADDER SYDNROME

iAluril is administered once a week for four weeks, then at weeks 6 and week 8. If the patient reports a satisfactory reduction in symptoms (> 20% improvement in O'Leary Sant questionnaire score), then administrations will occur monthly until resolution is achieved. Patients will be assessed every 3 months by a urology CNS, with consultant review every 6 months. Some patients may only need one maintenance instillation every 2 or 3 months depending on symptoms

RADIATION INDUCED CYSTITIS

iAluril is administered once a week for 4 weeks, then at weeks 6, 8 and 12.

CHEMICAL INDUCED CYSTITIS (INCLUDING BCG)

iAluril is administered once weekly for 8 weeks

RECURRENT UTI

iAluril is administered once weekly for 4 weeks, then once a month for 5 months.

Administration

iAluril can be administered via a catheter or iAludaptor® (included in pack). Patients can be trained to self-administer.

Administration via the catheter (with a Luer Lock adaptor)

1.After the patient has urinated spontaneously, empty the bladder of all traces of urine by inserting a suitable sterile catheter through the external urethral meatus and wait for all the urine in the bladder to be evacuated (use of an 8 Ch catheter is recommended during this stage).

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2.Screw the plunger rod supplied with the prefilled syringe, until it is perfectly in place.

3.Mount the Luer-Lock adapter on the top of the prefilled syringe and apply onto it the sterile catheter previously placed in the bladder.

4.Instill all the solution contained in the syringe into the bladder through the catheter.

5.Keep iAluRil in the bladder for as long as possible (minimum time recommended is 30 minutes).

Administration via the iAluadapter®

1. The patient urinates spontaneously.

2. Screw the plunger rod supplied with the prefilled syringe, until it is perfectly in place.

3. Fasten the iAluadapter® to the top of the prefilled syringe.

4. Instil all the solution contained in the syringe into the bladder through the iAluadapter®.

5. Keep iAluRil in the bladder for as long as possible (minimum time recommended is 30 minutes)

Related guidance:

National Guidelines

The Royal College of Obstetricians and Gynaecologists (RCOG) in conjunction with the British Society of Urogynaeocology (BSUG) – Management of Bladder Pain Syndrome (Joint RCOG and BSUG Greentop Guideline 70) – published 09/12/2016.

If conservative or oral treatment has failed, other therapies such as bladder instillations can be substituted or added. Recommended options include intravesical hyaluronic acid and intravesical chondroitin sulphate. The grade of recommendation for hyaluronic acid, and thus robustness of evidence, is higher (B) than for chondroitin sulphate (D).

NICE Guidance

BLADDER PAIN SYNDROME / INTERSTITIAL CYSTITS

There are no current NICE guidelines for treatment of painful bladder syndrome or interstitial cystitis.

RECURRENT UTIS

NG 112 (Urinary Tract Infections – recurrent – antibiotic prescribing – October 2018) recommends patients are

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referred to a specialist in the following scenarios

•men aged 16 years and over

•people with recurrent upper UTI

•people with recurrent lower UTI when the underlying cause is unknown

•pregnant women

•children and young people under 16 years in line with the NICE guideline on urinary tract infection in under 16s

•people with suspected cancer in line with the NICE guideline on suspected cancer: recognition and referral.

The above guidelines do not review use of bladder instillations for recurrent UTI.

International guidelines

The EAU Guidelines for Chronic Pelvic Pain 2019 recommends intravesical treatments such as hyaluronic acid and chondroitin sulphate (i.e. iAluril®) for bladder pain syndrome before more invasive options are considered. The EAU acknowledges that despite intravesical GAG replenishment being prescribed for about twenty years for BPS/IC, most available studies are uncontrolled with small number of patients. The evidence behind this recommendation is thus considered by the EAU to be weak, as most available studies are non-randomised, lack a placebo arm, and/or have small study numbers.

Local Guidelines

The UHNM Guideline for the Investigation and Management of Bladder Pain Syndrome in women (2018) recommends bladder instillations such as sodium hylauronate if oral treatment (amitriptyline, cimetidine) is ineffective or not tolerated. Sodium hyaluronate instillations are recommended weekly for the initial 6 weeks, followed by monthly instillations for 3 months. If there is no response after 6 weeks, it is recommended that treatment is discontinued.

Background information:

PAINFUL BLADDER SYNDROME (formerly known as INTERSTITIAL CYSTITIS) AND RADIATION/CHEMICAL INDUCED CYSTITIS

Bladder pain syndrome (BPS) can result from depletion of the bladder epithelium due to trauma or recurrent infection. Symptoms include increased urinary frequency, urinary urgency and pain or stinging upon urination. This can have significant impact on quality of life.

The current pathway for treatment of bladder pain syndrome and radiation or chemical induced cystitis is as

below. Introducing iAluril® to the NSJF will provide a 2nd line bladder instillation option for patients who do not respond satisfactorily to options available in the current pathway.

Patients with painful bladder syndrome, chemical or radiation induced cystitis are currently offered a trial of the following treatment options

1. Lifestyle modification (e.g. caffeine reduction, bladder retraining, FODMAP diet)
2. Physiotherapy, psychosocial support and support groups
3. Mirabegron and anticholinergics
4. Tamsulosin
5. Analgesia e.g. NSAIDs and amitriptyline
6. Cytoscopic fulguration of Hunners lesions, ulcers

If the above treatments are ineffective, patients may be offered a course of Hyacyst® bladder instillations (sodium hyaluronate 40mg weekly for 4 weeks). If there is a satisfactory reduction in symptoms (> 20% reduction in O'Leary Sant score compared to baseline), patients will continue on 40mg sodium hyaluronate once per month until satisfactory symptom resolution.

If patients achieve < 20% symptom reduction on sodium hyaluronate 40mg, dose can be escalated to 120mg once weekly for 4 weeks. If dose escalation achieves > 20% reduction in O'Leary Sant Score, patient will continue on 120mg once monthly until satisfactory symptom resolution.

It is estimated that up to 50% of patients will not achieve >20% reduction in O'Leary Sant Score despite dose escalation of sodium hyaluronate and good adherence to treatment. The urology team at UHNM estimate up to 10 patients per annum would be in this cohort. Should iAluril® be introduced to the NSJF, patients refractory to Hyacyst® 120mg would be offered a course of iAluril® instead

Patients are reviewed every 3 months by a urology Clinical Nurse Specialist and every 6 months by the consultant urologist.

RECURRENT URINARY TRACT INFECTIONS

Treatment for patients with recurrent urinary tract infections (UTIs) resistant to chemoprophylaxis is currently under review. As the treatment pathway for this cohort is not well established, it is suggested that a sizeable proportion of patients are prescribed antibiotic prophylaxis and a combination of analgesia longterm, which could receive satisfactory reduction in number of symptomatic UTIs if treated with a 6 month course of iAluril®, which

would replenish the bladder epithelium, thus reducing symptoms. It is proposed that patients with recurrent, bacteriologically proven symptomatic UTIs resistant to antibiotic prophylaxis for 6 months could be offered iAluril®

Patients will be reviewed regularly by a urology Clinical Nurse Specialist and every 6 months by the consultant urologist.

Efficacy:

EFFICACY IN BLADDER PAIN SYNDROME

Cervigni et al evaluated the efficacy and tolerability of intravesical instillations of hyaluronic acid (HA) 1.6% and chondroitin sulfate (CS) 2.0% in patients with refractory PBS/IC and the subsequent impact on QoL. The results of the study were published in 2008. Twenty-three women were enrolled. They received bladder instillations with HA and CS weekly for 20 weeks and then monthly for 3 months. Mean follow-up after completion of therapy was 5 months. The authors observed a significant improvement in urinary symptoms on voiding diaries and Visual Analogue Scale for frequency (Pretreatment mean score = 7.43, post treatment mean score = 5.45 p = 0.045), urgency (Pre-treatment mean score = 6.23, post treatment mean score = 3.63 p = 0.005), and pain (pretreatment mean score = 5.65, post treatment mean score = 3.83 p = 0.001). The O'Leary-Sant Interstitial Cystitis Symptom Index and Interstitial Cystitis Problem Index resulted in a significant improvement in both scores (Symptom index pre-treatment = 8-23 (mean 13.87, SD 3.67) and post-treatment = 6-20 (mean 11.22, SD 3.75)p = 0.004 and 0.01, respectively). The Pelvic Pain and Urgency/Frequency Symptom Scale only showed significant improvement in the symptom score (Pretreatment mean score for symptoms = 13.7 SD 3.35 pretreatment, mean score post-treatment = 11.61 SD 4.60 p = 0.001).

The authors concluded that this treatment offers an additional therapeutic option in patients with refractory PBS/IC.

EFFICACY IN RECURRENT UTI

Damiano et al assessed the clinical efficacy of iAluril in recurrent UTI. 57 women (mean age 34.8 years) with 3 or more recurrent UTIs in the past year were randomised to receive either iAluril (n=28) or placebo (n=29). Treatment or placebo was received weekly for 4 weeks followed by monthly treatment for 5 months. Instillations were left in the bladder for at least 2 hours before voiding. No prophylactic antibiotics were given before, during or after instillations. Urinalysis and urine culture were carried out 3 days prior to instillations to check urine sterility.

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Follow-ups were carried out at month 1, month 3, month 6, month 9 and month 12. Patients were assessed for UTI status (midstream specimen of urine), storage and voiding. Patients also received a QoL questionnaire at each followup. Mean UTI rate pre-treatment = 4.69 +/1.3 in the placebo arm and 4.71 +/- 1.5 in the iAluril arm. Post treatment, the placebo arm reported a UTI rate of 4.19 +/- 0.98 whilst the iAluril arm reported a post-treatment UTI rate of 0.67 +/- 0.68 (p value <0.001). The pelvic pain/urgency/frequency score (PUF score) for the placebo arm pre-treatment was 22.3 +/- 6.1 and 21.6 +/- 5.9 for the iAluril arm. Post treatment the placebo arm reported a PUF score of 20.44 +/- 4.76 whilst the iAluril arm reported a PUF score of 14.87 +/- 5.32 (p<0.001). Mean time to UTI recurrence was 52.7 days +/- 33.4 days for the placebo arm, and 185.2 +/- 78.7 days for the iAluril arm. The authors concluded that compared with placebo, iAluRil intravesical instillations significantly reduced UTI rate without severe side effects while improving symptoms and QoL over a 12-month period in patients with rUTI.

Cicione A et al conducted a retrospective multicentre study to assess the efficacy of iAluril® for recurrent UTI. The study involved 157 women, mean age 54.2 ± 4.1 years, with a documented history of at least 3 episodes of uncomplicated UTIs (with the isolation of >103 CFU/mL of an identified pathogen with clinical symptoms in the last 12 months). Patients received iAluRil weekly for 4 weeks then monthly for 5 months (a total of 9 instillations). 28% of patients received a different regimen due to further instillations up to 12 months. Instillations for positive urine culture was delayed in 23 cases (14.6%). Following baseline data capture, patients were assessed at 1 month, 6 months and 12 months At every visit patients completed: Pelvic Pain and Urgency/Frequency Symptom Scale (PUF) and SF-36 QoL questionnaire. Urinalysis and urine culture were performed before each instillation and at each follow-up visit.

At 12 months, the following results were reported:

- 89.35% reduction in mean UTI rate per person from 4.13 to 0.44 (p=0.01)
- 28.32% reduction in mean total PUF score from 20.09 to 14.4 (p=0.01)
- 29.93% reduction in mean total symptom score from 13.7 to 9.6 (p=0.01)
- 31.51% increase in mean QoL SF-36 score from 59.25 to 77.92 (p=0.01)

The authors concluded that the study results suggest that intravesical HA-CS administration is an effective and well tolerated non-antibiotic treatment option in women with rUTI.

EFFICACY IN RECURRENT BACTERIAL CYSTITIS

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De Vita and Giordano reviewed the efficacy of iAluril for recurrent bacterial cystitis in a 2012 study. 28 women with a mean age of 60 +/- 13 years were studied. n = 14 received iAluril weekly for 4 weeks then fortnightly for 4 weeks. N = 14 received prophylactic sulfamethoxazole 200mg and trimethoprim 40mg for 6 weeks. Evaluations included: cystitis recurrence at 2 and 12 months, subjective pain symptoms (Visual Analogue Scale [VAS]), 3-day voiding, sexual function, QoL (King's Health Questionnaire [KHQ]), PUF, and maximum cystometric capacity (MCC). Patients were evaluated at baseline, weekly for the first 4 weeks after initial treatment and months 2 and 12 post-treatment. Patients treated with iAluRil showed a reduction in the number of cystitis (UTI) recurrences, this was not statistically significant at a 2-month follow-up, but it was significantly reduced at 12-month follow-up (p=0.02).

The authors concluded that intravesical HA and CS in combination significantly reduced cystitis recurrence and improved urinary symptoms, QoL, and cystometric capacity in recurrent bacterial cystitis patients at 12 month follow-up versus antibiotic prophylaxis. Study limitations include a small sample and relatively short follow-up.

EFFICACY IN POST RADIATION CYSTITIS

Gacci et al conducted a study in 30 men who were treated with iAluril after suffering lower urinary tract symptoms (LUTS) and symptomatic cystitis after radiotherapy for prostate cancer. 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

HA-CS significantly reduced postradiation LUTS (P < .001) and bother (P = .006). Age, Gleason score, and radiation dose were the main determinants of worsening of LUTS after radiation (ICSI score baseline vs. postradiation: P = .047, .043, and .023). In multivariate analysis, only age influenced LUTS worsening after RT (P = .01). Age, radiation dose, and radiation toxicity were related to recovery of LUTS (ICSI score postradiation vs. post-HA-CS P = .041, P = .050, and P = .046). In multivariate analysis, no factor was statistically significant. The authors concluded that 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.

EFFICACY IN BCG-INDUCED CHEMICAL CYSTITIS UNRESPONSIVE TO CONVENTIONAL THERAPY

Impetore et al conducted a retrospective review of 20 patients who received combined HA and CS after suffering grade 2 BCG induced chemical cystitis. The results were published in 2018. All patients received 8 instillations of weekly HA/CS. Mean baseline visual analogue scale (VAS) scores ± Standard Deviation (SD) for urinary urgency and bladder pain were 7.8 ± 0.5 and 7.2 ± 1.0, respectively. Mean number of voids/24 hours ± SD was 15.4 ± 2.3 and mean urine volume per void ± SD was 85.8 ± 21.0 mL. At the end of the treatment, mean VAS scores ± SD for

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urgency and pain significantly decreased to 4.7 ± 1.1 and 4.2 ± 0.9, respectively ($p < 0.05$ in both cases). Mean number of voids/24 hours ± SD decreased to 9.6 ± 1.4 ($p < 0.05$) and mean urine volume per void ± SD significantly increased to 194.1 ± 59.5 mL ($p < 0.05$). At six months and one-year followup, all outcome measures remained stable. The study authors concluded that a course of HA/CS bladder instillations provide significant and durable improvement of bladder pain, urinary urgency, urinary volume per void and urinary frequency in patients with refractory BCG-induced chemical cystitis

Safety:

Disadvantages include the need for intermittent catheterisation which can be painful in BPS patients and risk of infection

Contraindications
iAluril® is contraindicated in patients with hypersensitivity to hyaluronic acid or sodium chondroitin sulphate

iAluril® has not been studied in children, or during pregnancy or lactation

Drug interactions:

No drug interactions are known to be associated with iAluril®

Place in therapy:

BLADDER PAIN SYNDROME AND RADIATION OR CHEMICAL INDUCED CYSTITIS

It is proposed that iAluril® would be offered as a 2nd line bladder instillation treatment for patients who have not achieved satisfactory symptom relief despite adherence to treatment with Hyacyst® 120mg. These patients would have already trialled conservative management oral medications (eg tamsulosin, amitriptyline) before trialling intravesical treatments.

Patients would be reviewed every 3 months by a urology clinical nurse specialist, and every 6 months by a consultant urologist.

RECURRENT UTI

It is proposed that patients with recurrent, bacteriologically proven symptomatic UTIs resistant to antibiotic prophylaxis for 6 months could be offered iAluril®

Patients will be reviewed regularly by a urology Clinical Nurse Specialist and every 6 months by the consultant urologist.

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Cost:

iAluril costs £[redacted] excluding VAT per syringe (£[redacted] including VAT).

The urology clinic at UHNM estimate that up to 10 patients per annum will be prescribed iAluril® for painful bladder syndrome or radiation or chemical induced cystitis.

At the NMC presentation, the consultant was unable to predict how many patients would be treated with iAluril® for recurrent UTI, but numbers are predicted to be small.

The maximum number of instillations per patient per annum is 16 (once weekly for 4 weeks, followed by once every 2 weeks for 4 weeks, followed by monthly instillations). However a number of patients will receive only 7, 8 or 9 instillations depending on indication. It is difficult to determine what the average number of instillations will be, due to the predicted low patient numbers.

It is proposed that the cost of iAluril® will be offset by reduced expenditure on antibiotics and other oral treatments for BPS and recurrent UTI, plus reduction in longterm use of Hyacyst®. It is also predicted that introducing iAluril® to the fomulary will reduce use of more invasive treatments which require hospital administration

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