Gepan® instill

Effective GAG-replenishment

Product Monograph

For a colourful life

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Contents

1. Overview

Chronic forms of cystitis are serious diseases. A common feature of various forms of chronic cystitis – which include e.g. interstitial cystitis, the overactive bladder syndrome, radiation cystitis as well as chronically-recurring urinary tract infections – is the typical triad of symptoms: imperative urinary urgency, increased urinary frequency and pain in the area of the bladder and the lower abdomen – though with varying degrees of severity.

Affected patients experience a considerable degree of suffering, often associated with a massive decrease in quality of life. In many cases the extremely increased urinary frequency and urgency determine a patient´s life whose thoughts center on the nearest toilet. Frequent sleep disruptions ensuing from nocturia lead to increased fatigue during day time.

A key element in the pathophysiology of chronic forms of cystitis is the glycosaminoglycan (GAG)-layer which regulates the penetration of solutes from within the urine to the bladder wall. The physiological function of this layer is to protect the urothelium. Results of current research indicate that many forms of chronic cystitis not only have similar symptoms, but also a common pathophysiological feature, namely a defect of the GAG-layer, which can impair its protective function. This can initiate or maintain a chronic inflammatory process. A reduction of the barrier function of the GAG-layer can allow toxic components in the urine (such as potassium ions) to come into direct contact with the urothelium, leading to irritation and tissue damage. Moreover, a deficit in the GAG-layer facilitates the adhesion of bacteria to the urothelial cells and the development of urinary tract infections.

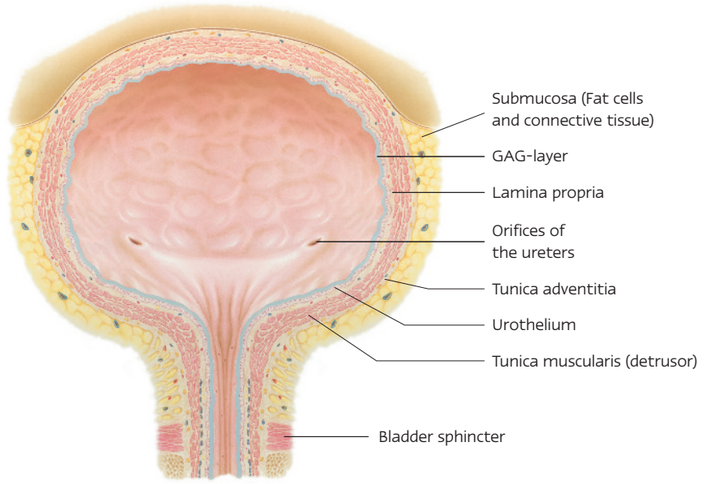
Such a deficit in the GAG-layer presents an important common feature of different forms of chronic cystitis. These diseases may be difficult to distinguish from each other in clinical practice, and establishment of a precise diagnosis often requires a complicated differential diagnostic approach. Treatment of chronic forms of cystitis is often also time-consuming and difficult. Particularly interstitial cystitis and overactive bladder syndrome are typical diagnoses by exclusion.

GAG-replenishment is an innovative form of therapy. Replenishment of missing components of the GAG-layer leads to the reestablishment of physiological conditions: the urothelium is protected from irritants and bacteria and given the possibility for regeneration. Chondroitin sulphate, a main component of the GAG-layer, is contained in **Gepan® instill** in a specially processed and highly purified form.

Current research supports the rationale of GAG-substitution with chondroitin sulphate which provides a promising therapeutic approach in patients refractory to other forms of treatment.

2. Structure of the bladder

The function of the bladder is to temporarily store urine. In order to fulfil this function the bladder must be able to adapt to various filling volumes. Its structure reflects its function and permits both filling and voiding. The following illustration shows the structure of the bladder wall.



The healthy bladder is protected by an intact GAG-layer

The bladder wall consists of several layers. The urothelium is the uppermost cellular layer of the bladder wall. The cells of this layer are tightly interconnected by so called tight junctions. In connection with the glycosaminoglycan (GAG)-layer this particularly dense cellular structure prevents irritants from within the urine from reaching or permeating into deeper layers of the bladder. The function and structure of the GAG-layer are discussed in detail in chapter 3.

The *lamina propria* is found underneath the urothelium. This layer is made up of connective tissue containing elastic fibres. Here, nerve fibre endings can be found which can e. g. register the degree of bladder filling.

The t*unica muscularis*, the muscle layer, is the thickest layer of the bladder wall. The muscular tissue is referred in its entirety as detrusor muscle (*musculus detrusor*). The bladder sphincter is a circular muscle located at the base of the bladder around the urethra. During bladder filling this muscle is contracted thus preventing the bladder passing urine; at the same time the detrusor muscle is not contracted. During micturition, the activity of these two antagonists is opposite: The detrusor contracts while the bladder sphincter dilates.

The submucosal tissue is made up of loose connective tissue and fatty cells and fills the space to the adjacent organs.

In the illustration the orifices of the ureters can additionally be seen.

3. The glycosaminoglycan (GAG)-layer

The GAG-layer protects the urothelium against irritants from the urine

The luminal side of the urothelium is covered by the GAG-layer which may be referred to as the urine-bladder barrier, part of a complex system responsible for the impermeability of the urothelium. It is also known as the so called protective layer of the bladder.

The GAG-layer is located at the border between the urine and the urothelium. The functions of the GAG-layer are based on the biophysiological and biochemical properties of the GAGs. GAGs can bind water molecules and lead to an elastic, smooth, well hydrated, anti-adhesive surface. They attract bipolar or positively charged molecules and repel negatively charged molecules. These properties are important for the regulation of permeability at the bladder surface. One function of the GAG-layer is to keep irritants – particularly potassium ions - away from the bladder wall because they might stimulate sensory nerves when penetrating the urothelium or suburothelium. Amongst the possible consequences of this is urinary urgency. Another function of the GAG-layer is to prevent bacterial adhesion to the urothelial cells and thus to inhibit the first step of the process leading to a urinary tract infection.

4. Components of the GAG-layer: glycosaminoglycans

The GAG-layer consists of long-chained polysaccharide molecules carrying negative charges especially in the form of sulphate groups. Interactions with positively charged hydrogen ions of water molecules lead to the attraction and adsorption of water molecules to the glycosaminoglycan. Thus, a well hydrated mucus layer is established which is bound to the urothelium.

The main glycosaminoglycans of the GAG-layer are:

- chondroitin sulphate
- dermatan sulphate and
- heparan sulphate

(Hurst 2006, Hurst 2003 & Zebrowski 1994)

The glycosaminoglycan chondroitin sulphate is a main component of the GAG-layer

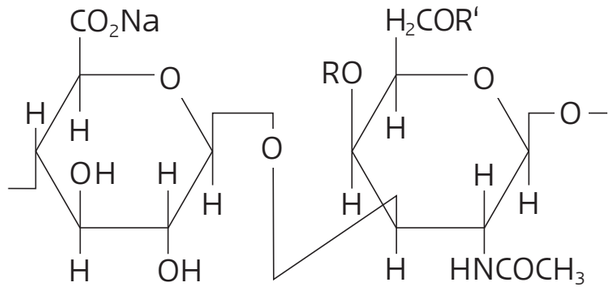
Chondroitin sulphate is of a particular importance as a specific deficit of this glycosaminoglycan has been found in the GAG-layer of patients with certain forms of chronic cystitis (Slobodov 2004, Kurth 2003, Hurst 2003, Hurst 1996).

Glycosaminoglycans can also be found in many other tissues. Outside of the GAG-layer of the bladder glycosaminoglycans may be found in high concentrations e.g. in joint cartilage. The tear fluid of the eyes also contains large quantities of GAGs, which play a major role in the protection of the ocular surface.

Heparin, a molecule involved in blood coagulation, is another physiologically occurring glycosaminoglycan. Hyaluronic acid is a further physiologically occurring glycosaminoglycan which can be found in the connective tissue of various areas of the body.

The glycosaminoglycans chondroitin sulphate, dermatan sulphate and heparan sulphate have similar chemical structures as shown here.

Chondroitin sulphate

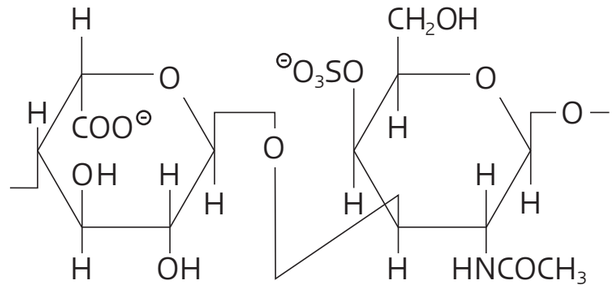


R=$SO_3^{\ominus}$ and R'=H

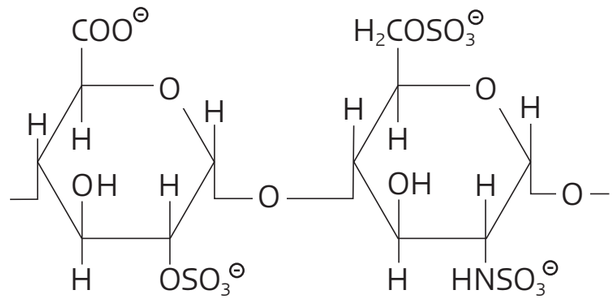
or

R=H and R'=$SO_3^{\ominus}$

Dermatan sulphate



Heparan sulphate



5. Consequences of a deficit in the GAG-layer

"Frequency-urgency-pain" is a common symptom triad of many forms of chronic cystitis

If the GAG-layer is inadequately developed or totally missing this can have a number of serious consequences (Kurth 2003, Parsons 1990).

On the one hand affected patients typically suffer from greatly increased urinary frequency, a bothersome urinary urgency as well as pain in the area of the bladder and the lower abdomen. This can be explained by the direct contact of irritating solutes contained in the urine – such as proteases, potassium ions and microcrystalline calcium compounds – which can lead to initiation or maintenance of an inflammatory tissue reaction.

On the other hand such patients are particularly prone to urinary tract infections. This observation may be explained by the lack of protection from bacterial adhesion usually rendered by the GAG-layer.

The symptoms described above are typical for various forms of cystitis. A deficit of the GAG-layer is an important element in the pathophysiology of various diseases.

An untreated chronic inflammation can lead to shrinkage of the bladder

In the course of months or years a chronic inflammation can lead to progressive tissue destruction. The resultant functional reduction in bladder capacity is reversible initially but as the condition progresses, this can become more and more anatomically fixed due to progressive bladder wall fibrosis. Ultimately, development of pronounced shrinkage is possible with a remaining bladder capacity of only a few millilitres.

Quality of life and everyday activities of patients with chronic cystitis are severely impaired

The reduction in quality of life can reach drastic dimensions for patients with chronic forms of cystitis. Up to 60 micturitions during daytime and up to 40 micturitions during the night accompanied by extreme urinary urgency can make a normal life impossible for many of the affected patients. The "nearest toilet" can become the patient´s main concern. Due to this severity of symptoms patients with chronic forms of cystitis are often no longer able to pursue normal work or leisure activities which is beside economical outcome also often accompanied by a personal withdrawal from social life. Nocturia is often particularly difficult for patients to deal with. Consequences can be pronounced sleep disorders which in turn lead to daytime fatigue. Chronic pain is a cardinal symptom especially of interstitial cystitis.

Frequently the use of strong opioid analgesics is required (Michael 2000). Not surprisingly, an increase in the rate of suicide has been found. In extreme cases, cystectomy can be the only possibility for re-establishing a minimal level of quality of life (Kurth 2003).

Fortunately thorough and early treatment of the underlying disease can halt and to a certain extent even reverse the destructive inflammatory process leading to bladder shrinkage, especially if begun in early stages (Kurth & Parsons 2003). In advanced disease stages where bladder shrinkage has already occurred the prognosis is much worse.

6. Testing the integrity of the GAG-layer: the potassium sensitivity test

A positive potassium chloride test is an indication for a higher permeability of the GAG-layer

An important common pathophysiological feature of various forms of chronic cystitis is a deficit in the GAG-layer. This leads to increased permeability at the bladder surface. With the potassium chloride test (KCl test – also termed PTS = potassium sensitivity test) – the integrity of the barrier function at the bladder surface can be tested.

Potassium ions can reach ten-fold higher concentrations in the urine in comparison to serum. If the GAG-layer on the bladder surface is insufficiently developed or totally missing the permeability is increased and potassium ions can permeate into suburothelial tissue and depolarise nerve fibre endings there. Pain sensations and urgency can result despite only minor bladder filling. A direct depolarisation of muscular tissue is also possible. This can explain the classical symptom triad frequency-urgency-pain observed in chronic forms of cystitis (Parsons 1998, Parsons 1994).

The potassium chloride test is based on these principles: a KCl solution is instilled into the previously emptied bladder and the appearance of pain or a reduction of the bladder capacity in comparison to a saline solution is evaluated.

A positive result of KCl testing indicates an increased urothelial permeability and refers to a defect of the GAG-layer. A positive KCl test is typically seen in cases of interstitial cystitis, overactive bladder syndrome, radiation cystitis and chronically-recurring cystitis.

The KCl test has a high prognostic value for a positive effect of GAG-replenishment therapy.

There are two different ways of performing the test. Originally a 3% potassium chloride solution is used. If permeability disruption is present, this will lead to a sensation of pain (Parsons 1994). An alternative less painful for the patient is the comparative KCl test with a lower concentration potassium chloride solution (1.5%). Here the reduction of the bladder capacity compared to a previously instilled saline solution is assessed. If bladder capacity more than 15% lower, it may also be assumed that increased urothelial permeability is present (Daha 2003, Hohlbrugger 1999).

Chronic forms of cystitis are usually diagnosed clinically. Potassium chloride testing is not an obligatory diagnostic procedure in clinical practice. This test does, however, underscore the common pathophysiological feature of increased urothelial permeability in different forms of chronic cystitis.

7. Diseases associated with a deficient GAG-layer

A deficit in the GAG-layer is regarded as responsible for the symptoms of various diseases, especially:

- interstitial cystitis
- overactive bladder syndrome
- radiation cystitis and
- chronically-recurring cystitis

These conditions all have the pathophysiological feature of increased urothelial permeability in common, which explains the occurrence of the same cardinal symptoms, namely “frequency-urgency-pain”. The extent and severity of each symptom varies from patient to patient.

The diagnosis of all forms of chronic cystitis requires exclusion of a number of other conditions and is often tedious and time-consuming

All these conditions are often associated with a severe reduction in quality of life for affected patients. In clinical practice diagnosis is often time consuming since a number of other diseases with similar symptoms require exclusion. Accordingly patients often have a long history until a diagnosis is established.

GAG-replenishment with **Gepan® instill** can restore the protective function of the GAG-layer. In this way therapy with **Gepan® instill** can significantly improve the symptoms and at the same time increase quality of life.

Therapeutic efficacy has been established in each of the conditions described above. The clinical investigations documenting treatment efficacy with **Gepan® instill** are detailed in chapter 9.

7.1 Interstitial cystitis

Interstitial cystitis (IC) is a chronic inflammatory condition of the bladder of non-bacterial origin and unknown cause. The disease is characterised by the clinical symptom triad “frequency-urgency-pain”. The leading symptom is typically pain. Pain is often so pronounced that patients require strong analgesics including opioids. In some cases cystectomy is the only possibility to restore an acceptable quality of life.

Pain is one of the leading symptoms of IC. Untreated, IC typically is a progressive disease.

Data on the prevalence of interstitial cystitis vary greatly. This may be explained with the still generally low level of awareness for this disease. Experts estimate that up to 0.5% of a given population is affected. Interstitial cystitis is typically regarded as a female disease. However, more and more experts are of the opinion that many men diagnosed with chronic non-bacterial prostatitis actually suffer from interstitial cystitis. Due to the low level of awareness for the disease, both in the general public as well as among professionals, on average 5 years elapse between first symptoms and the establishment of the correct diagnosis.

The course of interstitial cystitis is usually progressive. In the first years of the disease symptoms are generally unspecific. In advanced stages more or less typical lesions may be found on cystoscopy, namely so called glomerulations or in some patients so called Hunner´s lesions. These changes are, however, not found in all cases, and may be lacking even in very advanced disease stages.

In many cases increased numbers of mast cells in the detrusor muscle are found as a sign of the chronic inflammatory process. During the course of the

A specific deficit of chondroitin sulphate in the GAG-layer of the bladder has been demonstrated in IC-patients

disease, progressive fibrosis can occur which leads to a first only functional reduction in bladder capacity and in later stages may progress into an anatomically fixed form of bladder shrinkage.

Interstitial cystitis is a diagnosis established by exclusion. In clinical practice the exclusion of urinary tract infections including those by specific organisms such as bacteria, mycoplasma, and chlamydia is required as well as the exclusion of stones and carcinoma (including superficial bladder carcinoma) or diseases of the adjacent organs.

The cause of interstitial cystitis is still not resolved. In the meantime the concept of the permeability disorder at the bladder surface as a key element in the pathophysiology is increasingly gaining acceptance. Immunohistochemically a specific deficit of chondroitin sulphate has been found in the GAG-layer of the bladder of IC-patients. If this key component of the GAG-layer is replaced by means of **Gepan® instill**, a rapid improvement in symptoms is seen in a majority of patients (Kurth 2003).

Treatment of interstitial cystitis typically requires a multimodal approach in which various medications are combined. Intravesical GAG-replenishment provides a causally orientated approach and is a particularly important element in the therapeutic concept. GAG-replenishment therapy with **Gepan® instill** is accomplished by instillation of the chondroitin sulphate-solution with a catheter directly into the bladder. In this way a particularly high concentration of the chondroitin sulphate-solution can be achieved at the target organ.

Oral medication including analgesics, spasmolytics, and antidepressants generally follow a symptom orientated approach. Their use is often limited by systemic side effects.

Gepan® instill offers the possibility of particularly effective replenishment of missing chondroitin sulphate. Intravesical instillation treatment provides a high concentration of exogenous GAGs at the bladder wall. Specific systemic side effects are not to be anticipated. Accordingly, the IC-experts Kurth and Parsons consider intravesical GAG-replenishment therapy to be a cornerstone of therapy that should never be discontinued (Kurth & Parsons 2003, Kurth 2003). Two studies document improvement of symptoms by instillation of chondroitin sulphate (Steinhoff 2003, Sorensen 2003). Furthermore a large multinational, multi-centre, prospective observational clinical trial confirms positive experience with **Gepan® instill** (Nordling & van Ophoven 2008).

GAG-replenishment with chondroitin sulphate provides a causally oriented therapeutic approach

7.2 Overactive bladder syndrome

Increased urinary urgency usually in combination with increased urinary frequency characterize the OAB

Overactive bladder syndrome (OAB) encompasses a range of symptoms. The major symptom is a significantly increased urge to urinate which is in most cases associated with excessively frequent voiding. A distinction is drawn between *OAB dry*, a form of overactive bladder without involuntary voiding, and *OAB wet*, a form of overactive bladder involving episodes of incontinence. As with interstitial cystitis, OAB is diagnosed by ruling out other conditions. This generally makes it necessary to consider a broad range of possible differential diagnoses.

There is a certain degree of overlap of both conditions. The symptom pain can be decisive for the diagnosis. While pain is a key symptom in interstitial cystitis this is not typically present in overactive bladder syndrome (Ueda 2003).

Urodynamic procedures reveal autonomous detrusor contractions in some patients with overactive bladder syndrome. However, many patients do not experience this so called motor urge; in these cases sensory urge in other words, pathologically increased bladder sensitivity, predominates.

A study found that approximately 12% of the population suffer from overactive bladder syndrome (EPIC study, Irwin 2006). The disease becomes more prevalent as age increases. Patients already taking medical treatment are usually first treated with anticholinergic drugs. However, this drug group does not lead to improvement of symptoms in every patient. In addition, side effects may occur which may limit quality of life.

As with interstitial cystitis, the symptoms experienced by patients with overactive bladder are attributed to a defect in the GAG-layer. This is confirmed on the one hand by a positive potassium chloride test in patients with overactive bladder syndrome (Hohlbrugger 1999); on the other hand, a study involving OAB patients showed significant and sustained improvement in the symptoms through instillation of chondroitin sulphate (Gauruder-Burmester 2006, Gauruder-Burmester & Popken 2009). Furthermore, positive results with **Gepan® instill** were confirmed in a major application study (Nordling & van Ophoven 2008).

7.3 Radiation cystitis

Radiation cystitis can manifest during radiation therapy, or – as late form – months or years later

Radiation cystitis occurs as a consequence of radiation treatment extending to the lower abdomen, such as in prostate, cervical and rectum carcinoma. The same cardinal symptoms as in interstitial cystitis are present, namely the symptom triad "frequency-urgency-pain". Haemorrhages often occur additionally and these may be extremely difficult to manage. In contrast to interstitial cystitis, radiation cystitis has a well defined cause by the preceding radiation treatment.

An early form of radiation cystitis may be distinguished from a late form. The early form is characterised by acute irritative symptoms which occur during or shortly after radiation treatment. In many cases these symptoms are temporary and slowly disappear again after radiation treatment has been terminated. In contrast, the late form of radiation cystitis often manifests months or years after radiation therapy. This form often follows a progressive course and ultimately leads to bladder shrinkage. Severe trophic damage of the blood vessels by radiation is assumed to be the cause. Treatment can prove to be extremely frustrating.

While improvements of radiation techniques have decreased the incidence of severe forms of radiation cystitis in last decades, new procedures such as brachytherapy of prostate carcinoma have led again to an increase in the frequency of radiation induced symptoms.

In radiation cystitis, a deficit of the GAG-layer is typically found and accordingly, the potassium sensitivity test is usually positive (Parsons 1994). Therapeutic success with various forms of GAG-replenishment therapy have been reported for many years (Hampson & Woodhouse 1994, Strohmeier 1989).

Since the availability of intravesical GAG-replenishment therapy, for example with **Gepan® instill**, the therapeutic options have improved significantly (Ueda 2003). A recently presented observational study with **Gepan® instill** showed very positive results for patients with radiation cystitis (Nordling & van Ophoven 2008).

Furthermore there are now indications that preventive instillation of **Gepan® instill** in patients receiving radiation therapy can prevent acute radiation cystitis (Hazewinkel 2009). As the appearance of late form radiation cystitis is dependent on the emergence of symptoms directly after the radiotherapy, prevention of this late form of radiation cystitis might be possible as well.

7.4 Chronically-recurring cystitis

Four or more acute episodes a year characterize chronically-recurring cystitis

The occurrence of four or more acute episodes of urinary tract infection (UTI) is typically referred to as chronically-recurring cystitis. Generally each episode is caused by a new infection. Much less frequently the persistence of a bacterial pathogen is found. The symptoms are the same as in non-bacterial forms of cystitis: frequency, urgeny, pain.

Predisposing factors include e.g. anatomic abnormalities and obstructions. A shorter urethra is one of the reasons why UTIs occur more often in women than in men; 50-80% of all women suffer once in their lives from a UTI, and at least 25% of them have relapses (Ludwig 2006). A deficit of the GAG-layer is also a predisposing factor for the occurrence of chronically-recurring cystitis due to the reduced protection from bacterial adhesion. In addition every acute UTI damages the protective GAG-layer, thus setting in train a vicious circle which may lead to chronically-recurring cystitis developing into (abacterial) interstitial cystitis.

Acute episodes of UTI are usually relatively easy to manage with appropriate antibiotic treatment taking into account the resistance situation. In contrast, frequently recurring or chronic forms of cystitis are often much more difficult to manage. In some cases of frequent recurrences of UTI a permanent antibiotic prophylaxis is required (typically in low dosages). Unfortunately in many cases the results are unsatisfactory and despite all efforts, frequent recurrences remain a problem. Especially for these patients GAG-replenishment therapy with **Gepan® instill** is a promising option which can impressively reduce the frequency of the infections through reinforcement of the protective GAG-layer of the bladder.

In urinary tract infections, the potassium sensitivity test is typically positive indicating an increased permeability of the bladder wall (Parsons 1994). Accordingly, GAG-replenishment therapy provides a rational pathophysiological approach and indeed, therapeutic success for this form of treatment was documented in a number of studies (Lipovac 2007). Within the context of a multinational surveillance study the efficacy of **Gepan® instill** in the treatment of chronically-recurring cystitis was recently impressively demonstrated (Nordling & van Ophoven 2008).

8. GAG-replenishment therapy with **Gepan® instill**

Gepan® instill provides an effective product for replenishment of the GAG-layer. It contains 0.2% chondroitin sulphate, a quantitatively and qualitatively important component of the GAG-layer which is typically impaired in patients with chronic forms of cystitis. **Gepan® instill** is intravesically instilled into the bladder and restores or reinforces the protective function of the GAG-layer. The vicious cycle of chronic inflammation and inflammatory damage by noxious urine components is interrupted, and the urothelium is given the chance to regenerate.

In clinical practice **Gepan® instill** has demonstrated its efficacy in various forms of chronic cystitis including e.g. interstitial cystitis, overactive bladder syndrome, radiation cystitis and chronically-recurring cystitis.

The causally oriented approach provided by the substitution of the chondroitin sulphate component of the GAG-layer with **Gepan® instill** can restore the physiological protective function of GAG-layer.

Instillation of **Gepan® instill** into the bladder provides a high concentration of chondroitin sulphate at the urothelial surface and thereby a high availability, directly at the target tissue. The intravesical application provides the advantages of a parenteral application, without any loss of active ingredients in the gastrointestinal tract. This also explains the lack of specific systemic side effects.

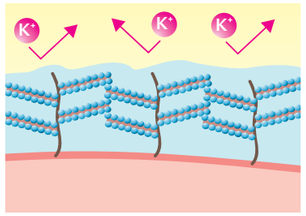
Continuous improvement during treatment with **Gepan® instill**

In clinical practice many patients reports improvement of their symptoms already after the first instillation. Studies have shown that in the further course of treatment a continuous improvement is seen. At the same time an increasingly positive global efficacy rating by patients and by attending physicians was documented, and excellent tolerability was seen.

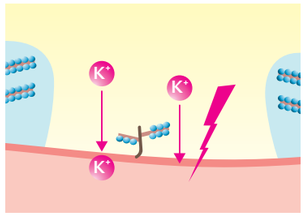
In patients with chronic forms of cystitis quality of life is typically severely impaired. During treatment with **Gepan® instill** an increase in quality of life was seen parallel to the decrease in symptoms.

A high degree of satisfaction with **Gepan® instill** *– rating by physicians and patients parallels a marked increase in quality of life*

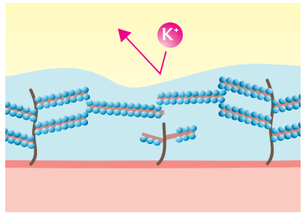
The following illustrations demonstrate the mode of action of **Gepan® instill**.



Normally glycosaminoglycans together with water form a mucous layer that protects the urothelium. Direct contact of irritants from within the urine with the urothelium is prevented (Metts 2001). Chondroitin sulphate is a major GAG-component (Hurst 1997).



A defect in the GAG-layer can cause symptoms of interstitial cystitis and other chronic forms of cystitis. Irritating substances such as potassium ions may leak through the urothelium, causing inflammation, tissue irritation and injury as well as sensory nerve depolarisation resulting in frequency, urgency and pain (Parsons 1994).



Gepan® instill contains highly purified and specially processed chondroitin sulphate. **Gepan® instill** provides effective temporary GAG-replenishment and reestablishes the protective layer of the urothelium and thus leads to symptomatic relief of interstitial cystitis and other chronic forms of cystitis (Steinhoff 2002).

The instillation volume of 40 milliliters is particularly advantageous in patients with considerable bladder atrophy and a small remaining bladder volume. **Gepan® instill** should remain in the bladder for as long as possible, a minimum time of half an hour is recommended.

Before instillation **Gepan® instill** can, if necessary, be warmed to body temperature.

The duration of therapy depends on the clinical development of symptoms in each individual case. While some patients require a continuous maintenance therapy, some attending physicians have reported a permanent healing of their patients who received intravesical GAG-replenishment therapy.

The frequency of instillations is dependent on clinical symptoms. Generally it is recommended to begin with four to six instillations in weekly intervals and then to switch to maintenance therapy once per month. The intervals between instillations can, however, also be adjusted depending on the severity and / or the reoccurrence of symptoms.

Gepan® instill is generally very well tolerated. Specific side effects have not been reported.

Treatment protocol

According to severity of symptoms.

Initial

- Instill one vial per week during the first 4 to 6 weeks of treatment.

Maintenance

- Instill one vial per month.

9. Scientific documentation

9.1 Preclinical studies

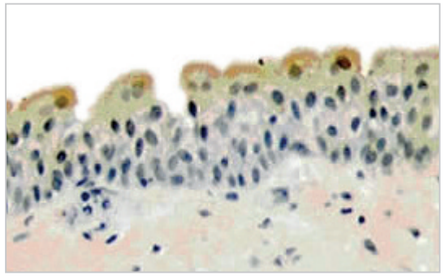
Numerous investigations conducted during the last ten to fifteen years have intensively studied the structure of the GAG-layer and elucidated the particular importance of its chondroitin sulphate component.

These investigations reveal that the GAG-layer of the bladder is made up mainly of chondroitin sulphate, dermatan sulphate and heparan sulphate.

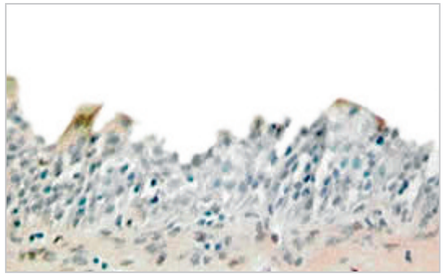
Immunohistochemical investigations have demonstrated a largely specific deficit of chondroitin sulphate, which is contained in **Gepan® instill**, in the GAG-layer of patients with interstitial cystitis (Slobodov 2004, Hurst 2003). The difference in the chondroitin sulphate content of the GAG-layer in biopsies in patients with interstitial cystitis in comparison to control persons is statistically highly significant ($p<0.0001$).

The following first illustration shows a normal urothelium. The brown colour indicates immunohistochemically stained chondroitin sulphate. It can be seen that the chondroitin sulphate is found in smaller quantities in the suburothelial tissue. Much more pronounced, however, is the high chondroitin sulphate concentration in the GAG-layer on the surface of the bladder cells.

In contrast the second illustration shows the tissue of a patient with interstitial cystitis. The lack of chondroitin sulphate at the urothelial surface is clearly evident (Kurth 2003).



Normal urothelium



IC urothelium

In GAG-replenishment treatment, intravesically applied chondroitin sulphate is deposited on the urothelium only where there is a defect in the GAG-layer. This has been confirmed in a preclinical study with fluorescent labeled chondroitin sulphate (Kyker 2005).

Overview of important studies

Title	***Bladder surface glycosaminoglycans: an epithelial permeability barrier***
Authors	***Parsons CL, Boychuk D, Jones S, Hurst RE, Callahan H***
Source	***J Urol (1990) 143(1): 139–142***
Methods	*In vitro* investigations of the significance of the GAG-layer for the regulation of the permeability of the bladder wall of rodent bladders for ions
Main results	• Evidence of a major contribution of the GAG-layer to the regulation of permeability at the bladder surface • Evidence of efficacy of exogenously administered GAGs in reestablishment of physiological bladder wall impermeability • Description of anti-adhesive properties of GAG-layer

Title	***Identification of proteoglycans present at high density on bovine and human bladder luminal surface***
Authors	***Hurst RE, Zebrowski R***
Source	***J Urol (1994) 152(5): 1641–1645***
Methods	*In vitro* investigations on bovine bladders and human bladder biopsies
Main results	Identification of chondroitin sulphate, heparan sulphate and dermatan sulphate as major components of GAG-layer

Title	***A deficit of proteoglycans on the bladder uroepithelium in interstitial cystitis***
Author	***Hurst RE***
Source	***Eur Urol Suppl (2003) 2: 10–13***
Methods	Immunhistochemical *in vitro* investigations and comparison of biopsies of the bladder of patients with interstitial cystitis and control patients (incontinence patients)
Main results	Evidence of a specific chondroitin sulphate deficit in the GAG-layer of patients with interstitial cystitis (Statistically highly significant difference $p < 0.001$)

Title	***Abnormal expression of molecular markers for bladder impermeability and differentiation in the urothelium of patients with interstitial cystitis***
Authors	***Slobodov G, Feloney M, Gran C et al.***
Source	***J Urol (2004) 171(4): 1554–1558***
Methods	Comparison of various glycosaminoglycans and proteins in the bladder surface in patients with interstitial cystitis and control persons
Main results	In interstitial cystitis highly significant lack of chondroitin sulphate as well as of *Zona occludens* protein ZO-1

Title	***Exogenous glycosaminoglycans coat damaged bladder surfaces in experimentally damaged mouse bladder***
Authors	***Kyker DK, Coffman J, Hurst RE***
Source	***BMC Urol (2005) 5: 4–8***
Methods	Instillation of fluorescent labeled chondroitin sulphate into damaged mouse bladder
Main results	Intravesically applied chondroitin sulphate binds to damaged bladder surface only.

9.2 Clinical studies

Steinhoff: The efficacy of chondroitin sulphate in treating interstitial cystitis

Steinhoff investigated 18 patients with advanced stages of interstitial cystitis. These patients were diagnosed according to the so called NIH/NIDDK criteria of 1987/1988. These criteria provide a research definition and only include patients with advanced forms of disease and the presence of typical cystoscopic findings.

A potassium chloride test was also conducted to demonstrate the presence of a GAG-layer deficit.

At the beginning of therapy patients received chondroitin sulphate 0.2% once per week for four weeks. Then maintenance therapy with one instillation per month was administered.

After a total of thirteen months the follow-up was conducted. At this time thirteen patients were available for investigation. In twelve of these patients efficacy of chondroitin sulphate could be documented by use of the ICSI (Interstitial Cystitis Symptom and Problem Indices) proposed by O'Leary and Sants.

An improvement of five to fourteen points on the problem scale (from 0 to 16) and eight to thirteen points on the symptom scale (from 0 to 20) was defined as a good response. A moderate response was assumed when improvement of two to three points on the symptom scale and three to five points on the problem scale was seen. A partial response was considered when the symptom scale showed an improvement by one point or one to four points of improvement was seen on the problem scale. Of the included thirteen patients six had a good response, two a moderate response and four patients had a partial response to chondroitin sulphate. Only one patient showed no improvement.

No adverse events were seen during the course of treatment. Of importance is also that some of these patients showed a further improvement in the further course of treatment in the second year, whereas a decrease of the improvement was not observed in any patient.

Summary

Title	***The efficacy of chondroitin sulfate in treating interstitial cystitis***
Author	***Steinhoff G***
Publication	***Steinhoff G (2003) Eur Uro Suppl 2: 14-16***
Further Publications	• Steinhoff G, Ittah B, Rowan S (2003) The efficacy of intravesicular sterile sodium chondroitin sulfate 0,2 % in potassium tested positive patients with interstitial cystitis, Adv Exp Med Biol 539: 731-739 • Steinhoff G, Ittah B, Rowan S (2002) The efficacy of chondroitin sulfate 0,2 % in treating interstitial cystitis, Can J Urol 9(1): 1454-1458
Study design	Open study
Number of patients included	18
Patient characteristics	Interstitial cystitis diagnosed according to the restrictive NIH/NIDDK criteria and positive potassium sensitivity test 17 females, 1 male
Treatment	Chondroitin sulphate 0.2% administered for four weeks once per week and then once per month
Duration of observation	13 months
Parameters	ICSI proposed by O'Leary and Sants
Results	Data of thirteen patients were available at thirteen months' follow-up Response to chondroitin sulphate positive in twelve of thirteen patients (good response six times, moderate response two times, partial response four times) These twelve patients continued the treatment and further improvement was seen in some patients during the second year of treatment. No adverse events

Gauruder-Burmester et al.: Treatment of overactive bladder with sodium chondroitin sulphate

In a controlled, randomized clinical study, Gauruder-Burmester investigated the use of chondroitin sulphate in the treatment of overactive bladder syndrome in 82 female patients. Before they were included in the study and at the end of the treatment, the women were provided with voiding diary, in which they had to keep precise records for one week. In addition, each underwent urodynamic testing.

Half of the patients were treated over a period of 12 months with 0.2% chondroitin sulphate. The instillations were performed weekly for the first month and monthly thereafter. At the end of the study, 32 of the patients treated with chondroitin sulphate were available for follow-up examination. These patients exhibited a significantly reduced urinary frequency (from 14 to 7 times during the day and from 4 times to once during the night). Urodynamic testing showed 6 patients to have a reduced bladder capacity as opposed to 19 before the start of treatment.

There was also a significant improvement in sensory urge from an initial 28 patients to 12 patients, and in motor urge from an initial 13 to just 3 patients. In the subjective evaluation of the treatment, 72% of the patients treated with chondroitin sulphate exhibited improved symptoms. A significant improvement in quality of life was also observed as a result of the instillation of 0.2% chondroitin sulphate.

The other half of the patients received tolterodine, an anticholinergic, at a daily dose of 4 mg. In this group, 35 patients were available for the final evaluation. Urinary frequency was also reduced in this half of the patients. However, no significant improvement was observed. The number of patients with sensory or motor urge was also reduced in this group, albeit not so greatly as in the group treated with chondroitin sulphate. A subjective improvement in symptoms was observed in 43% of the patients.

Overall, the study provides impressive evidence for the efficacy of a GAG-replenishment therapy consisting of 0.2% chondroitin sulphate administered intravesically in patients with overactive bladder syndrome.

Summary

Title	***Treatment of overactive bladder with sodium chondroitin sulphate***
Authors	***Gauruder-Burmester A, Wildt B, Tunn R***
Publication	***Gauruder-Burmester A et al. (2006) Zentralbl Gynakol 128(6): 336-340***
Study design	Prospective controlled, randomized clinical study
Number of patients included	82
Patient characteristics	Patients with chronic overactive bladder
Treatment	Group A tolderodine (daily 4 mg retard) Group B chondroitin sulphate 0.2% (1 instillation weekly for one month, thereafter 1 instillation monthly)
Term of treatment	12 months
Parameters	Micturition frequency Motor and sensory urge (urodynamic testing) Bladder capacity (urodynamic testing) Quality of life score

continued on next page

continued from page 35

Results group A (tolterodine)	35 women completed the entire course of treatment (12 months)	
	Daytime micturition frequency	16→12
	Nocturia	5→ 3
	Incidence of motor urge (number of patients)	9→ 8
	Incidence of sensory urge (number of patients)	32→23
	Bladder capacity < 300ml (number of patients)	27→20
	Improvement of symptoms (subjective assessment)	43% of patients
	Quality of life	Improved
Results group B (chondroitin sulphate 0.2%)	32 women completed the entire course of treatment	
	Daytime frequency	14→ 7
	Nocturia	4→ 1
	Incidence of motor urge (number of patients)	13→ 3
	Incidence of sensory urge (number of patients)	28→12
	Bladder capacity < 300ml (number of patients)	19→ 6
	Improvement of symptoms (subjective assessment)	72% of patients
	Quality of life	Improved
Comparison of both groups	Considering the two forms of treatment, chondrotin sulphate 0.2% produced significantly better results than the anticholinergic agent.	

Nordling, van Ophoven: Intravesical glycosaminoglycan replenishment with chondroitin sulfate in chronic forms of cystitis — A multi-national, multi-centre, prospective observational clinical trial

From 2004 until December 2005 the most comprehensive observational study with intravesical instillation therapy to date was conducted during the conditions of normal clinical practice. Chondroitin sulphate 0.2% was administered to nearly 300 patients with different bladder diseases associated with a GAG-layer deficit.

An interim analysis was conducted in July 2005 and the results were presented at a scientific symposium held in Hamburg in September 2005 by Prof. J. Nordling from the University of Copenhagen Denmark.

In the final analysis data of 286 patients were available. About 91% of these patients were female. The countries of origin were Germany, the Netherlands, Denmark, Austria and Sweden.

The overlap between the various diseases was again confirmed in this trial. A number of patients had been assigned multiple diagnoses. Especially, often combinations of interstitial cystitis and overactive bladder were diagnosed, frequently in combination with chronically-recurring cystitis.

An impressive improvement in all symptoms was seen. Particularly noteworthy: this improvement was seen from the first instillation and during the course of treatment a continuous further improvement was observed.

Patients frequently report that they can deal comparatively well with frequent daytime micturitions, but that nocturia, pain and urinary urgency are particularly bothersome and detrimental to the quality of life. Results of this

investigation clearly show improvement especially in these parameters during the course of treatment with chondroitin sulphate. The excellent response to chondroitin sulphate is also reflected in the generally very positive global ratings both by patients and physicians.

Hereinafter the summary and detailed results of the different patients groups are shown.

Summary

Title	***Intravesical glycosaminoklycan replenishment with chondroitin sulfate in chronic forms of cystitis — A multi-national, multi-centre, prospective observational clinical trial***
Authors	***Nordling J, van Ophoven A***
Publication	***Nordling J, van Ophoven A (2008) Arzneimittelforschung (Drug Research) 58(7): 328-335***
Study design	Post marketing surveillance study
Number of patients included	286
Patient characteristics	Diagnoses: Interstitial cystitis, OAB, radiation cystitis, chronically-recurring cystitis Age (mean): 60.5 years Gender: female 90.6% male 9.4%
Treatment	Weekly instillation during the first 4 to 6 weeks, thereafter monthly
Term of treatment	Average duration of observation: 3 month
Parameters	Urinary frequency Urinary urgency* Pain score* Volume of first morning voiding (optional)
Results	Daytime frequency 12,7→ 9,2 x Nocturia 4,0→ 2,1 x Urinary urgency* 6,8→ 3,4 Maximum pain score* 6,3→ 3,6 Average pain score* 4,8→ 2,6 Minimum pain score* 3,3→ 1,8 Global efficacy: Positive rating by 82% of patients and 84% of physicians Increase in volume of first morning voiding from 158ml to 187ml Excellent tolerability, few non-specific adverse events

* on scales of 0 to 10

Summary of results

Gepan® instill in patients with interstitial cystitis

Interstitial cystitis		
– 165 patients	Daytime frequency	13.9→ 10.0 x
– Development of symptoms during up to 8 instillations	Nocturia	4.1→ 2.2 x
	Urgency*	6.9→ 4.0
	Maximum pain-score*	6.8→ 4.3
	Average pain-score*	5.2→ 3.3
	Minimum pain-score*	3.6→ 2.2
	Positive rating of global efficacy by 77% of patients and 79% of physicians	

Gepan® instill in patients with radiation cystitis

Radiation cystitis		
– 15 patients	Daytime frequency	10.7→ 7.4 x
– Development of symptoms during up to 8 instillations	Nocturia	4.7→ 2.0 x
	Urgency*	7.2→ 2.3
	Maximum pain-score*	5.9→ 2.6
	Average pain-score*	4.5→ 1.8
	Minimum pain-score*	2.7→ 1.7
	Positive rating of global efficacy by all patients and all physicians	

* on scales of 0 to 10

Gepan® instill in patients with overactive bladder syndrome

Overactive bladder syndrome		
– 38 patients	Daytime frequency	12.3→ 10.0 x
– Development of symptoms during up to 8 instillations	Nocturia	3.8→ 2.5 x
	Urgency*	7.7→ 4.2
	Maximum pain-score*	5.4→ 3.3
	Average pain-score*	4.4→ 2.3
	Minimum pain-score*	3.3→ 1.6
	Positive rating of global efficacy by 78% of patients and 92% of physicians	

Gepan® instill in patients with chronically-recurring cystitis

Chronically-recurring cystitis		
– 86 patients	Daytime frequency	10.7→ 7.5 x
– Development of symptoms during up to 8 instillations	Nocturia	3.4→ 1.7 x
	Urgency*	6.4→ 2.7
	Maximum pain-score*	6.0→ 2.8
	Average pain-score*	4.5→ 2.0
	Minimum pain-score*	3.1→ 1.2
	Positive rating of global efficacy by 91% of patients and 94% of physicians	

* on scales of 0 to 10

Gauruder-Burmester, Popken: Follow-up at 24 months after treatment of overactive bladder with 0.2% sodium chondroitin sulfate

Two years after inclusion in the study (Gauruder-Burmester 2006, see page 34) Gauruder-Burmester performed a follow up investigation. All 67 patients were available for the follow up control. Each patient underwent the same examination procedure as before. 56% of patients of the chondroitin sulphate group still reported an improvement of symptoms one year after the study while only 14% of patients of the tolterodine group could confirm that.

Authors acknowledge that chondroitin sulphate results in a more long-term improvement or cure of the symptoms of overactive bladder due to reinstatement of the glycosaminoglycan layer. Thus the positive results confirm the sustained efficacy of therapy with **Gepan® instill**.

Summary

Title	***Follow-up at 24 months after treatment of overactive bladder with 0.2% sodium chondroitin sulfate***
Authors	***Gauruder-Burmester A, Popken G***
Source	***Gauruder-Burmester A, Popken G (2009) Aktuel Urol 40(6): 355-359***
Further publications	Gauruder-Burmester A, Popken G (2008) Geburtsh Frauenheilk; 68: 1077-1081
Study design	Controlled randomised clinical study
Number of patients included	67
Follow-up	24 months after inclusion into the study
Results group A (tolterodine)	Re-evaluation after 24 months (Comparison with data from before beginning of the study) Micturition (frequency/day) 16→14 Nocturia (episodes/night) 5→ 6 Incidence of motor urge 9→11 Incidence of sensory urge 32→30 Number of patients with bladder capacity < 300 ml 27→25 Improvement of symptoms (subjective rating) 14% of patients Quality of life Improved
Results group B (chondroitin sulphate 0.2%)	Re-evaluation after 24 months Micturition (frequency/day) 14→ 9 Nocturia (episodes/night) 4→ 3 Incidence of motor urge 13→ 5 Incidence of sensory urge 28→17 Number of patients with bladder capacity < 300 ml 19→10 Improvement of symptoms (subjective rating 56% of patients Quality of life Improved significantly
Comparison of both groups	The results show that treatment with 0.2% chondroitin sulphate can lead to a sustained improvement in symptoms.

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