iAluRil®

GAG Layer Therapy for PBS/IC & rUTIs*

iAluRil® is the first intravesical glycosaminoglycan (GAG) layer replacement therapy containing both hyaluronic acid and chondroitin sulfate[1], making it an ideal therapeutic option to re-establish the GAG layer of the urothelial vesical tissue[1-2], restoring impermeability[3] and reducing bacterial adherence to the urothelium[4].

iAluRil® facilitates effective relief from PBS/IC[5-6], rUTIs[7-9], chemical[9] and radiation induced cystitis[10-11] and is well tolerated and easy to use[1,7].

iAluRil® ...efficacy, without resistance

Hyaluronic acid (1.6 % - 800mg/50mL), sodium chondroitin sulphate (2% - 1g /50mL) and calcium chloride (0.87% - 440mg/50mL)

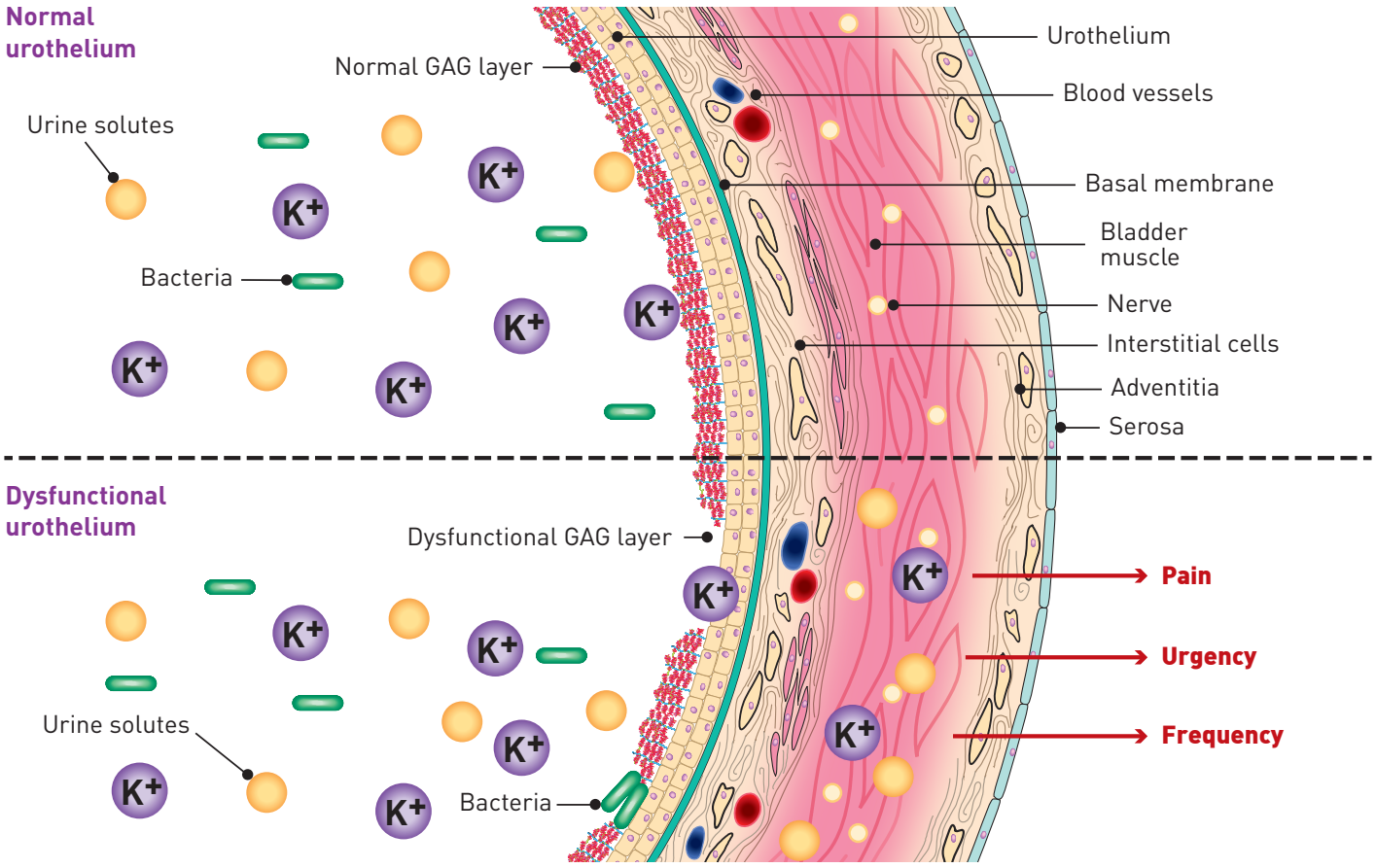
Mode of Action

Pathology

GAG replacement therapy is based upon the principle postulated by Parsons[12]; a deficiency in GAG results in increased epithelial permeability. This permeability allows the passage of urinary irritants toward the urothelium where insult and injury can occur. The classical symptoms of pain and urgency of urination are directly borne out of this damaged epithelium as a result of the body's reaction to potassium ions. Additionally, exposure of the bladder epithelium to urine can lead to a higher risk of infection as a result of increased bacterial adherence.[13, 14]

The brain interprets sensory signals from the bladder as the need to urinate. In the healthy bladder, this perception of urgency is regulated by the increasing passage of ions through the epithelial lining as the bladder gets stretched during filling.

Once a threshold of perception has been reached, urination is triggered and micturition occurs. In the diseased bladder, where GAG deficiency has resulted in a leaky epithelial lining, the perception of urgency can be almost constant as the passage of potassium ions toward the urothelium goes unchecked and normal control mechanisms are bypassed. In this state, the brain is tricked into perceiving that the bladder is 'about to burst', although upon micturition, only relatively small volumes are voided. It is this misperception that gives rise to the constant feeling of urgency, resulting in high frequency and potassium-mediated pain that is so classical of the PBS/IC disease state[15, 16].



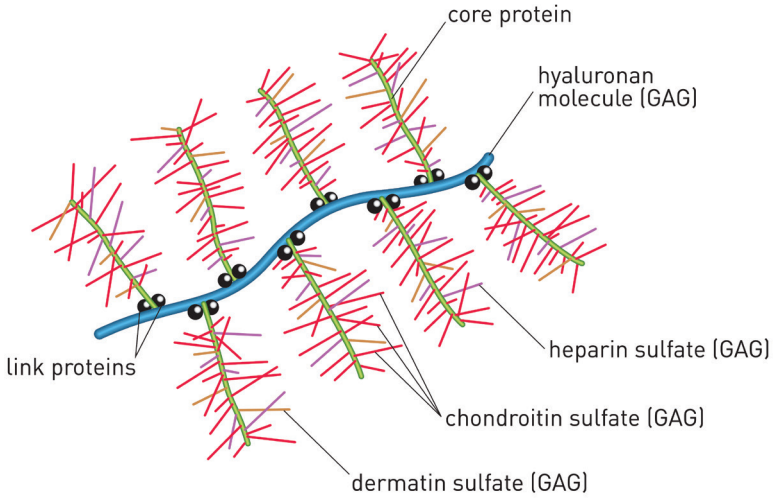
Achieving Impermeability

It is the goal of GAG replacement therapy to replenish the pool of GAG molecules from which a cohesive barrier can be constructed. The process by which GAG molecules bind to each other and, therefore, form an impermeable barrier is well defined.[17]

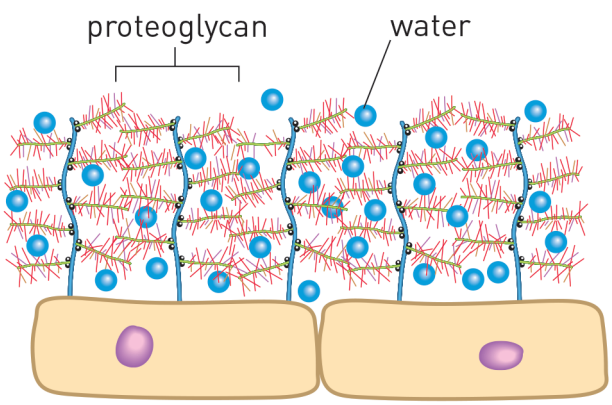
The central building block of bound GAG is the non-sulfated hyaluronate molecule. Extremely long in comparison to its sulfated GAG cousins, hyaluronate facilitates the association of a core protein every 30 nm along its length. Promoted by a small linking protein, the associated core protein acts as a branch onto which the sulfated GAG molecules covalently bind themselves[17]. Of the sulfated GAG molecules found abundantly in the bladder, it is CS that is present in the greatest number. The purpose of the sulfated GAG components is to bind water molecules on the surface of the epithelial lining conferring the waterproof and impermeable nature of a healthy bladder.[18]

Previously the therapeutic choice for GAG replacement therapy has been limited to either instilling the core building block of the GAG structure, hyaluronate (as a sodium salt 0.08% or 0.24%) or the most abundant water binding sulfated GAG, chondroitin sulfate (as a sodium salt in either 0.2 or 2% form).[18, 17] The success rates for these individual therapies have ranged between 50% and 85% for hyaluronate[19, 20], and 40 and 60% for CS[21], prompting the practice by some urologists of alternating treatments in an attempt to maximise patient response. Combining high concentrations of both these integral GAG components has helped iAluRil® achieve significant[22] results in treating recurrent UTIs,[7-9] PBS/IC,[5-6] chemical[9] and radiation[10-11] induced cystitis. By utilising a 20-fold increase in the concentration of the core GAG component HA (compared with conventional therapy, which contains 0.08% HA), iAluRil® allows for more association sites for the link/core protein complex, which in turn facilitates a greater number of sulfated side chains that can bind the all important water molecules to the surface. iAluRil® represents an effective therapeutic option for clinicians wishing to effectively replenish GAG deficient bladders, restoring impermeability and reducing bacterial adherence to the urothelium[1-4]. For patients requiring GAG replacement therapy, iAluRil® has been shown to be effective in clinical trial[2-11] and clinical practice settings where existing therapies have failed[22], and as a first line treatment.[5]

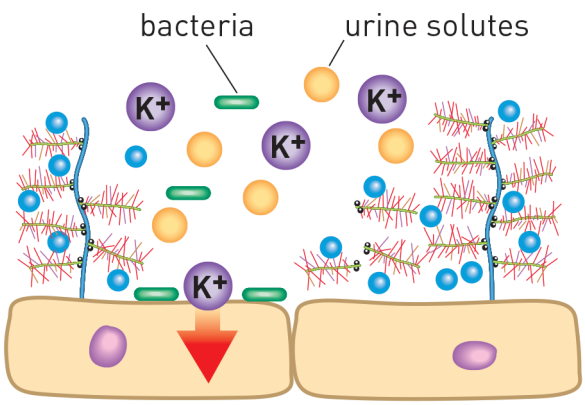
Sulfated GAG molecule



Normal GAG layer (inner bladder wall)



Dysfunctional GAG layer (inner bladder wall)



Clinical Paper Summary

Intravesical hyaluronic acid and chondroitin sulfate for recurrent urinary tract infections: systematic review and meta-analysis[23].

Jonathan Charles Goddard, Dick A.W. Janssen
International Urogynecology Journal 2017

Introduction

Urinary tract infections (UTI) are a major female healthcare concern. Over a lifetime, some estimated 40-50% of women experience at least one episode of UTI's, which have a tendency to recur.

Aim

To analyse the available clinical data on intravesical hyaluronic acid and chondroitin sulfate, for urinary tract infections in adult female patients using a systematic review and meta-analysis:

Primary objective was to investigate whether HA and CS, alone or in combination, are more effective than other prophylactic treatments or placebo in reducing the occurrence of RUTIs in adult female patients.

Methodology

- Manual and cross-referenced search of MEDLINE, Embase and Cochrane databases up to 9 November 2016.
- Randomized and nonrandomized trials of adult female patients with a documented history of rUTI's who received HA, CS or HA plus CS were included.
- In all studies, the main inclusion criterion was a documented history of rUTI, defined as at least three episodes of uncomplicated UTI with clinical symptoms and/or positive culture (>103 CFU/mL) in the past 12 months, in adult female patients.
- Random effects model was applied to all pooled analyses.
- Statistical analysis was performed using R Statistical Software.

Primary Outcomes

- Mean rate of UTI episodes per patient-year and
- Mean time to first UTI recurrence (in days).

Secondary Outcomes

- The number of patients with UTI recurrence,
- Number of 3-day voids,
- Pelvic pain and urgency/frequency (PUF) total,
- Symptom scale scores and quality of life measures (VAS, SF-36, and KHQ).

Studies were included if they reported at least one of the above outcomes.

Results

- Eight articles met the eligibility criteria and were included in the systematic review and meta-analysis.
- 2 studies were randomized controlled studies, and 6 studies were nonrandomized. Duration of treatment ranged from 2 to 6 months and duration of total follow-up ranged from 12 to 18 months.
- The 8 studies included a total of 800 patients, with 478 receiving intravesical instillations of HA plus CS (iAluRil®), 108 patients receiving HA alone, and 214 receiving comparator therapy with placebo, oral sulfamethoxazole and trimethoprim prophylaxis or other standard of care prophylaxis.
- Overall, the individual studies showed a positive treatment effect with HA or HA plus CS for mean UTI rate (fig 1), time to UTI recurrence (fig 2), pelvic pain and urgency/frequency (PUF) (fig 3).

Conclusion

Intravesical instillation of HA, alone or in combination with CS, may be a promising and feasible treatment option for female patients with RUTIs and is generally well tolerated.

This treatment may therefore offer an alternative to the widespread use of antibiotic prophylaxis."

Treatment and control study summary

Study	Treatment (HA OR HA + CS)	Control
Constantinides 2004[24]	HA	Retrospective review of patient records before treatment
Lipovac 2007[25]	HA	Retrospective review of patient records before treatment
Damiano 2011[7]	HA + CS	50 mL placebo (saline)
Centemero 2011[26]	HA R	Retrospective review of patient records before treatment
De Vita 2012[27]	HA + CS	Sulfamethoxazole and trimethoprim
Cicione 2014[8]	HA + CS	Retrospective review of patient records before treatment
Gugliotta 2015[28]	HA + CS	Sulfamethoxazole and trimethoprim
Ciani 2016[29]	HA + CS	Standard of care prophylaxis

Fig 1.

Mean UTI Rate Per Patient Per Year

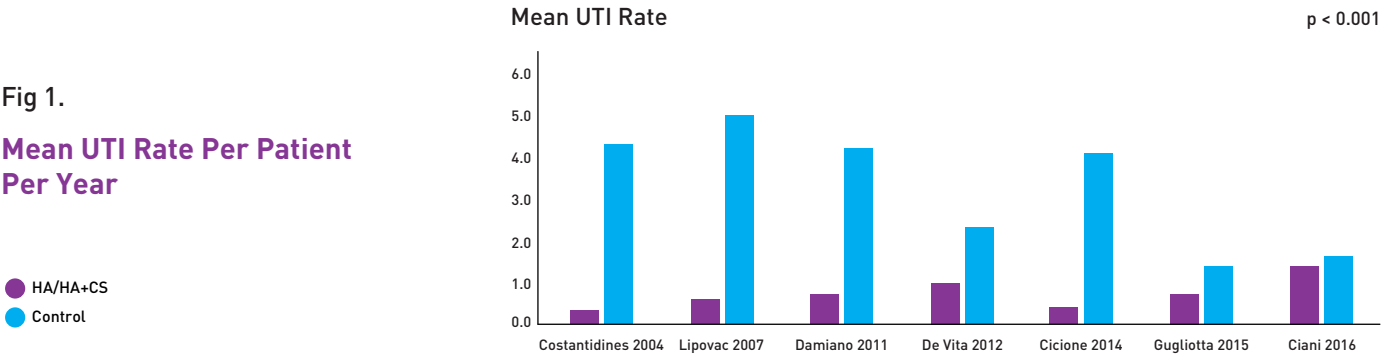


Fig 2.

Time to First UTI Recurrence (days)

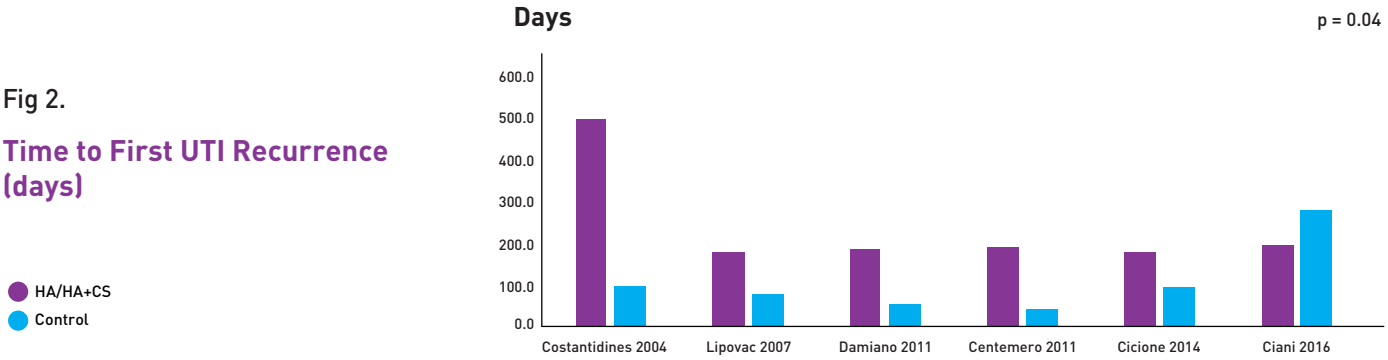
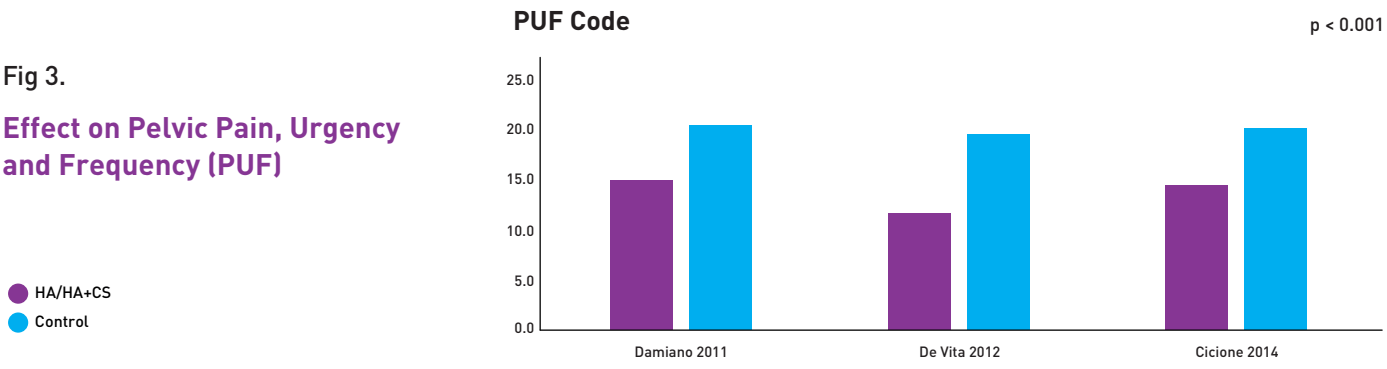


Fig 3.

Effect on Pelvic Pain, Urgency and Frequency (PUF)



Clinical Efficacy PBS/IC

A randomised, open-label, multicenter study of the efficacy and safety of intravesical hyaluronic acid and chondroitin sulfate versus dimethyl sulfoxide in women with bladder pain syndrome/interstitial cystitis[6].

Cervigni M et al. 2016
Neurourology and Urodynamics 2016. 9999: 1-9.

Introduction

Bladder pain syndrome/interstitial cystitis (BPS/IC) is a chronic bladder condition, characterized by pelvic pain, increased urinary frequency and urgency, in addition to high levels of sexual dysfunction, sleep disturbance, and impairment in quality of life.

Aim

Intravesical instillation of hyaluronic acid (HA) plus chondroitin sulfate (CS) in women with bladder pain syndrome/interstitial cystitis (BPS/IC) has shown promising results. This study compared the efficacy, safety, and costs of intravesical HA/CS (iAluRil®, IBSA) to dimethyl sulfoxide (DMSO, RIMSO® Bioniche).

Methodology

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 noninvasive 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 iAluRil® or 50% DMSO given with a 2:1 allocation ratio (iAluRil®:DMSO).

Patients were evaluated at 3 months (end-of-treatment) and 6 months.

Primary Endpoint

- Reduction in pain intensity at 6 months by Visual Analogue Scale (VAS) versus baseline.

Secondary Endpoints

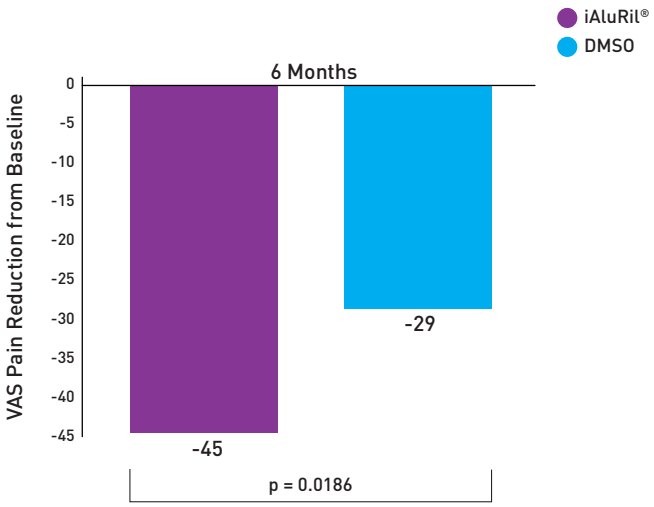
- Reduction in pain intensity after the 3-month treatment period, and changes from baseline in other urinary symptoms recorded using the ICSI/ICPI, the Pelvic Pain and Urgency/Frequency Symptom Scale (PUF) and a 3-day voiding diary.

Results

A total of 88 patients were evaluated of whom 61 had iAluRil® and 27 had DMSO 22 patients, 15 (20.3%) in the iAluRil® group and 7 (19.4%) in the DMSO group, withdrew before the end of the study).

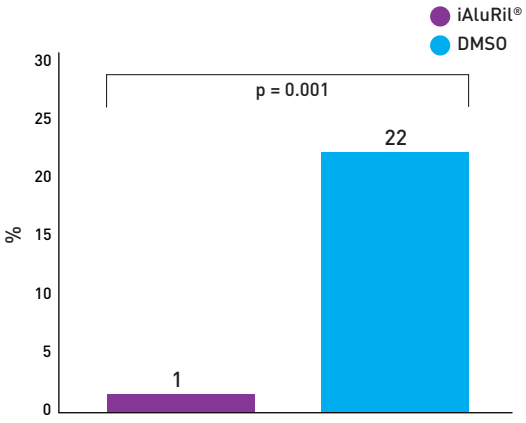
- A significant reduction in pain intensity was observed at 6 months in both treatment groups versus baseline ($P < 0.0001$) in the intention to treat (ITT) population.
- A significant reduction in pain intensity at 6 months in favour of iAluRil® in the per protocol population was observed with a mean VAS reduction of 44.77 versus 28.89, $p = 0.0186$.
- There were significantly fewer treatment-related adverse events for iAluRil® versus DMSO (1.4% versus 22.2%, $p = 0.001$).

Mean VAS Pain Score - per protocol population

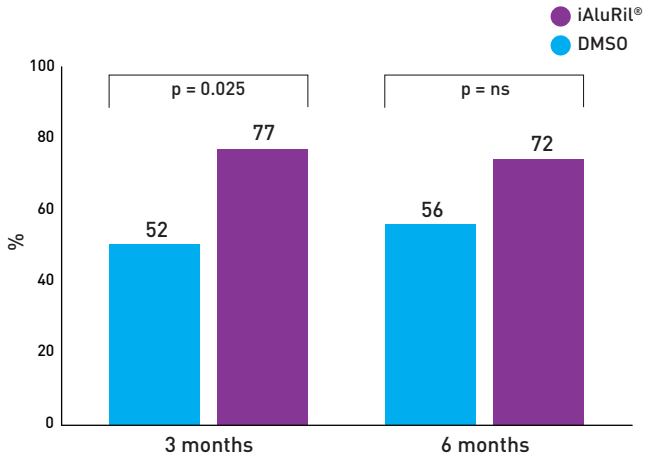


Clinical Efficacy PBS/IC & UTIs

Treatment related side effects



Positive response to treatment



Mean change from baseline after 3 and 6 months between treatment groups for secondary endpoints (ITT) population.

Measure	End of treatment (13 weeks)			Follow up (6 months)		
	iAluRil®	DMSO	p value	iAluRil®	DMSO	p value
ICSI	-6.33*	-5.61*	0.37	-6.14*	-5.42*	0.38
ICPI	-6.68*	-5.64*	0.54	-6.47*	-5.86*	0.86
PUF	-10.18*	-8.94*	0.46	-10.01*	-9.75*	0.85
EQ Index	+0.39*	+0.39*	0.94	+0.39*	+0.31*	0.38
EQ Vas	+9.79*	+3.54*	0.71	+13.56*	+5.74*	0.58
Urinary frequency	-1.99*	-2.38*	0.49	Not recorded	Not recorded	NA
Bladder capacity	+38.07**	+20.60**	0.06	Not recorded	Not recorded	NA

* Significant improvement over baseline (p<.0001) ** Significant improvement over baseline (p=.0004)

Conclusion

This trial provides further support to previous data showing sustained improvement in symptoms following treatment of BPS/IC with iAluRil®, in addition to subjective improvement in the quality of life and a more favorable safety profile compared with DMSO.

Product Information

Product Name

iAluRil® Prefill

Sterile solution of sodium hyaluronate (1.6.% - 800 mg/50 mL) and sodium chondroitin sulphate (2.% - 1 g /50 mL).

50 mL pre-filled syringe for intravesical instillation.

Product Description

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 nonionic 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 cystitises of various kinds (e.g. interstitial cystitis, recurring cystitises caused by infections, cystitises induced by antitumoral agents, cystitises induced by radiation, traumatic cystitises).

iAluRil® Prefill, 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.

Indications

iAluRil® Prefill 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, interstitial cystitis, bladder pain syndrome, treatment and prevention of recurrent urinary tract infection, cystitis as a result of Bacillus Calmette – Guerin therapy, or chemical and radiation therapy.

iAluRil® Prefill 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.

Composition

Each 50 mL pre-filled syringe of iAluRil® Prefill contains: water, calcium chloride, hyaluronic acid sodium salt, sodium chondroitin sulphate.

Frequency of Use

The contents of one syringe should be instilled according to the following plan: 1 instillation a week the first month 1 instillation every two weeks the second month In the following months, 1 instillation a month until the stable remission of the symptoms is recommended.

Instructions For Use

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 the full leakage of urine collected in the bladder (use of an 8 Ch catheter is recommended during this stage); 2. Screw the plunger rod supplied with the pre-filled syringe, until it is perfectly in place; 3. Mount the Luer-Lock Adapter on the top of the pre-filled syringe and apply on it the sterile catheter previously placed in the bladder; 4. Instil into the bladder all the solution contained in the syringe through the catheter; 5. Keep iAluRil® Prefill in the bladder for as long as possible (minimum time recommended: 30 minutes).

Precautions For Use

Administration of iAluRil® Prefill by catheter may only be carried out by qualified personnel. All the operations must be carried out under controlled sterility and delicately as, for example in the case of interstitial cystitis, the patient:

- is particularly exposed to the onset of bacterial cystitises which exacerbate the symptoms of the pathology in course
- complains of pelvic pain
- deliberately urinates less frequently in order not to aggravate the pelvic pain triggered off by the act of urination (muscular hypertone induced by pain).

Wash hands thoroughly possibly using an antibacterial/detergent and then wear sterile gloves before proceeding with the preparation and administration of iAluRil® Prefill.

Carefully follow the operations suggested by the normal protocol for vesical catheter management.

Warning

Do not use iAluRil® Prefill after the "use by" date shown on the packaging.
Do not use iAluRil® Prefill if the packaging is open or damaged.
Do not use the Luer-Lock Adapter if the packaging is open or damaged.
Do not use iAluRil® Prefill if there are visible impurities or precipitates in the product.
Do not sterilise again. iAluRil® Prefill is for use once only.
Do not reuse portions of unused solution.
Do not reuse to avoid any risk of contamination.
After opening, the device must be used immediately and disposed of after use.
Store at between 0° and 25°C and far from sources of heat.

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN

Interactions

No interactions between iAluRil® Prefill and medicinal products normally used by patients with cystitises of varying etiology are known at the present time. There is currently not enough clinical data to determine if iAluRil® interferes with BCG efficacy.

Contraindications

No contraindications deriving from the use of the device are known. Do not use iAluRil® Prefill in the case of known hypersensitivity to any of the components. iAluRil® has not been tested in pregnant women, lactating women, and children.

Side Effects

Clinical trial data indicate a low risk profile for iAluRil® Prefill: urinary tract infections (likely associated with repeat catheterisation) and urinary storage symptoms were the only adverse events reported in the clinical development. According to post-marketing experience, the urinary storage symptoms (increased frequency and urgency) has been recorded with very rare frequency. Contact your health professional in case of any unexpected adverse effect.

Each Pre-Filled Syringe is for One Patient Only

iAluRil® Prefill – 50 mL pre-filled syringe is steam sterilized.

iAluRil® Prefill – 50 mL pre-filled syringe is Latex Free.

Luer-Lock Adapter is sterilised using ethylene oxide.

To Be Sold on Medical Prescription Only

It may only be administered by a doctor or by qualified personnel under the direct responsibility of a doctor.

Date of preparation: July 2014. Year of CE certification: 2013.

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