North Staffordshire Clinical Commissioning Group

Stoke-On-Trent Clinical Commissioning Group

University Hospitals of North Midlands NHS Trust

Midlands Partnership NHS Foundation Trust

North Staffordshire Combined Healthcare NHS Trust

New Medicines Committee Briefing

Date of submission: October 2019

Drug: Hyacyst® (sodium hyaluronate) 40mg/50ml and 120mg/50ml pre filled syringe

is to be reviewed for use within:

Primary care	
Secondary care	X

Summary

Hyacyst® (sodium hyaluronate) is a bladder instillation indicated for the temporary replenishment of the glycosaminoglycan (GAG) layer in painful bladder syndrome.

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 in current European Association of Urology (EAU) guidelines for pharmacological treatment of Chronic Pelvic Pain (2019). Intravesical sodium hyaluronate is also recommended in national guidelines (Joint BSUG and RCOG guidelines 2016). Sodium hyaluronate is recommended as a treatment option when oral treatment and conservative management has failed, but before more invasive measures are considered.

Hyacyst® is available in strengths of 40mg/50ml and 120mg/50ml which are supplied as Pre-Filled Syringes (PFS) or Vials. Hyacyst® PFS packs include a catheter adaptor to enable Hyacyst® PFS to be used with a wide variety of available catheters, making them suitable for self-instillation at home.

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).

It is intended that treatment will be initiated by a specialist urology or urogynaecology clinician. Patients will be prescribed one instillation per week for 6 weeks, with monthly instillations thereafter if treatment is assessed as efficacious and tolerated. If treatment is recommended after 6 weeks, patients will be offered the choice to self catheterise and self-administer. The responsibility for treatment monitoring will lie with the secondary care urology team.

Hyacyst® (sodium hyaluronate) is available for prescribing on FP10s

Formulary application

Consultants submitting application: Ms Tina Mistry-Pain, consultant urologist, UHNM

Clinical Director supporting application: Mr Anurag Golash, consultant urologist, UHNM

Background

Hyacyst® (sodium hyaluronate) is a bladder instillation indicated for the temporary replenishment of the glycosaminoglycan layer in painful bladder syndrome and interstitial cystitis.

The European Association of Urology defines bladder pain syndrome (BPS) as the occurrence of persistent or recurrent pain perceived in the urinary bladder region, accompanied by at least one other symptom, such as pain worsening with bladder filling and day-time and/or night-time urinary frequency. There is no proven infection or other obvious local pathology. Bladder pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract and sexual dysfunction. BPS is believed to represent a heterogeneous spectrum of disorders.

Hyacyst® is prescribed as 2nd line treatment after trialling conservative management (diet management, analgesia) or amitriptyline or cimetidine.

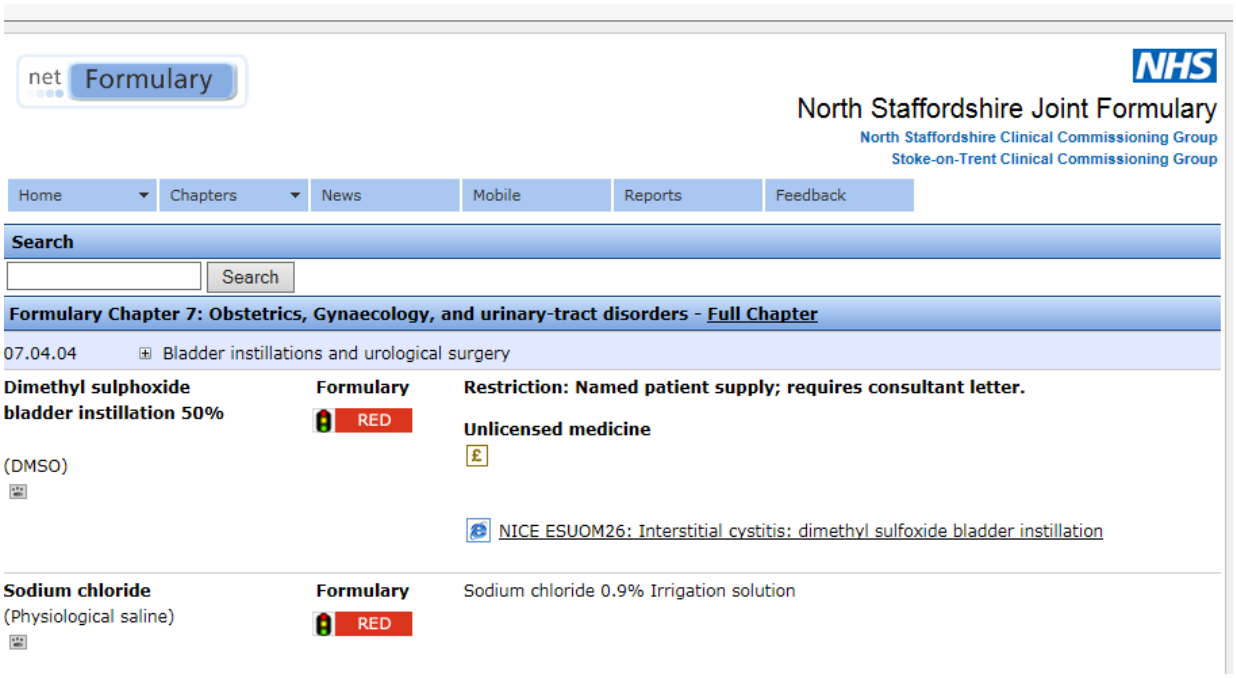
Sodium hyaluronate bladder instillations have been prescribed for a number of years within UHNM and other NHS Trusts for treatment of bladder pain syndrome. Historically these instillations (eg Cystistat® - sodium hyaluronic acid 40mg/50ml) could only be administered within hospital due to the nature 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.

The urology department predicts that up to 50 patients per annum will be treated with hyaluronic acid. Patient drop-out rate is estimated to be high – it is unknown how many patients persist with treatment after the initial 6 week period.

Current formulary status

North Staffordshire Joint Formulary

At present, the only bladder instillations included in the North Staffordshire Joint Formulary are dimethyl sulphoxide bladder instillation 50% (DMSO -an unlicensed preparation) and sodium chloride 0.9% irrigation solution. Both are restricted to secondary/tertiary care prescribing only. Neither treatment is recommended in the 2019 EAU guidelines for Chronic Pelvic Pain.



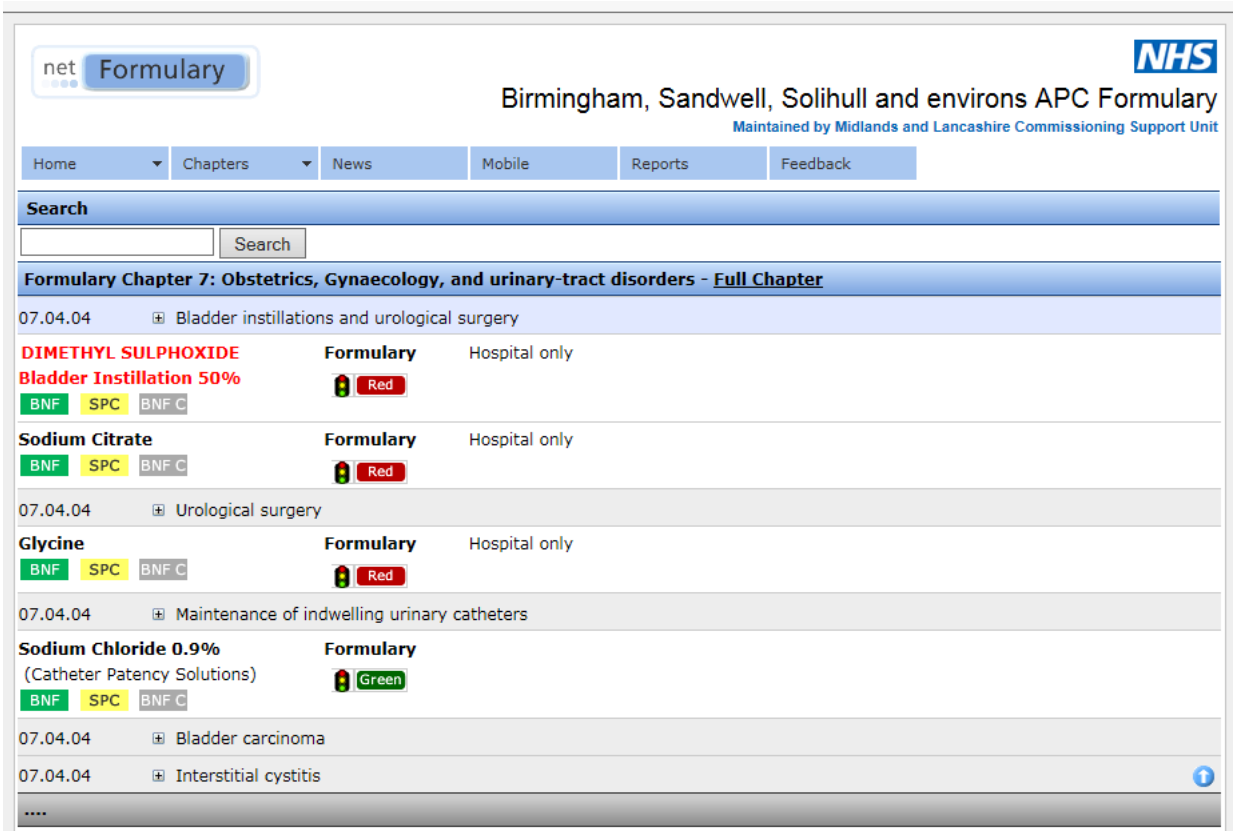
In practice, DMSO 50% bladder instillation is not prescribed for bladder pain. Sodium hyaluronate is prescribed regularly by urology consultants for treatment for bladder pain and chronic cystitis, and has been for a number of years. Until November 2018, Cystistat® (sodium hyaluronate 40mg/50ml vials) were prescribed for instillation within hospital. Since November 2018, Hyacyst® 40mg/50ml pre-filled syringes have been prescribed instead, which is more cost-effective compared to Cystistat®, and has the added advantage of being suitable for self-administration.

South Staffordshire Joint Formulary

At present, all bladder instillations are not included in the South Staffordshire Joint Formulary

Birmingham, Sandwell, Solihull and environs APC formulary

The only bladder instillations included in the Birmingham, Sandwell, Solihull and environs APC Formulary are dimethyl sulphoxide bladder instillation 50%, sodium chloride 0.9% irrigation solution, sodium citrate and glycine. Only sodium chloride 0.9% catheter patency solution is categorised for primary care prescribing.



Wolverhampton Joint Formulary

The following instillations are included in the Wolverhampton Joint Formulary.

-Sodium hyaluronate /Chondroitin sulphate bladder irrigation - Specialist/ Hospital prescribing only

- Sodium hyaluronate solution - Specialist/ Hospital prescribing only

Derbyshire Joint Formulary

Bladder instillations are not included in the Derbyshire Joint Formulary

Central and Eastern Cheshire Joint Formulary

Bladder instillations for interstitial cystitis or chronic bladder pain are not included in the Central and Eastern Cheshire Joint Formulary

Therapeutic class and mode of action

Hyacyst® is a medical device containing sterile hyaluronic acid (sodium hyaluronate).

Urothelial inflammations can lead to a loss of hyaluronic acid in the mucous membrane.

A loss of hyaluronic acid in the vascular mucous membrane especially occurs with interstitial cystitis. The urothelium can be regenerated through the substitution of hyaluronic acid.

The following occurs:

− Regulation of the permeability of the bladder wall.

− Containment of the inflammatory response.

− Support of wound healing.

Hyacyst® is a sterile hyaluronic acid solution which is instilled into the urinary bladder with the help of a catheter. This solution/lavage fluid serves for the regeneration of destroyed/altered urothelium in the urinary bladder and the deferent urinary passages.

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.

Dosage and administration

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. 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.

Safety and adverse effects

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.

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 drug interactions are known to occur with Hyacyst®

Presentation

HYC-1250 S 50ml Syringe contains 50 ml of HYACYST solution (120mg sodium hyaluronate).

HYC-4050 S 50ml Syringe contains 50 ml of HYACYST solution (40mg sodium hyaluronate).

Patent Status

Hyacyst® was first marketed in the UK in 2016.

Guidance and Evidence Summary

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.

NICE Guidance	**N**

Scottish Medicines Consortium (SMC)	**N**

All Wales Medicines Strategy Group (AWMSG)	**N**

Regional Drug and Therapeutic Centre (RDTC)	N

Midlands Therapeutics Review and Advisory Committee (MTRAC)	**N**

Efficacy

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 after the 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

Cost Analysis

Current expenditure (October 2018-September 2019)

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.

Patients who were prescribed Hyacyst® 40mg 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 (12)

The 2 patients who received the 120mg strength only were dispensed 6 and 10 syringes respectively.

Predicted expenditure

It is estimated up to 50 patients per annum will be prescribed Hyacyst®. It is predicted that most patients will be prescribed the 40mg/50ml strength. This is line with current patient numbers at UHNM.

It is estimated that up to 20% of patients may require the 120mg strength if satisfactory symptom control is not achieved with the 40mg dose. At the time of writing only 7% of patients (4 out of 52 Hyacyst patients between October 2018-September 2019) had received the 120mg dose.

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]

Over 52 weeks (one year), the maximum number of instillations a patient could be prescribed is 17 (one instillation once weekly for 6 weeks, then every 4-6 weeks thereafter during the 1st year of treatment) . This is greater than the current average number of doses prescribed to patients per annum (7.45). Current average number of doses per patient per annum indicate that the average course of treatment is less than one year or that there is a high drop-out rate from treatment.

As uniform follow-up pathway for these patients is not currently in place within the health economy, it is difficult to estimate what the average course of treatment will be, as this will depend on patient's response and adherence to treatment.

Current average annual cost of treatment with Hyacyst® prefilled syringes (7.45 syringes per annum – rounded to 8 syringes per annum)			
Primary care expenditure per patient		Secondary care expenditure per patient (incl. 20% VAT)	
40mg/50ml	[redacted]	40mg/50ml	[redacted]
120mg/50ml	[redacted] ** NB not currently prescribed in primary care*	120mg/50ml	[redacted]

Annual cost of treatment with Hyacyst® prefilled syringes if patient persists with treatment for one year (52 weeks) – YEAR 1 (17 syringes) – THIS IS THE MAXIMUM PRESCRIPTION COST OF PER PATIENT			
Primary care expenditure per patient *NB – Proposed RAG rating = RED		Secondary care expenditure per patient (incl. 20% VAT)	
40mg/50ml	[redacted]	40mg/50ml	[redacted]
120mg/50ml	[redacted]	120mg/50ml	[redacted]

Annual cost of treatment with Hyacyst® prefilled syringes – YEAR 2 ONWARDS (13 syringes over 52 weeks – 1 instillation every 4-6 week)			
Primary care expenditure per patient *NB – Proposed RAG rating = RED		Secondary care expenditure per patient (incl. 20% VAT)	
40mg/50ml	[redacted]	40mg/50ml	[redacted]
120mg/50ml	[redacted]	120mg/50ml	[redacted]

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