North Staffordshire and Stoke-on-Trent Area Prescribing Committee

Medicine Review Summary

Hyacyst®: Sodium hyaluronate 40mg and 120mg bladder instillation

Verdict:	
Formulary inclusion:	Approved by the Area Prescribing Committee (APC) for inclusion in the North Staffordshire Joint Formulary
Formulary category:	Red
Prescribing restrictions	
Reason for inclusion:	The APC were satisfied with the evidence for efficacy and safety, dosing convenience, cost implications and intended place in therapy
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 Hyacyst® 40mg and 120mg sodium hyaluronate 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:

Hyacyst® (sodium hyaluronate) is a medical device. Hyacyst® 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), haemorrhagic cystitis, recurrent bacterial cystitis, radiation induced cystitis and chemotherapy induced cystitis.

Dosing and administration:

Author: Xin Wei Tan, Secondary/Primary Care Interface Pharmacist, UHNM Date approved by APC: 27/11/2019

50ml of either 40mg/50ml or 120mg/50ml is instilled into the bladder and left for 30 minutes to 2 hours once weekly for 4-6 weeks, then at monthly intervals until symptoms resolve. Suitable patients can be trained by urology specialists to self-catheterise and self-administer. Patients are advised to aim to leave the instillation in for 2 hours.

The UHNM urology team intends for patients treated with intravesical hyaluronic acid to receive 1 instillation each week for 6 weeks and then 1 instillation monthly. Treatment will be reviewed at week 4 and week 6 by the secondary care urology team for efficacy and tolerability. Treatment continues until the patient decides to discontinue treatment despite treatment being recommended, or if symptoms resolve and treatment is no longer deemed necessary. The patient would be seen in a secondary care specialist urology- nurse-led clinic every 6 months for follow-up. The intention is that responsibility for monitoring treatment will lie with the secondary care urology team.

Current UHNM guidelines for treatment of bladder pain syndrome in women (September 2018) recommend weekly instillations for 6 weeks, followed by monthly instillations for 3 months.

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.

International guidelines

The EAU Guidelines for Chronic Pelvic Pain 2019 recommends intravesical hyaluronic acid as a treatment option before more invasive measures are considered. However, the evidence behind this recommendation is considered by the EAU to be weak, as most available studies involving intravesical hyaluronic acid 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:

GAG replacement such as sodium hyaluronate has been in use for about 20 years for bladder pain syndrome and interstitial cystitis, however most studies are uncontrolled and with a small number of patients.

Sodium hyaluronate is recommended as a treatment option when oral treatment and conservative management has failed, but before more invasive measures are considered.

The patient cohort being treated tends to be young females who have already tried more conventional treatments (amitriptyline, NSAIDS, cimetidine). Males can be treated but bladder pain syndrome tends to be less common in men and is usually secondary to another intervention (i.e. radiation induced cystitis, chemotherapy induced cystitis).

Sodium hyaluronate bladder instillations have been prescribed for a number of years within UHNM and other NHS Trusts for treatment of bladder pain syndrome. Historically these instillations (eg Cystistat® - sodium hyaluronic acid 40mg/50ml) could only be administered within hospital due to the nature of the formulation. Hyacyst® (sodium hyaluronic acid) is available as a 40mg/50ml pre-filled syringe and 120mg/50ml pre-filled syringe. Both strengths of Hyacyst® include a catheter adaptor, therefore patients can be trained to self-administer. Since November 2018, Hyacyst® has been the first line sodium hyaluronate bladder instillation at UHNM, with appropriate patients trained to self-catheterise and administer.

Efficacy:

Whilst use of intravesical sodium hyaluronate for bladder pain syndrome is well established, most studies are uncontrolled and involve a small number of patients.

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Akbay et al aimed to evaluate the short term efficacy of intravesical instillation of hyaluronic acid in patients with Bladder Pain Syndrome/Interstitial Cystitis (BPS/IC). The study included 54 women with BPS/IC who received intravesical instillation of hyaluronic acid treatment (120 mg/50 mL) for 6 weeks. Visual Analogue Scale (VAS), The O'Leary Sant Questionnaire (ICSI/ICPI) forms of the patients were filled by the clinician and the health technician separately before and 3 months after the treatment. Demographic characteristics of the patients were recorded, and effectiveness of the treatment was investigated according to these data. Decrease in mean VAS and mean total scores of ICSI and ICPI was observed after three months of intravesical instillation of hyaluronic acid treatment

(55%, p<0.05 and 48.5%, p<0.05 and 45.5%, p<0.05, respectively). In most of the patients, all scores of VAS, ICSI and ICPI improved (minimum: 75.9%, maximum: 94.4%). Mostly the symptoms of nocturia and pollakiuria were seen, and treated after the instillation treatment. Some (42.6%) patients had received amitriptyline, hydroxyzine, cimetidine, gabapentin and pentosan polysulfate sodium as concomitant medications in varied combinations. The patients continued their concomitant medications during instillations and three months following the last instillation. It was been concluded that in the short-term follow-up of intravesical instillation of hyaluronic acid treatment, the symptoms have highly improved.

A systematic review of controlled and observational studies (Barua et al, 2016) evaluated hyaluronic acid, given in a weekly regimen for up to 4–10 weeks, with varying follow-up times. It appears to be an effective intravesical treatment with a number needed to treat of 1.31.

Gulpinar et al conducted a clinical comparison of intravesical hyaluronic acid and hyaluronic acid- chondroitin sulphate therapy for patients with painful bladder syndrome/interstitial cystitis in 2014. Patients with a history of bladder pain syndrome/ interstitial cystitis (BPS/IC) and who responded poorly or unsatisfactorily with previous treatment were compared taking intravesical hyaluronic acid (Hyacyst® 120mg/50ml) or hyaluronic acid-chondroitin sulphate (Ialluril® - 800 mg sodium HA, and 1 g sodium chondroitin and 440mg calcium chloride in 50ml water). The study did not involve Hyacyst® 40mg/50ml. Patients were treated with intravesical instillation with Hyacyst® 120mg /50ml (n = 32) or Ialuril® (n = 33)on weekly basis in first month, every 15 days in the second month and monthly in third and fourth months, for a total of 8 doses. Patients were evaluated using a visual analogue pain scale (VAS), interstitial cystitis symptom index (ICSI), interstitial cystitis problem index (ICPI), voiding diary for frequency/nocturia, cystometric bladder capacity and voided volume at the beginning and at 6 months. Wilcoxon and Mann-Whitney U tests were used for statistical analysis. 12 patients were eventually lost to follow up, leaving n = 23 in the Hyacyst® group, and n = 30 in the iAlluril® group. The study authors concluded that responses for VAS, ICCS, ICPS, 24-hour frequency/nocturia statistically improved in both groups at 6 months. Eight patients had mild adverse effects. The study authors concluded that Hyacyst® and iAlluril® can be effective in BPS/IC patients who do not respond to conservative treatment. The study authors acknowledged that strength of evidence from the study is limited, due to the short follow-up time, lack of placebo arm and different strengths of sodium hyaluronate in each treatment arm. The authors stated that larger prospective RCTs with long-term follow up are required to provide a definitive answer regarding comparable efficacy of both agents.

A 2016 review and meta-analysis (Pyo J-S, Cho W J) of intravesical hyaluronic acid and combined hyaluronic

acid/chondroitin bladder instillations reviewed 10 studies involving 390 patients. Most patients were female (385 out of 390 patients). Doses used were variable but most studies adopted a treatment strategy of weekly instillations for several weeks followed by maintenance doses. The authors concluded that both sodium hyaluronate and combined hyaluronic acid/chondroitin showed a significant positive effect after 6 months, however follow-up periods for studies varied from 5.5 months to 4.9 years. The study authors were unable to determine any difference between results for hyaluronic acid and combined hyaluronic acid/chondroitin.

Additional supporting information presented post- NMC

Ms Mistry Pain, Mr Kitchen and other members of the UHNM urology team assessed and compared patient-reported outcome measures (PROMS) from patients receiving nurse-administered 'in-hospital' and patient-led self-administered 'at-home' intravesical hyaluronic acid (Cystistat®and Hyacyst®, respectively). The audit also assessed impact of introducing self-administered Hyacyst® and Cystistat® on patient waiting times for treatment, frequency of treatments, number of clinician and nurse clinic appointments, and estimated financial costs. 60 consecutive patients commencing intravesical hyalruonaci acid for bladder pain syndrome were audited between 1st January 2016 and 31st March 2019. O'Leary-Sant Interstitial Cystitis Symptom Index questionnaires were completed prior to, and following, six treatments. Relevant clinical and demographic data were also collected. 76.6% of the patients had improvement in symptoms after HA treatment. Mean O'Leary-Sant questionnaire symptom and problem scores were significantly improved following HA treatment (11.8 (range6–17) to 8.5 (range 4–13) (p=0.00005) and 11.4 (range 4–16) to 7.9 (range 4–14) (p=0.0002), respectively. The paper's authors also concluded that the mean average waiting time to start treatment reduced from 16.7 weeks (for administration as an outpatient) to 14.9 weeks (self-administration; p=0.169) . It as also concluded that mean number of instillations reduced from 12.0 per annum (if administered as an outpatient) to 10.4 (self administered). Mean number of nurse clinic appointments per annum reduced from 12.0 (if administered in outpatient clinics) to 7.1 (p=0.0001) (patient self-administered). The mean number of consultant outpatient appointments per annum reduced from 1.0 to 0.3 (administered in clinic vs self-administration; p=0.001). There were no significant differences in symptom improvements between patients on either pathway

Safety:

Hyacyst® is well tolerated and causes few, if any side effects. Occasionally, the insertion of the catheter into the bladder may cause irritation.

As with any urological application, a urinary tract infection can arise during the placement of the catheter.

Hyacyst® should not be used in patients with a known sensitivity to hyaluronic acid.

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Hyacyst® should not be patients under the age of 18 years old, or to pregnant women, as there is no available data supporting use in these cohorts.

Drug interactions:

No known drug interactions are known to be associated with Hyacyst®

Place in therapy:

The urology team propose that Hyacyst® is included in the North Staffordshire Joint Formulary as 2nd line treatment for bladder pain syndrome, where conservative management (change in diet, analgesia, cimetidine, amitriptyline) has been unsuccessful.

Cost:

Primary care price for Hyacyst ® pre-filled syringe per instillation		Secondary care price for Hyacyst® pre-filled syringe (inclusive VAT 20%) per instillation	
40mg/50ml	[redacted]	40mg/50ml	[redacted]
120mg/50ml	[redacted]	120mg/50ml	[redacted]

During October 2018-September 2019, 52 patients received Hyacyst 40mg or 120mg.
Of these 52, 48 received the 40mg strength only, 2 received a combination of 40mg and 120mg syringes, and 2 received the 120mg strength only. (Note the 120mg strength was first issued in January 2019.) The urology team predict that with establishment of the bladder pain patient pathway, approximately 50 patients per annum would be treated with Hyacyst®, and approximately 20% (10) patients would have doses escalated from 40mg to 120mg.

Patients who were prescribed Hyacyst® 40mg between October 2018 and September 2019 received on average 7.45 (8) syringes within a 12 month period. This is below the maximum number of doses a patient could receive during their first year of treatment (17), or if treatment continued beyond year 1 for a full calendar year (13). This suggests that average duration of treatment is less than 1 year, either due to satisfactory symptom control or patient disengagement. With establishment of the bladder pain pathway, the average duration of treatment may

change. It is difficult to predict whether this is likely to increase or decrease.

References:

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