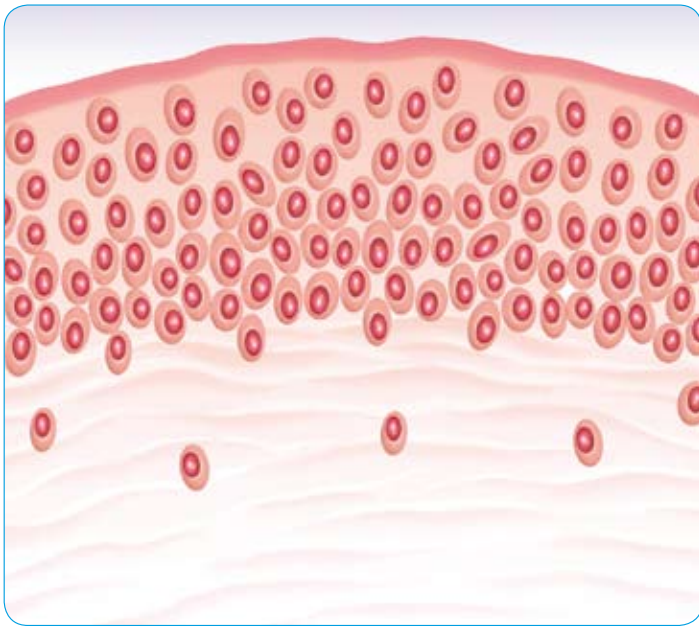


# cystistat<sup>®</sup>

CYSTISTAT<sup>®</sup>  
PRODUCT MONOGRAPH



# 1. BLADDER MUCOSA-EPITHELIUM



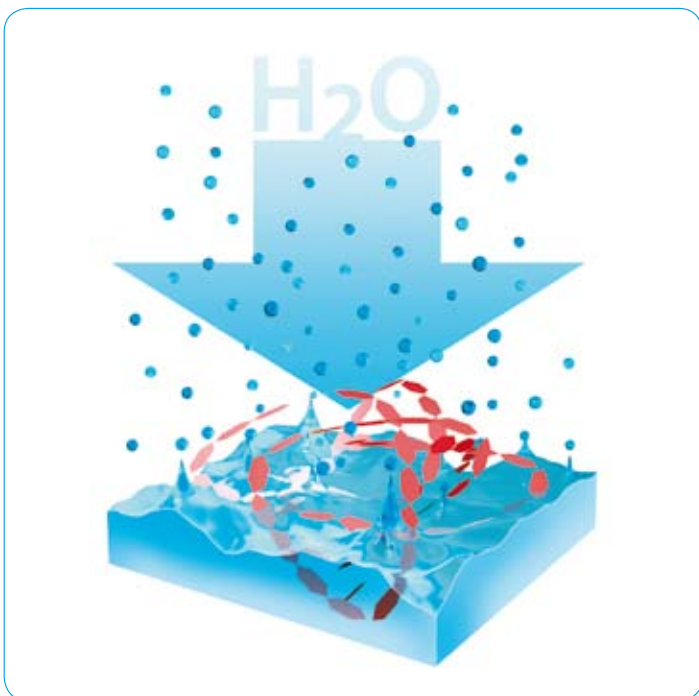
## Hyaluronan

The Ground Substance constitutes the matrix, in which the cells are embedded and through which tissue fluids diffuse, as well as a defensive barrier that regulates permeability. Glycosaminoglycans (GAGs) are the most important compounds of this intercellular space.<sup>[22]</sup>

Hyaluronan (HA) is considered the predominant GAG in connective tissues, serving as a backbone for the assembly of other GAGs.

As a consequence to the special characteristics of HA the Ground Substance builds a continuous three-dimensional molecular sieve in the interstitial space of the connective tissues. The restricted motility of larger molecules in the extracellular space also inhibits the spread of microorganisms, decreasing their pathogenicity.

It is also found that HA acts as a “biofilm” around bacteria in all vertebrate animals.



HA is a macromolecule composed of disaccharide chains of D-Glucuronic acid and N-Acetylglucosamine.

HA is extremely hydrophilic<sup>[26]</sup>, binding water up to 1.000 times its volume, and attracting water in the extracellular matrix. This moisturizing capability facilitates regeneration of the urothelium by producing an adequate environment for cell proliferation.

The larger size of the hyaluronan molecules compared to other GAG substitutes suggests an improved barrier function.

HA is predominantly found at the basal cell membrane, where it may function to reinforce the urine-tissue barrier. In contrast to superficial GAGs which are not covalently bound and may be washed out with urine, HA builds a more consistent permeability barrier at the urothelial cell base.

## 2. HYALURONAN



### HA Properties<sup>[25,26]</sup>

- Mechanical effect: Barrier / Lubrication
- Moisturization properties: High water binding properties
- Healing properties: Normalization of cell migration and proliferation
- Nutrient effect: Transport of essential molecules from the blood stream to the epithelial cells
- Space filling
- Ancillary Function: Interruption of the inflammatory cascade

### Indications

HA acts by restoring the GAG layer and protection and regeneration of the urothelium.

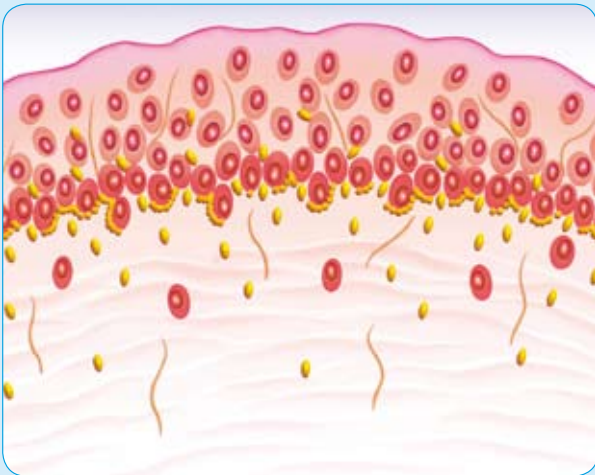
This is essential for chronic urothelial diseases such as:

- Painful Bladder Syndrome / Interstitial Cystitis (PBS/IC)
- Radiation induced Cystitis (RIC)
- Recurrent Bacterial Cystitis (RBC)

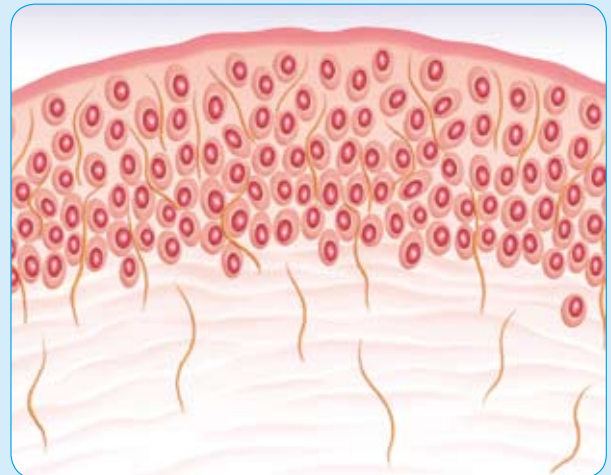
### Restoring the Bladder Mucosa

Hyaluronan is a fundamental agent to restore the GAG layer, acting from the submucosa where the epithelium starts the renewal process. The urothelial regeneration extends over 6-week cycles.

Hence, this process requires a certain take-off time allowing to trigger and to facilitate the restoring of the urothelium and, thereafter, the improvement of the symptoms.



DESTROYED



RESTORED

## 3. CLINICAL EXPERIENCE

PAINFUL BLADDER SYNDROME / INTERSTITIAL CYSTITIS (PBS/IC)

### Experience

Up to date, more than 400'000 instillations of Cystistat have been administered worldwide.

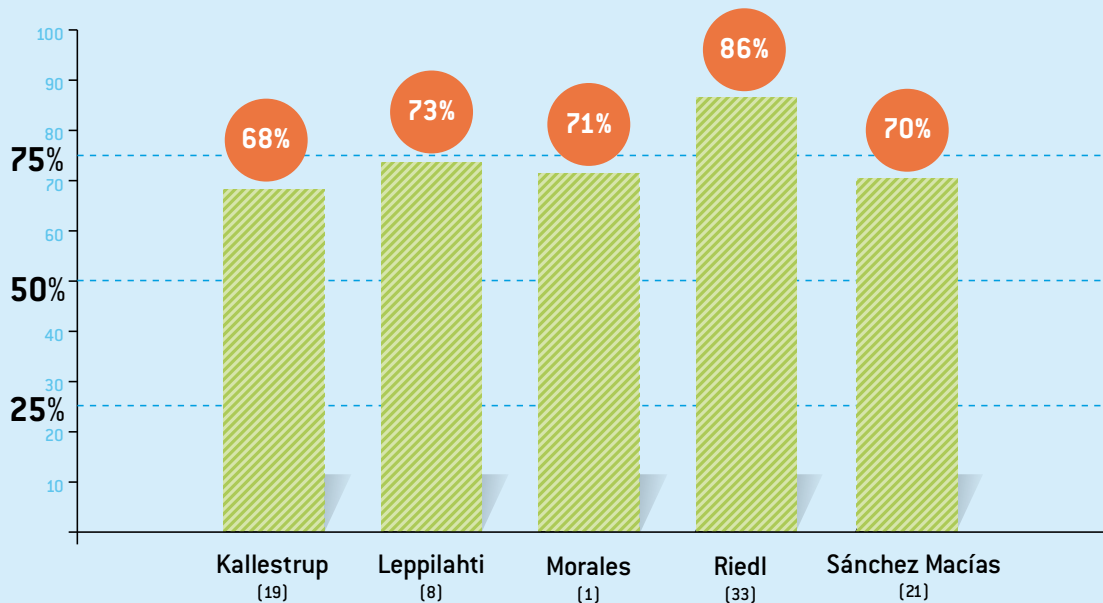
### Safety

Cystistat is well tolerated as reported in numerous clinical studies involving more than 1'000 patients.

### Efficacy

Clinical studies have shown high response rates with Cystistat.

Response rates in selected clinical studies with CYSTISTAT





# Hyaluronan treatment of interstitial cystitis/painful bladder syndrome<sup>[33]</sup>

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## Objective

The aim of this study is to evaluate the efficacy of intravesical hyaluronan therapy in interstitial cystitis/painful bladder syndrome (PBS/IC).

## Methods

121 patients with PBS/IC and an average disease duration of 6,1 years were treated with weekly instillations of a 50 cm<sup>3</sup> phosphate-buffered saline solution containing 40 mg sodium hyaluronate. To be eligible for hyaluronan treatment, a positive modified potassium test was requested as a sign of a urine–tissue barrier disorder. Data were obtained by a visual analogue scale (VAS) questionnaire rating from 0 to 10 that asked for global bladder symptoms before and after therapy. Additional questions evaluated the therapeutic impact on quality of life.

## Results

A positive and durable impact of hyaluronan therapy on PBS/IC symptoms was observed— 103 (85%) of the patients reported symptom improvement (≥2 VAS units). The mean initial VAS score of 8,5 decreased to 3,5 after therapy (p<0,0001). Out of 121 patients, 67 (55%) remained with no or minimal bladder symptoms after therapy (VAS 0–2). The majority (101/84%) reported significant improvement of their quality of life. Intravesical therapy had to be initiated again with good success in 42 patients (35%) as symptoms recurred after discontinuation of treatment, while the rest stayed (65%) free of symptoms for up

to 5 years. In general, hyaluronan therapy was well tolerated and, with the exception of mild irritative symptoms, no adverse reactions were reported for a total of 1'521 instillations.

## Conclusion

Timely hyaluronan instillation therapy may lead to complete symptom remission or even cure in part of the PBS/IC patients, while some responders need continuous intravesical therapy. The present results suggest that selection of patients for hyaluronan therapy by potassium testing improves the outcome of intravesical therapy with a response rate of >80%.

VAS SCORE	
BEFORE TREATMENT	AFTER TREATMENT
8,5	3,5

# Prevention of recurrent bacterial urinary tract infections by intravesical of hyaluronic acid<sup>(29)</sup>

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## Objective

To evaluate the efficacy of intravesical instillations of hyaluronic acid against recurrent urinary tract infections.

## Methods

Twenty women with a history of recurrent urinary tract infections each received 9 intravesical instillations of HA acid over 6 months. Their status was assessed prospectively over 47,6 weeks and compared with a retrospective review of patient charts covering 36,2 ± 6,2 weeks.

## Results

The total numbers of urinary tract infections were 67 before and 10 after treatment (p < 0,001). Thirteen patients (65%) were free of recurrences until the end of the study. One had a recurrence during

treatment, and 6 (30%) during follow-up. The number of infections per year per patient was reduced from 4,99 ± 0,92 to 0,56 ± 0,82 (p < 0,001).

In women with recurrences, time to recurrence was 178,3 ± 25,5 days, compared with 76,7 ± 24,6 days before treatment (p < 0,001). The instillations were well tolerated by all patients.

## Conclusion

Intravesical instillation of hyaluronic acid is effective in preventing recurrent urinary tract infections.

	BEFORE TREATMENT	AFTER TREATMENT
N° INFECTIONS	67	10
INFECTIONS / YEAR	4,99	0,56
TIME TO RECURRENCE (days)	77	178

65% free of recurrences until the end of the study.



## URINARY TRACT INFECTIONS (UTI) PREVENTION

# Prevention of urinary tract infections in palliative radiation for vertebral metastasis and spinal compression: A pilot study in 71 patients<sup>(24)</sup>

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## Objective

To assess the impact of bladder instillations of hyaluronic acid (HA) on the prevalence of urinary tract infection (UTI) in patients receiving emergency radiotherapy for metastatic spinal cord compression.

## Methods

Patients were recruited consecutively at one center and assigned to usual care (UC) (n=34, mean age 62,2 years) or UC with once-weekly HA instillation (UC±HA) (Cystistat: 40 mg in 50 mL phosphate-buffered saline) (n=37; mean age, 63,1 years). All patients had an indwelling catheter and received radiotherapy. UTI status was assessed at baseline and during hospitalization.

## Results

At baseline, patient groups were comparable, except for the prevalence of UTI at baseline, which was 11,8% and 0% in the

UC and UC±HA patients, respectively (p< 0,0477). During hospitalization, 76,5% (vs. 11,8% at baseline, p< 0,0001) of the UC patients had a UTI compared with 13,5% (vs. 0% at baseline, p< 0,0541) of the UC±HA patients (p< 0.0001). Both groups were hospitalized for similar periods (19,8 days [UC] vs. 18,5 days, p< 0,4769) and received equivalent radiotherapy sessions (4,6 [UC] vs. 5,8 sessions, p< 0,2368).

## Conclusion

Patients receiving Usual Care+HA had a 5,7-fold decrease in UTI prevalence over the hospitalization period compared to UC patients, suggesting that bladder instillations of HA effectively prevent UTI in patients with indwelling catheters receiving radiotherapy for nerve compression.

In this group of patients, infection means, on average, around 6 more days in the hospital than those without a UTI.

Better response to the therapy in the HA group	
Usual Care (34 pat.)	Usual Care + HA (37 pat.)
76,5% UTI (x5,7)	13,5%

# Hyaluronic Acid in the prevention of Radiation Induced Cystitis<sup>[9]</sup>

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Hospital Militar Central de la Defensa, Madrid*

## Objective

The objective of this study was to assess the efficacy of Hyaluronic acid (HA) bladder instillation on bladder radiation-induced toxicity and its impact on the scheduled pelvic radiotherapy.

## Methods

Radiation-induced cystitis limits the possibility of complete treatment which is linked to the respect of the radiation treatment schedule. We studied retrospectively 90 patients charts with cervix or uterine cancer stage FIGO 3, recruited consecutively in 2001-2002 and treated in a single center with the same standard ambulatory radiation protocol (external radiotherapy: 46-50Gy, brachytherapy: 20-22Gy). The first 45 patients received standard care. The last

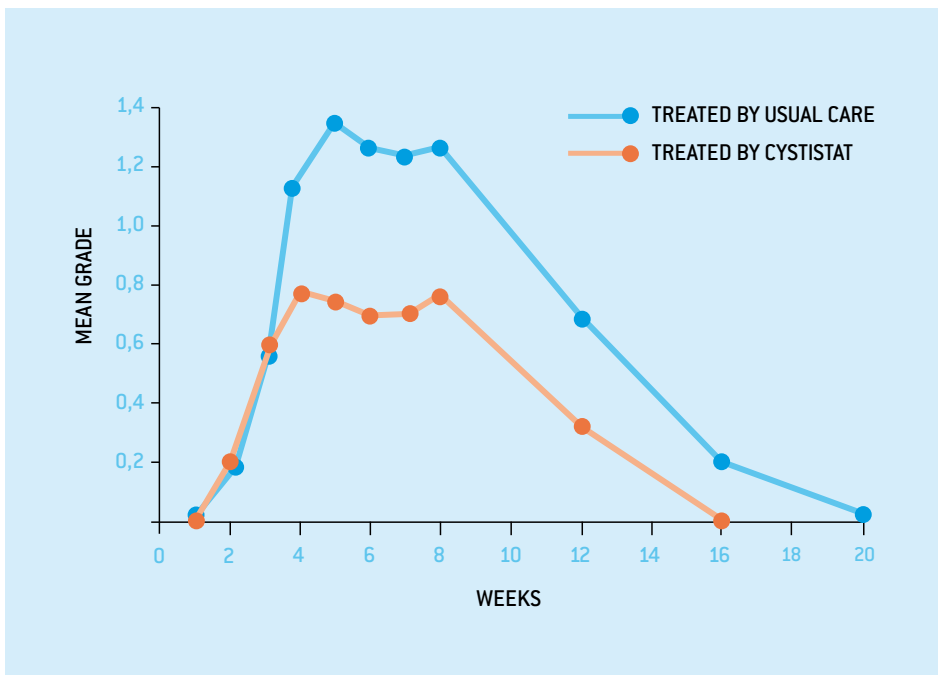
45 patients were treated with standard care plus HA bladder instillations (40 mg/50 ml solution, for 30-35 minutes) given during the brachytherapy weekly planning, through a urethral catheter used for the opacification of the bladder and kept during the dose calculation time.

## Results

Evaluation was done in both cohorts at baseline, 48 hours after each brachytherapy session, and monthly for 3 months. The toxicity (Radiation Toxicity Score) was on average at week 4: 1,33 in the usual care group versus 0,71 in the HA group ( $p < 0,005$ ) and at the end of the radiotherapy: 1,24 in the usual care group versus 0,71 in the HA group ( $p < 0,004$ ). 2 patients of the usual care group reached the grade 3 toxicity versus none in the HA group ( $p < 0,04$ ). 4 patients of the usual care group had an episode of bacterial cystitis versus none in the HA group ( $p < 0,002$ ). 9 patients were still experiencing grade 1 toxicity at 2 months of follow-up in the usual care group versus none in the HA group ( $p < 0,002$ ). The radiotherapy schedule needed to be delayed for 2 patients in the usual care group versus none in the HA group ( $p < 0,04$ ).

## Conclusion

This retrospective study showed that weekly bladder instillations of HA protected the bladder, decreased radiation-induced toxicity and risk of infection (probably enhancing the quality of life) and allowed the completion of the treatment in the scheduled time. Prospective studies are underway to confirm this protective effect in this indication.





## HAEMHORRAGIC CYSTITIS (HC)

# Treatment of post-hematopoietic stem cell transplantation hemorrhagic cystitis with intravesicular sodium hyaluronate<sup>[25]</sup>

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P. TSIRIGOTIS  
R. OR  
M. BITAN  
IB. RESNICK  
B. GESUNDHEIT  
I. ZILBERMAN  
L. IOFFE  
A. LEUBOVIC  
S. SLAVIN  
MY. SHAPIRA

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## Objective

Hemorrhagic cystitis (HC) is a well-known complication of HSCT. Its overall incidence has been reported to vary from 7–68%. The spectrum of clinical presentation varies from asymptomatic microhematuria to life-threatening bleeding. Sodium hyaluronate is a glycosaminoglycan present on the bladder mucosa, which serves as an important protective substance against uroepithelial damage. Preparations of this component have been shown to be effective in the treatment of interstitial cystitis.

## Methods

We report our experience in the treatment of post-transplant HC with intravesical instillation of sodium hyaluronate.

## Results

Five out of the seven patients included in this study achieved complete response, while one patient had only a partial response. Sodium hyaluronate administration was not associated with any local or systemic adverse effects.

## Conclusion

We consider that the results of our study are promising and the efficacy of sodium hyaluronate in the treatment of post-transplant HC should be tested in larger cohorts of patients.

71,42% Complete response to HA instillations



## 4. CYSTISTAT CLINICAL REFERENCES\*

\* This list is a selection of the main clinical studies with Cystistat having been published or presented at congresses.

### 1 PAINFUL BLADDER SYNDROME/ INTERSTITIAL CYSTITIS (PBS/IC)

INVESTIGATOR	YEAR	Nº PATIENTS	RESPONDERS	%	
MORALES, et al. <sup>[1]</sup>	1996	25	17	71	Publication
KALLESTRUP, et al. <sup>[19]</sup>	2005	20	13	65	Publication
LEPPILAHTI, et al. <sup>[8]</sup>	2002	11	7	64	Publication
DAHA, et al. <sup>[7]</sup>	2005	48	43	89	Publication
GUPTA, et al. <sup>[18]</sup>	2005	36	20	55	Publication
SÁNCHEZ MACÍAS, et al. <sup>[21]</sup>	2005	21	15	70	Abstract
AHMAD, et al. <sup>[31]</sup>	2008	23	17	74	Publication
RIEDL, et al. <sup>[33]</sup>	2008	121	103	84	Publication
<b>TOTAL</b>		<b>305</b>	<b>220</b>		

### 2 RECURRENT BACTERIAL CYSTITIS (RBC)

INVESTIGATOR	YEAR	Nº PATIENTS	% RESPONDERS	
CONSTANTINIDES, et al. <sup>[13]</sup>	2004	40	N/A	Publication
LIANOS, et al. <sup>[20]</sup>	2005	20	70	Abstract
LIPOVAC, et al. <sup>[29]</sup>	2007	20	N/A	Publication
<b>TOTAL</b>		<b>80</b>		

N/A = not applicable

### 3 UTI PREVENTION

INVESTIGATOR	YEAR	Nº PATIENTS	
SEARLES, et al. <sup>[5]</sup>	2001	8	Abstract
MAÑAS, et al. <sup>[24]</sup>	2006	37	Publication
RAPIDI, et al. <sup>[28]</sup>	2006	20	Abstract
<b>TOTAL</b>		<b>65</b>	

### 4 RADIATION INDUCED CYSTITIS (RIC)

INVESTIGATOR	YEAR	Nº PATIENTS	% RESPONDERS	
DELGADO, et al. <sup>[9]</sup>	2003	45	N/A	Abstract
DIAMANTOPOULOS, et al. <sup>[14]</sup>	2004	20	80	Abstract
GONZÁLEZ, et al. <sup>[32]</sup>	2008	14	N/A	Abstract
<b>TOTAL</b>		<b>79</b>		

N/A = not applicable

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# cystistat®

Get on with life.



## STERILE SODIUM HYALURONATE SOLUTION

For temporary replacement of the glycosaminoglycan (GAG) layer in the bladder.

### DESCRIPTION:

The glycosaminoglycan (GAG) layer on the luminal surface of the bladder wall is believed to provide a protective barrier against microorganisms, carcinogens, crystals and other agents present in the urine and has been identified as the primary defense mechanism in protecting the transitional epithelium from urinary irritants. Deficiencies in this GAG layer of the bladder epithelium may destroy its barrier function and allow the adherence of bacteria, microcrystals, proteins and ions, or the movement of ionic and non-ionic solute residues (i.e. urea) across the epithelium. CYSTISTAT® has been developed to temporarily replenish the deficient GAG layer on the bladder epithelium. The active substance is a highly purified sodium salt of hyaluronic acid.

### Each CYSTISTAT® vial contains:

40mg sodium hyaluronate.

### DIRECTIONS:

Instill the entire volume of this solution into the bladder after any residual urine has been removed. Discard any unused portion. For best results, CYSTISTAT® should be retained in the bladder for as long as possible (a minimum of 30 minutes).

There is evidence that the GAG layer of the bladder is deficient in cystitis. This deficiency contributes to the clinical symptoms in the diseases such as interstitial cystitis, cystitis caused by infections, trauma, urolithiasis, urinary retention, neoplasia and radiation induced cystitis. To alleviate cystitis associated with these conditions, it is recommended that CYSTISTAT®

be instilled into the bladder each week for 4-12 treatments and then monthly until symptoms resolve. The attending physician, urologist or radiologist should direct any prophylactic use of CYSTISTAT®.

### PRECAUTION:

Do not administer to patients with known hypersensitivity reactions. Discontinue use if adverse reactions are experienced.

### WARNING:

KEEP OUT OF THE REACH OF CHILDREN.

### STORAGE:

Store at room temperature (15-30°C). Do not freeze.

### SUPPLIED:

1 x 50 mL vial of CYSTISTAT® 40 mg.  
For single use only. Discard after use.

DATE OF PREPARATION: July 2000.

REVISED: January 2009.

®Bioniche Teoranta, Ireland

Manufactured by: Bioniche Teo., Inverin, Co. Galway, Ireland

European Patent No. 0813417

US Patent No. 5,591,724; 5,880,180; 5,888,986

Canadian Patent No. 2,203,621

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**BIONICHEPHARMA**