

S62 2008
A SUPPLEMENT TO

The Female Patient[®]

YOUR GUIDE TO TOTAL HEALTH CARE

- > **Symptoms
of Interstitial
Cystitis**
- > **Diagnosis
of IC/PBS**
- > **Tests and
Treatments**
- > **Attaining and
Maintaining
Quality of Life:
A Personal
Experience**

Interstitial Cystitis and Painful Bladder Syndrome

Sponsored and Developed by
Ortho Women's Health & Urology™

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Learn all about IC at
www.allaboutic.com.

Pelvic pain.

Frequent trips to the bathroom.

Painful urination.

You are not alone. You may have IC.

Millions of people may suffer from pelvic or lower abdominal pain that lasts 6 months or longer. In many cases, this pain is the result of a long-term bladder condition called interstitial cystitis (IC), also known as painful bladder syndrome.

The most important thing to know about IC is that it's treatable. With the right information, advice and support, you can find relief from IC. From detailed symptoms to self-diagnosis tests to treatments, **www.allaboutic.com** is a great resource for anyone suspecting she might have IC.

If you've been treated for recurring urinary tract infections, overactive bladder and endometriosis without success, it might be time to talk to your doctor about IC.



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July 2008

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What Are the Symptoms of Interstitial Cystitis?

Gita Singh, MD

There was a time when people with persistent but unexplained urinary tract symptoms and pelvic pain were told the problem was imaginary or caused by depression. Both patients and their healthcare professionals were relieved when research identified and named the problem.

The condition, called interstitial cystitis (IC), means inflammation between the layers of the bladder. Although IC can develop in men, 9 out of 10 people with IC are women. In 2002, a survey of a large managed-care population revealed that 6% to 11% of women self-reported a diagnosis of IC/painful bladder syndrome (PBS). Because symptoms vary in different patients,

scientists think that IC may be a group of similar disorders, rather than one specific disease. To reflect this, they have begun to add the term PBS to describe these disorders. “Syndrome” means a group of symptoms and physical findings that together are typical of a disease or medical condition. Women with IC/PBS have the following 3 symptoms in common:

Bladder Pain, Discomfort, or Pressure.—In addition to blad-

der pain, there may also be pain in other parts of the pelvis such as the lower abdomen, below the belly button, and between the hip bones. The pain can come and go, or it may be constant and vary from mild to severe. Often the pain is worse when the bladder is full and improves after urination.

Urinary Frequency.—There is the need to urinate often, sometimes every hour or less.

Urinary Urgency.—There is a need to urinate right away.

All 3 symptoms often worsen around the time of a period or during or after intercourse. They also interfere with sleep, work, social activities, and quality of life. Some women with IC/PBS don't want to leave home for fear they will not be able to find a bathroom, or that their pain will become unbearable when they are at work or a social event.

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Talking to Your Healthcare Professional About IC/PBS

Interstitial cystitis/PBS can be challenging to treat and diagnose. It has no known cause and no specific diagnostic test. Other problems, such as urinary tract infections, also called bladder infections, cause similar symptoms and are often confused with IC/PBS. Despite these obstacles, a diagnosis of IC/PBS can be based on symptoms of chronic bladder pain, usually with urinary urgency and frequency, for which no other causes can be found.

How specific you are in describing your symptoms can provide the important clues your healthcare professional needs to diagnose you correctly. There are some aids to organizing your thoughts. For example, if you have access to a computer (many libraries provide free access), you can find guidance about recording symptoms at www.allaboutIC.com.

Interstitial cystitis/PBS can be challenging to treat and diagnose. It has no known cause and no specific diagnostic test.

It will be helpful for your physician if you can answer the following questions in detail and bring your answers to your first visit:

Pain.—When did the pain start? Did it start suddenly or gradually? Is it always there or does it come and go? Where exactly do you feel it? Does it stay in one place or spread to other parts of your body? Does anything make it start, get better, or get worse? How bad is the pain? Describe your pain using a “pain scale” where 0 is no pain at all and 10 is the worst pain imaginable. What does it feel like: sharp like a knife, dull like a toothache, burning?

Bladder Symptoms.—How often do you use the bathroom during the day? At night? After you empty your

bladder, do you feel like you still need to urinate? If you have urgency, do you need to empty your bladder because of pain, or because you feel you might lose urine? Does your full bladder feel painful? Over time, has the problem gotten better, worse, or stayed the same? Have you been treated for bladder or vaginal infections recently or in the past? How many times? Did treatment help? You can also fill out and bring in the **Pelvic Pain and Urgency/Frequency Patient Symptom Scale (PUF)** (page 14).

Quality of Life.—Have these symptoms made you change anything about your life? For example, do you avoid going out unless you know the



time. I go to the bathroom every hour or two during the day, and at least 4 times at night. Even after I go, I feel like I haven't emptied my bladder. When my bladder is full, the pain is so bad I have to get to the bathroom right away. I filled out this PUF checklist to go over with you.

Dr Smith: Can you describe the pain for me?

Ms Jones: It's an ache that's worse when my bladder is full, but it comes and goes at other times, too. It's even stronger around my period. When it's really bad, it's about an 8 on the pain scale. If I lie down with a heating pad, it goes down to about a 2. In the past 3 months, I've called in sick 3 times because of pain.

As Dr Smith asks more questions, it's important that Ms Jones is prepared for them. She will need to let her doctor know how her life is changed by her condition. By working in partnership with her doctor, patients like Ms Jones can help her doctor make the correct diagnosis and provide her with the right treatment. Interstitial cystitis/PBS can be frustrating and painful, but it is treatable.

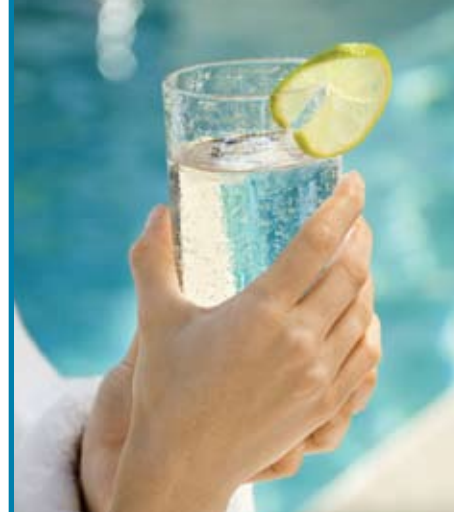
Gita Singh, MD, is a urologist at Northeast Indiana Urology, Fort Wayne. Dr Singh is a consultant speaker for Ortho Women's Health & Urology™. Dr Singh received an honorarium from *The Female Patient* for this article, with funding provided by Ortho Women's Health & Urology™.

Unmasking the Many Faces of IC

PATIENT SURVEY FACT SHEET

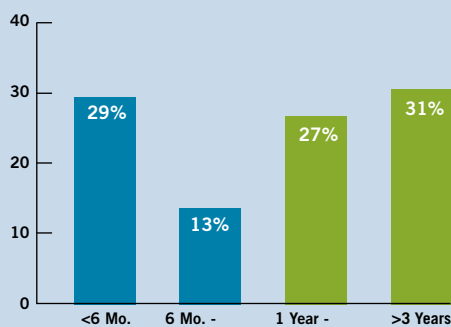
Interstitial Cystitis, or IC, is a painful, often debilitating bladder condition that is frequently misdiagnosed because its symptoms—pain in the pelvic area, urinary urgency and frequency, and pain during or after sexual intercourse—often “masquerade” as other pelvic conditions. Consequently, it can take years and several healthcare professionals to find a correct diagnosis.

In support of the annual National IC Awareness Day on October 31, Ortho Women’s Health & Urology™, along with the National Association of Nurse Practitioners in Women’s Health, conducted an online survey of 589 self-reported IC patients* to shed light on the condition’s physical and emotional burden. The following results were reported. Visit www.allaboutIC.com to see the “Many Faces of IC” unmasked and learn more about the condition.



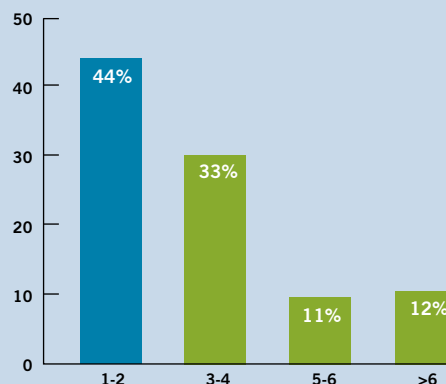
THE LONG JOURNEY TO DIAGNOSIS

The majority of responding IC patients said that their IC had taken a year or more to diagnose, and that they had seen 3 or more healthcare professionals (HCPs) before they received their IC diagnosis.



YEARS BEFORE IC DIAGNOSIS

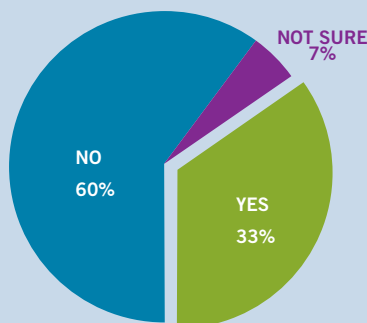
Over half of respondents (58%) said their IC diagnosis took a year or more. Nearly one third said it took 3 years or more.



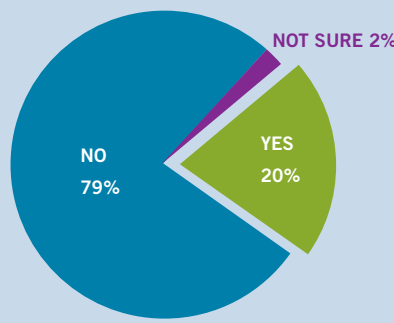
NUMBER OF HCPs SEEN BEFORE DIAGNOSIS

More than half of respondents (56%) reported seeing 3 or more healthcare professionals before diagnosis.

Before being diagnosed with IC, one third of respondents said that it had been suggested that their condition may be psychological, and one fifth said they have been directed to seek psychological help.



CONDITION SUGGESTED TO BE PRIMARILY PSYCHOLOGICAL



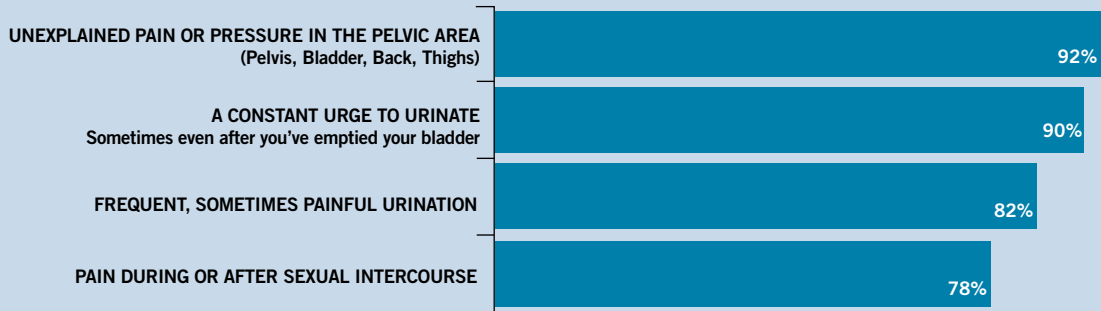
DIRECTED TO SEEK PSYCHOLOGICAL HELP

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THE PHYSICAL AND EMOTIONAL STRESS OF IC

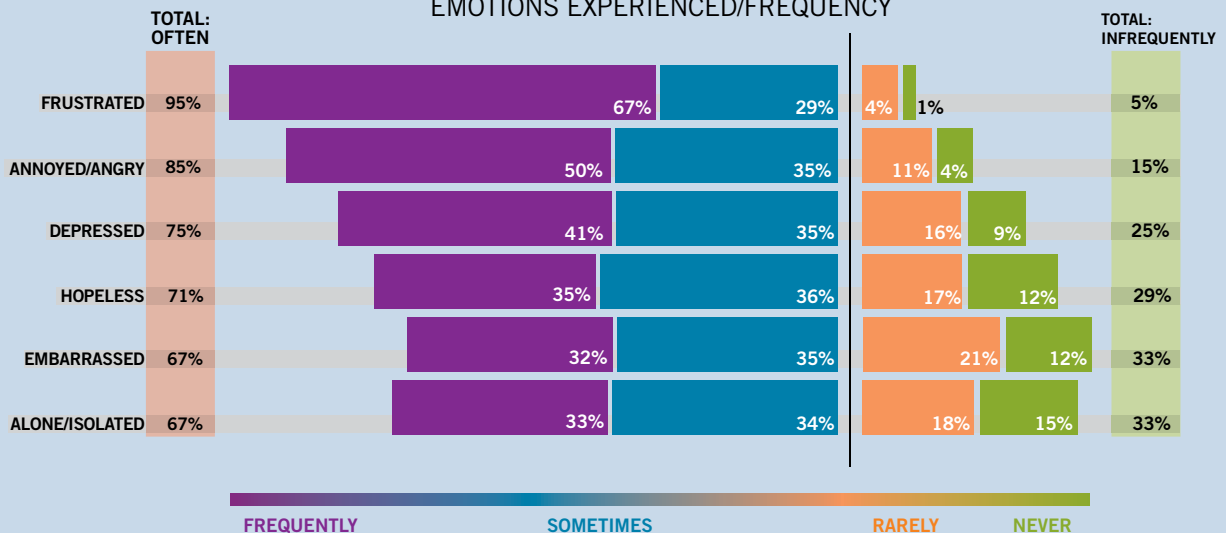
IC symptoms, which can appear at any age, are intermittent in the early stages and become chronic in subsequent years. Almost all respondents said they have experienced painful or uncomfortable symptoms. Nine in 10 reported experiencing unexplained pelvic pain or pressure and an urgent need to use the bathroom.

PHYSICAL SYMPTOMS EXPERIENCED



People with IC often experience emotional or social problems as a result of their condition. Survey respondents most frequently reported experiencing emotions such as frustration and anger, but many also reported feelings of depression, embarrassment, and isolation.

EMOTIONS EXPERIENCED/FREQUENCY



*ABOUT THE SURVEY

The "Unmasking the Many Faces of IC" patient survey was conducted online by KRC Research from September 14-28, 2007. A total of 589 self-reported IC patients responded to the survey from a database of patients who had opted to receive IC-related communications. Nearly all respondents were female (98%). The survey was sponsored by Ortho Women's Health & Urology™, Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc.

How Your Healthcare Professional Will Diagnose IC/PBS



Robert J. Evans III, MD

Although we'd like to think that healthcare professionals have all the answers, some medical conditions are difficult to diagnose. Interstitial cystitis/painful bladder syndrome (IC/PBS) is one of those conditions.

Often, women with IC/PBS are misdiagnosed with other conditions for years before a healthcare professional makes the correct diagnosis and provides the right treatment.

The problem with diagnosing IC/PBS is that it shares its main symptoms of chronic pelvic pain, urinary urgency (the need to urinate immediately), and frequency (the need to urinate unusually often) with other diseases. Fortunately, healthcare professionals are learning the differences between IC/PBS and the conditions it mimics.

IC/PBS

The Condition.—Interstitial cystitis/PBS is a syndrome marked by chronic pelvic or bladder pain, urinary urgency and frequency,

and sometimes painful intercourse. Recently, IC was expanded to IC/PBS to include all causes of urinary tract pain that cannot be explained by other problems, such as infection, bladder or kidney stones, or the conditions discussed in this article. Pelvic pain, pressure, or discomfort is the most common and disabling symptom of IC/PBS. The pain typically worsens with bladder filling and may improve after the bladder is emptied. The urgency occurs because of a desire to relieve the pain. If IC/PBS is undiagnosed and untreated, it can significantly interfere with a woman's ability to work, sleep, care for her family, and have a normal home and social life.

The Cause.—It appears that in IC/PBS, the protective lining of the bladder is damaged, leaving it

exposed to irritation. The reason for this is unknown. Some researchers recently found a substance called antiproliferative factor (APF) that, with few exceptions, occurs only in the urine of women with IC/PBS. They believe that APF may play a role in IC/PBS by blocking the growth of the cells that line and protect the bladder.

The Tests.—There are several tests that can be used to diagnose IC/PBS. For an explanation of these tests, see page 8.

Chronic or Recurrent Bacterial Cystitis

The Condition.—The most common misdiagnosis of IC/PBS is chronic bacterial cystitis, a long-lasting infection of the bladder caused by bacteria that is also called recurrent urinary tract infection. Many women eventually diagnosed with IC/PBS were first told they had chronic bacterial cystitis because both conditions share the symptoms of urgency, frequency, and pain. Urinary tract infections are very common among women in their childbearing years, and most women have been treated for one at some time.

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CONDITION	SYMPTOMS	CAUSE	DIAGNOSTIC TOOLS
Interstitial Cystitis/ Painful Bladder Syndrome	Chronic pelvic pain Urinary urgency, frequency Painful intercourse	Damage to protective lining of bladder	Pelvic Pain and Urgency/ Frequency Scale Cystoscopy with or without hydrodistension
Recurrent Bacterial Cystitis	Urinary urgency, frequency Pain	Bacterial infection	Urine culture and sensitivity
Overactive Bladder Syndrome	Urinary urgency Urge incontinence	Overactive bladder muscles	Urodynamics
Endometriosis	Pelvic pain, menstrual cramps, painful intercourse, urinary frequency/urgency	Endometrial tissue grows outside the uterus	Laparoscopy
Vulvodynia: Vulvar Vestibular Syndrome	Pain, soreness, burning/stinging in the vulvar area—especially at the opening of the vagina	Unknown—depends on classification	Depends on classification Physical examination

With early IC/PBS, the symptoms of urgency, frequency, and pain seem to come and go. So if a patient is diagnosed with chronic bacterial cystitis and the problem clears up after taking the antibiotics, it will seem that the antibiotics solved the problem, when in fact the symptoms would have gone away even without treatment. Later on in the course of IC/PBS, the pain occurs daily or almost every day. At that point, most healthcare professionals will check the urine, using a culture to see which bacteria are present and which antibiotics will work. When the culture shows no bacteria, the healthcare professionals will start thinking about other problems. Sometimes they will refer to the problem of ongoing urgency, frequency, and burning without bacteria in the urine as “urethritis”—inflammation of the tube through which urine drains out of the bladder—but the most likely problem is IC/PBS.

The Cause.—Chronic bacterial cystitis is caused by bacteria in the urine. Urine is normally sterile (contains no bacteria).

The Tests.—A urine culture to check for bacteria will be positive, meaning that bacteria are present.

The Difference.—The most important difference between IC/PBS and chronic bacterial cystitis is that with

chronic bacterial cystitis, a urine culture grows bacteria.

Overactive Bladder

The Condition.—Overactive bladder (OAB) is a condition marked by the urge to urinate immediately and a sudden, unwanted loss of urine called urinary urge incontinence. Overactive bladder is common in women of all ages but is more likely to occur in older women. There are effective medications for managing OAB, but if the real problem is IC/PBS, they won’t work.

The Cause.—In OAB, patients feel the need to urinate because the bladder muscles become too active. These muscles send a signal to start pushing urine out even when there is very little urine in the bladder. Overactive bladder medications work by calming the bladder muscles, allowing the bladder to become fuller without signaling the need to empty.

The Tests.—Tests may include urodynamics, which measures how well bladder muscles and nerves work and how much urine your bladder can hold.

The Difference.—In OAB, the need to urinate immediately, or urgency, is caused by a feeling that you are about to leak urine or “have an accident.” In IC/PBS, the urgency is caused by a strong need to relieve the pain of a full or partially full bladder. If your

healthcare professional suggests that you have OAB, but your urgency comes from a need to relieve pain rather than a desire to prevent an accident, ask your healthcare professional to consider a diagnosis of IC/PBS. There is usually no pain with OAB, but there is with IC/PBS.

Endometriosis and Chronic Pelvic Pain

The Condition.—Endometriosis and IC/PBS can and often do occur in the same patient. Endometriosis is a common cause of pelvic pain in women during their childbearing years. Symptoms of endometriosis can include urgency, frequency, pelvic pain, menstrual cramps, and painful intercourse. Treatment with hormones such as birth control pills or injections may be tried to see if the symptoms get better. Interstitial cystitis/PBS pain may be felt in the pelvic area—the area below the belly button and enclosed by the hip bones—rather than just in the bladder, and like endometriosis, it may worsen before and during menstrual periods.

The Cause.—Endometriosis occurs when the endometrial tissue that normally lines the uterus grows in places outside the uterus. The uterine lining is shed every month through the vagina as a menstrual period if a

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Tests and Treatments for IC/PBS

José Hernández-Gräulau, MD

If chronic pelvic or bladder pain, or urinary urgency and frequency are interfering with your life and no cause can be found, your healthcare professional may suspect interstitial cystitis/painful bladder syndrome (IC/PBS).

Finding the Right Healthcare Professional

Your choice of healthcare professional will be influenced by whether you have health insurance, what type of insurance you have, and your financial resources. What is most important is that you see a healthcare professional who will listen carefully to your health concerns.

Some healthcare professionals diagnose and treat IC/PBS themselves; others may refer you to specialists for testing and/or treatment. Specialists include urologists, experts in problems of the bladder and urinary tracts of women and men; gynecologists, experts in women's reproductive health; and urogynecologists, a specialist gynecologist who treats all pelvic-floor problems.

Healthcare professionals are more aware of IC/PBS than ever before.



In the past, women with IC/PBS were often told that their symptoms were caused by stress or depression. If your healthcare professional suggests this and you disagree, ask for a referral. You can appeal the decision with your insurer if your healthcare professional is reluctant to refer you. The Web site www.allaboutIC.com has useful tips on talking with your healthcare professional. You can find a physician who treats IC/PBS by going to www.orthoelmiron.com. Enter your zip code into the Find a Doctor search function.

Associated Conditions

Many patients who have IC/PBS may commonly have a history of migraine or frequent headaches, seasonal allergies, constipation, irritable bowel syndrome (IBS), fibromyalgia, heartburn, or mild to moderate depression. Make sure your healthcare professional is aware if you have any of these associated conditions.

Tests for IC/PBS

There is no one test that can diagnose IC/PBS. In order to diagnose IC/PBS, your healthcare professional will first have to rule out other medical problems (like a urinary tract infection, endome-

triosis, or most importantly, bladder cancer) that can be the cause of your symptoms. Other tests that can help your healthcare professional make a diagnosis include the following:

The Pain and Urgency/Frequency Patient Symptom Scale (PUF).

—This self-scoring test is free, you can do it yourself, and it helps your healthcare professional decide if further tests are necessary. If your health history and physical examination suggest IC/PBS, a PUF score of 10 or more makes the evidence stronger.

Cystoscopy.—The doctor inserts a thin, lighted instrument (cystoscope) into your bladder through the urethra and inspects the bladder lining for problems such as inflammation, ulcers, or tumors. The bladder is stretched with fluid to a fairly high pressure, a procedure called “hydrodistension.” This painful procedure should be performed under general anesthesia. In general, IC/PBS patients can tolerate only a relatively low volume of fluid instilled into the bladder. After hydrodistension, some women experience a worsening of symptoms that lasts from 1 to 3 weeks. However, many experience significant symptom relief that can last several months.

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Treatment

Once a diagnosis of IC/PBS is made, your healthcare professional can discuss treatment options. Keep in mind that most treatments take time to work, and you will need to be patient. Many women are relieved to learn that they have a known condition that can be treated, but get discouraged when they wait days, weeks, or months to see improvement. In the meantime, understanding from your family, friends, or a support group can be very helpful. There is currently no cure for IC/PBS, but there are treatments that can improve your symptoms dramatically.

Dimethyl Sulfoxide (DMSO).—This is a liquid chemical that is inserted directly into the bladder through a soft rubber tube called a catheter. It is thought to work by directly reducing bladder-wall inflammation, blocking pain, and preventing bladder muscle contractions. The DMSO is often mixed with other medications (often called a “DMSO cocktail”) to work better. The DMSO is held in the bladder for about 15 to 30 minutes and then urinated out. Treatments need to be repeated every 1 to 2 weeks for about 6 to 8 weeks, and most women notice improvement about 3 to 4 weeks after the first treatment. The procedure is done in the office, but your healthcare professional may teach you how to do it at home. Dimethyl sulfoxide can be very irritating to the bladder at first. In fact, bladder discomfort and urinary frequency may actually worsen over the first few treatments, but this generally settles down and symptoms often begin to improve.

Over the years, healthcare professionals have instilled various medications into the bladder in an attempt to decrease IC/PBS symptoms. None except DMSO is FDA-approved. Some healthcare professionals have had success instilling anesthetic agents into the bladder, a procedure that can be particularly helpful during symptom flare-ups.

Pentosan Polysulfate Sodium (ELMIRON®).

—This is the first and only FDA-approved oral treatment for IC (more information is available at www.orthoelmiron.com). It is a capsule taken by mouth, usually 3 times a day. And while the exact mechanism of action is unknown, it is thought to add to the normally protective bladder lining. Pentosan polysulfate sodium takes a while to work, and relief occurs in stages. For example, pain decreases in about 2 to 4 months, but urgency and frequency may not lessen before 6 months. Pentosan polysulfate sodium should be tried for 3 to 6 months to give it a chance to work. Eventually, about 30% to more than 60% of women get moderate to significant relief from it. Pentosan polysulfate sodium is usually well tolerated.

The most common side effects, which occur in less than 4% of patients, are blood in stool, hair loss, diarrhea, nausea, headache, rash, upset stomach, abdominal pain, liver function abnormalities, and dizziness. When side effects do occur, they are generally mild and usually do not interfere with continuing treatment. Hair loss, when it occurs, is almost always limited to a single area of the scalp, and hair grows back when pentosan is discontinued. Pentosan polysulfate sodium is a weak anticoagulant (blood thinner), which may increase bleeding. Call your doctor if you will be undergoing surgery or will begin taking anticoagulant therapy, such as warfarin, heparin, or high doses of aspirin; or anti-inflammatory drugs such as ibuprofen.

Other Pain Medications.—Amitriptyline (Elavil), an oral tricyclic antidepressant, is often used to treat IC/PBS and other chronic pain syndromes. It is not FDA-approved for the treatment of IC/PBS, but it is



commonly used in clinical practice for this condition and other pain syndromes. Common side effects include dry mouth, fatigue, constipation, palpitations, and weight gain. Another medication that is not FDA-approved to treat IC/PBS is the antihistamine hydroxyzine (Atarax or Vistaril). Like amitriptyline, this medication helps patients sleep better. It also decreases the release of inflammation-causing chemicals such as histamine in the bladder wall. Antiseizure agents such as gabapentin (Neurontin) and pregabalin (Lyrica) are also sometimes used to block the pain that comes with IC/PBS. The most common associated side effect is fatigue.

Lifestyle Changes.—Although not supported by scientific evidence, some women find that avoiding certain foods such as caffeine, alcohol, tomato products, citrus, chocolate, soda, and supplements containing vitamin C and potassium help them (see page 15 for more information). Healthcare professionals may suggest an “elimination diet.” While on this diet, a patient begins with a bland diet, then slowly adds various foods and beverages one at a time to see which ones cause symptoms to appear or worsen. Stress is also believed to have a profound impact on disease

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Attaining and Maintaining Quality of Life: A Personal Experience

Lynne Kolton Schneider, PhD

Michelle (name changed to protect privacy) is a 27-year-old newlywed who has struggled with interstitial cystitis/painful bladder syndrome (IC/PBS) for more than 10 years. She remembers experiencing severe, debilitating pelvic pain and urinary symptoms for many years—but her doctors assumed she had recurrent urinary tract infections (UTIs). She was finally diagnosed with IC/PBS at age 21—which proved to be a blessing.

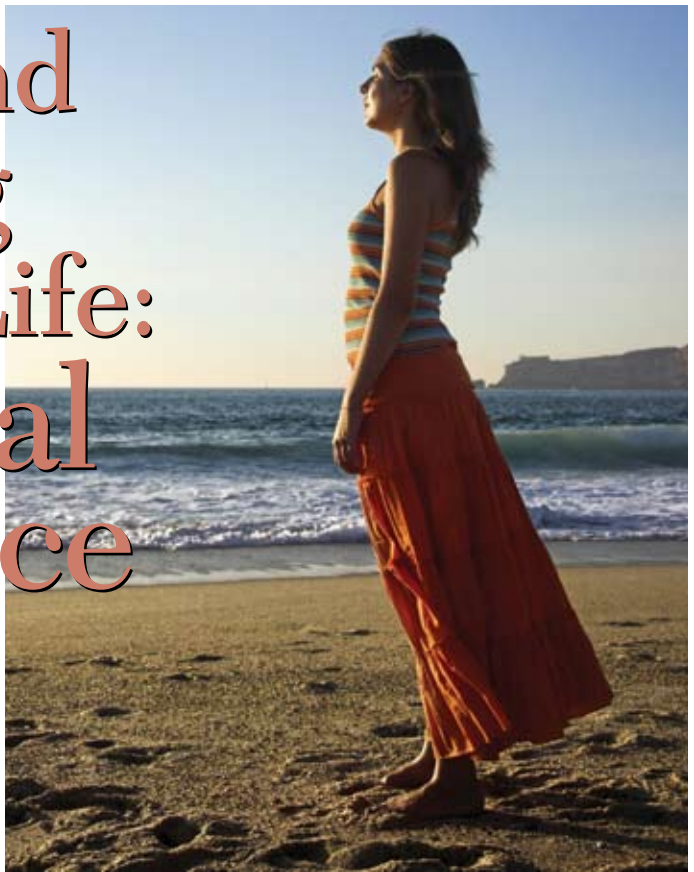
Growing up, Michelle complained of chronic pelvic pain (CPP) and pain with urination, and she was diagnosed with and treated for recurrent UTIs. Sometime during her teenage years, she realized that the antibiotics were no longer working for her. Since she had UTIs so often, her doctors had stopped culturing her urine to confirm a bacterial infection and just prescribed antibiotics whenever the symptoms appeared. She was sent from urologist to urologist, and each

doctor would try to convince her she was “fine.” None of them could figure out why she continued to have such severe CPP. To manage her urinary symptoms, Michelle conditioned herself to “hold it in as long as humanly possible” to avoid feeling the pain.

“Luckily, around the time that I turned 21, I moved to Albany, NY. I had to choose a gynecologist from a list of providers affiliated with my health insurance plan—and I amazingly ended up choosing a gynecologist who, although

not a true ‘urogynecologist,’ had a lot of knowledge about urogynecology. He put together my CPP, my symptoms of recurrent UTIs, and my pain with intercourse and suspected IC/PBS.” Looking back on it, Michelle now realizes how unusual it is to obtain this diagnosis so quickly—most women with IC/PBS see numerous clinicians and are diagnosed with a wide variety of conditions that share similar symptoms (including overactive bladder or endometriosis) before IC/PBS is ever even considered.

Clinicians didn’t have the paper-and-pencil test—the Pelvic Pain and Urgency/Frequency Symptom Scale—back then, so Michelle underwent the Potassium Sensitivity Test. Potassium was instilled into her bladder and she recalls, “I really felt those burning sensations!” Her gynecologist diagnosed her with IC/PBS, gave her a patient video on the condition, and prescribed oral pentosan polysulfate sodium (PPS [ELMIRON®]).



Surprisingly, her urologists never performed a cystoscopy while she was a teenager, despite all of her problems with UTIs. It is possible this test might have led her clinicians to a diagnosis of IC rather than recurrent UTIs. However, IC can be diagnosed without cystoscopy.

Work has always been a source of stress. Michelle began her professional career in a high-stress managerial position with a bank—and experienced numerous IC/PBS flares. “It’s hard to talk to your boss about an illness when he or she can’t see any of your symptoms.” The stress became so bad that she left that position and got a job as a salesperson. This position required her to spend a lot of time in the car driving, and that would often aggravate her IC/PBS. She perfected her ability to put off urinating during that time, and while she knows it is not healthy to do, she finds herself continuing that practice even today.

Michelle has been taking oral PPS (ELMIRON®) for the past 6 years. She began seeing improvements in her symptoms within a few months of beginning treatment, and continues to maintain those improvements as long as she remains consistent with her medication regimen. A few years ago, she discovered the IC diet on the Internet. She feels she has gotten tremendous benefit from the combination of these 2 interventions. She is aware of other pharmacologic interventions, including intravesical instillations with dimethyl sulfoxide, but has never personally utilized them. She does not suffer from severe nocturia, which could be helped by antihistamines, nor does she require prescription analgesics to help manage the pain. “I never had physical therapy or any other kind of treatment.

“Interstitial cystitis/PBS is one of those conditions that you always know is there—there’s always an aspect of ‘fear’ that you will have



another flare-up.” Currently, she does have flares from time to time—usually when things are going really well and she gets a little lax with her medicine and diet. “I’ll think I’m doing well, so I’ll miss a few pills and eat something I shouldn’t, and then I pay the price!” She noted that these flares highlight the importance of correctly and consistently adhering to her prescribed medication regimen.

Periods of high stress, such as planning her wedding, also cause flares. Flare-ups can be truly debilitating. She has had about 18 months without any “awful” flares, and her most recent flares have been minor. “But I am always on the lookout for new treatments to help me deal with my flare-ups.”

She admits that sexual intercourse has been an adjustment. “You need to have an extremely understanding partner.” She is currently using oral contraceptives for birth control but had used condoms in the past. She remembers that using condoms with spermicide would cause her to have severe flares; for some reason, the spermicidal agent caused her extreme pain. Although she is not quite ready to consider starting a family, she and her husband have talked about whether she should stay on her medication during the

pregnancy. “I’m almost afraid to go off it during a pregnancy!” Whether or not to stay on oral PPS is a decision Michelle and her obstetrician will need to make together.

Michelle has advice for women who might have IC/PBS: “No matter what your doctor tells you, you should not be experiencing this kind of pain. You need to find a doctor who will listen to you, who will do everything he or she can to help you, or who will help you find the right doctor. You need to take control and be an advocate for yourself.” Michelle is constantly researching the Internet for new information about IC/PBS and looking for new treatments to supplement her current regimen or help her better manage her flares. And while her gynecologist’s quick suspicion of IC/PBS and subsequent on-target treatment approach changed her life for the better and she feels great now, she knows that this is a condition that will most likely flare up from time to time.

Lynne Kolton Schneider, PhD, is a board-certified sex therapist and freelance writer, Flanders, NJ. Dr. Kolton Schneider received an honorarium from *The Female Patient* for this article, with funding provided by Ortho Women’s Health & Urology™.

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woman is not pregnant. The endometrial tissue outside of the uterus also bleeds, but the blood cannot escape from the body.

The Tests.—The “gold standard” for diagnosing endometriosis is a surgical procedure to look inside the abdomen with a laparoscope (lighted tube). This allows the clinician to see if there is endometrial tissue outside of the uterus.

The Difference.—It can be hard to tell the difference between endometriosis and IC/PBS, especially if the endometriosis involves the bladder. If laparoscopy is performed to check for endometriosis and none is found, your gynecologist may be able to do a diagnostic cystoscopy with bladder distension—looking inside the bladder while it is filled with liquid—at the same time.

Vulvodynia

The Condition.—Vulvodynia is a syndrome characterized by pain, soreness, burning or stinging, and rawness in the vulvar area (the area enclosed by the vaginal lips, just outside the vagina). It is diagnosed almost exclusively in white women. There are 5 different classifications of vulvodynia, but only one of these classifi-

cations—vulvar vestibular syndrome (VVS)—is linked to IC/PBS.

The Cause.—Clinicians do not yet know the cause(s) of vulvodynia, although many women ultimately diagnosed with vulvodynia report having used antifungal agents, but to no avail. Each classification of vulvodynia is associated with its own possible cause and treatment. For example, women with recurrent yeast infections often report vulvar pain prior to or during menses. In contrast, VVS is characterized by severe, chronic tenderness or pain with intercourse and primarily affects younger women.

The Tests.—There is no specific test to diagnose vulvodynia. Your clinician will examine your vulvar area or where you have pain to see if there is any evidence of fungal infection, skin disease, or viral infection (such as herpes or human papillomavirus).

The Differences.—Both IC/PBS and VVS are associated with premenopausal painful intercourse, and IC/PBS is frequently misdiagnosed as chronic VVS. However, women with IC/PBS do not typically have severe, chronic tenderness at the opening to the vagina, and women

with VVS do not typically report painful urination or chronic pelvic pain—just chronic vulvar pain.

Conclusion

The symptoms and severity of IC/PBS vary from woman to woman, and no one test can identify it for certain. If you are being treated for chronic bacterial cystitis, OAB, endometriosis, or vulvodynia and are not getting better, you may have IC/PBS. Evaluation and treatment for IC/PBS always starts with your healthcare professional taking a health history, performing a pelvic examination, and ordering urine testing. You can help your healthcare professional find the correct diagnosis by being specific about your symptoms and by asking for further evaluation if your condition is not responding to treatment.

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>> TESTS AND TREATMENTS FOR IC/PBS

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and often is associated with symptom flare-ups. Relaxation exercises, stress management, yoga, or massage may help reduce stress and its negative impact on your health.

Transcutaneous Electrical Nerve Stimulation (TENS).—This procedure uses mild electrical pulses sent through wires placed on the outside of the body or in the vagina. The electrical stimulation can block pain transmission within nerves.

Bladder Retraining.—This method does not relieve pain, but it can help frequency, and gradually increases the time between trips

to the bathroom. It teaches bladder control by scheduling times to urinate and using relaxation exercises. Some physical therapists and nurses teach this technique.

Surgery.—This may be an option for the few women whose severe, persistent symptoms are not lessened by other treatments.

Conclusion

Whatever treatment you choose, it is important to keep follow-up appointments with your healthcare professional. There is no way to know which treatment will work for

you, so you and your healthcare professional should watch your progress and decide if a different approach is necessary. It is not unusual to try more than one treatment, or a combination of treatments, to obtain relief. There is hope for the future, as research continues to reveal causes and new treatments for IC/PBS.

José Hernández-Gräulau, MD, is a urologist in private practice, Peoria, IL. Dr Hernández-Gräulau received an honorarium from *The Female Patient* for this article, with funding provided by Ortho Women's Health & Urology™.

Interstitial Cystitis/ Painful Bladder Syndrome Checklist

You and your healthcare professional are partners in managing interstitial cystitis/painful bladder syndrome (IC/PBS). Evaluation and treatment of bladder pain progresses step by step. Although healthcare professionals will differ in their approaches, the following is an example of what you might expect.



Visit 1

- Pelvic Pain and Urgency/Frequency (PUF) Scale.**— You can complete this in advance (see page 14) and bring it with you.
- Specific questions about your pain.
- Questions about other health problems possibly related to your pain.
- Physical examination.**—A check for “trigger points” on your abdomen or vulva (the area enclosed by the vaginal lips, just outside the vagina) and a pelvic exam to check the base of the bladder, muscles surrounding the bladder and vagina, and the uterus and ovaries.
- Laboratory tests.**—If there is blood in the urine, you may be referred to a specialist for a cystoscopy (looking into the bladder through a lighted tube).
- Discussion of the results of today’s questions, exams, and tests.**—If the findings suggest IC/PBS, you will be directed to reliable IC/PBS information and support groups. You should know what tests and treatments are planned for your next visit.

Visit 2

- Discussion about IC/PBS diagnosis and management.
- Planning for treatment.
- Discussion about diet.**—Certain foods aggravate pain for some women (see page 15).
- Physical therapy.**—This helps with trigger-point pain associated with IC/PBS.

Medication:

- **Amitriptyline.***—Originally used to treat depression, amitriptyline also improves nerve-initiated pain.
- **Dimethyl sulfoxide (DMSO).**—Unlike the other 3 medications listed here that are taken orally, this liquid chemical is put directly into the bladder. Treatment may require several visits.
- **Hydroxyzine.***—An antihistamine usually used for allergy problems, hydroxyzine works by decreasing the amount of a chemical substance in the body called histamine, which may aggravate the symptoms of IC/PBS.
- **Pentosan polysulfate sodium (ELMIRON®).**—The first and only FDA-approved oral medication for the relief of bladder pain or discomfort associated with IC, developed specifically for IC treatment. It is thought to work by protecting the bladder lining against irritants that may cause IC pain.

Visit 3

(4 to 6 weeks after treatment starts, or at the end of DMSO treatment)

- Fill out PUF Scale again to see how well treatment is working.
- Progress review, with treatment adjusted as necessary.

Visits 4 to 6

(3 to 4 months apart)

- Fill out PUF Scale.
- Progress review.

Tools for Diagnosis and Treatment

Pelvic Pain and Urgency/Frequency Patient Symptom Scale

For each question below, please circle the answer that best describes how you feel; then mark your score (0 to 4) for each answer in the column on the right. When you are finished, add up the numbers in this column for your total score.



	0	1	2	3	4	SCORE
1 How many times do you go to the bathroom during the day?	3-6	7-10	11-14	15-19	20+	
2 a. How many times do you go to the bathroom at night?	0	1	2	3	4+	
b. If you get up at night to go to the bathroom, does it bother you?	Never	Occasionally	Usually	Always		
3 Are you currently sexually active? YES _____ NO _____						
4 a. If you are sexually active, do you now or have you ever had pain or symptoms during or after sexual intercourse?	Never	Occasionally	Usually	Always		
b. If you have pain, does it make you avoid sexual intercourse?	Never	Occasionally	Usually	Always		
5 Do you have pain associated with your bladder or in your pelvis (vagina, labia, lower abdomen, urethra, perineum)?	Never	Occasionally	Usually	Always		
6 Do you still have urgency after you go to the bathroom?	Never	Occasionally	Usually	Always		
7 a. If you have pain, is it usually:		Mild	Moderate	Severe		
b. Does your pain bother you?	Never	Occasionally	Usually	Always		
8 a. If you have urgency, is it usually:		Mild	Moderate	Severe		
b. Does your urgency bother you?	Never	Occasionally	Usually	Always		

Be sure to bring this page with you to discuss your score with your healthcare professional.









TOTAL SCORE

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PHOTO: Shutterstock

Dietary Guidelines for Interstitial Cystitis*

	Food Category	Permitted Foods	Foods to Avoid or Use Cautiously
	Fruits	Blueberries, melons other than cantaloupes, and pears	All other fruits and juices made from them
	Vegetables	Potatoes, homegrown tomatoes, and vegetables other than those listed on the right	Fava beans, lima beans, onions, rhubarb, tofu, and store-bought tomatoes
	Milk/Dairy	White chocolate, cottage cheese, American cheese, milk	Aged cheeses, sour cream, eggs, yogurt, chocolate
	Carbohydrates/Grains	Pasta, rice, and breads other than those listed on the right	Rye and sourdough breads
	Meats/Fish	Poultry, fish, and meats other than those listed on the right	Aged, canned, cured, processed, and smoked meats and fish; anchovies; caviar; chicken livers; corned beef; and meats that contain nitrates or nitrites
	Nuts	Almonds, cashews, and pine nuts	Most other nuts
	Beverages	Bottled or spring water; decaffeinated, acid-free coffee and tea; and some herbal teas	Alcoholic beverages; beer and wine; carbonated drinks; coffee, tea, and cranberry juice
	Seasonings	Garlic and seasonings other than those listed on the right	Mayonnaise, miso, spicy foods (especially Chinese, Mexican, Indian, and Thai foods)
	Preservatives		Benzyl alcohol, citric acid, monosodium glutamate, aspartame, saccharin, and foods containing preservatives, artificial ingredients/colors

*Adapted with permission from the American Foundation for Urologic Disease, Inc. *On Course for Better Health.*

Recipe

Corn with Two Types of Rice†

Serves 3

- ¼ c wild rice
- ¼ c long-grain white rice
- 1 Tbsp margarine
- 1½ c water
- 1 Tbsp olive oil
- 2 cloves garlic, minced
- 2 c frozen corn kernels
- 1 Tbsp dried basil
- salt and pepper to taste

In covered saucepan, cook wild rice, white rice, and margarine in water until water is absorbed and rice is done (about half an hour). In a skillet, sauté minced garlic in the olive oil for a few seconds, just until tender.

Add frozen corn and cooked rice to the skillet, stirring to coat. Sprinkle basil on top and add about 2 Tbsp. of water. Cover and simmer over medium to low heat for 5 to 6 minutes. Stir to fluff rice and serve.

†From: Laumann B. *A Taste of the Good Life: A Cookbook for an Interstitial Cystitis Diet.* Tustin, CA: Freeman Family Trust Publications; 1998.

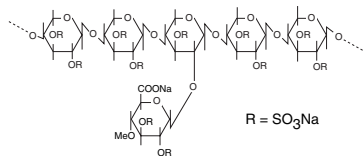
ELMIRON®-100 mg

(pentosan polysulfate sodium)
Capsules

Prescribing Information

DESCRIPTION

Pentosan polysulfate sodium is a semi-synthetically produced heparin-like macromolecular carbohydrate derivative, which chemically and structurally resembles glycosaminoglycans. It is a white odorless powder, slightly hygroscopic and soluble in water to 50% at pH 6. It has a molecular weight of 4000 to 6000 Dalton with the following structural formula:



ELMIRON® is supplied in white opaque hard gelatin capsules containing 100 mg pentosan polysulfate sodium, microcrystalline cellulose, and magnesium stearate. It also contains pharmaceutical glaze (modified) in SD-45, synthetic black iron oxide, FD&C Blue No. 2 aluminum lake, FD&C Red No. 40 aluminum lake, FD&C Blue No. 1 aluminum lake, D&C Yellow No. 10 aluminum lake, n-butyl alcohol, propylene glycol, SDA-3A alcohol, and titanium dioxide. It is formulated for oral use.

CLINICAL PHARMACOLOGY

General: Pentosan polysulfate sodium is a low molecular weight heparin-like compound. It has anticoagulant and fibrinolytic effects. The mechanism of action of pentosan polysulfate sodium in interstitial cystitis is not known.

Pharmacokinetics:

Absorption: In preliminary clinical studies with different doses of radiolabeled pentosan polysulfate sodium, absorption was approximately 3% of the administered dose (n=3).

Distribution: Preclinical studies with parenterally administered radiolabeled pentosan polysulfate sodium showed distribution to the uroepithelium of the genitourinary tract with lesser amounts found in the liver, spleen, lung, skin, periosteum, and bone marrow. Erythrocyte penetration is low in animals.

Metabolism: Preliminary literature studies of metabolism in 5 healthy volunteers with radiolabeled drug suggest that 68% of the dose, at about 1 hour after IV administration, undergoes partial desulfation in the liver and spleen. In another study of 3 healthy volunteers, partial depolymerization occurs in the kidney. Both the desulfation and depolymerization can be saturated with continued dosing.

Excretion: In preliminary clinical studies in 8 healthy male volunteers, the elimination half-life of pentosan polysulfate sodium had a mean value at 24 hours after IV injection of 40 mg.

The elimination half-life in urine following orally administered radiolabeled pentosan polysulfate sodium was determined to be 4.8 hours for the unchanged drug.

In preliminary human studies in 3 healthy male volunteers, after single doses of radiolabeled drug, urinary excretion averaged 3.5% of the administered dose. After multiple doses of pentosan polysulfate sodium, urine excretion of radioactivity averaged 11% of the administered dose.

Further analyses of the urinary fraction obtained after repeated dosing showed that about 3% of the dose may be unchanged pentosan polysulfate sodium.

Special Populations: Dose adjustments in geriatric patients and in patients with hepatic or renal impairment were not studied.

Pharmacodynamics:

The mechanism by which pentosan polysulfate sodium achieves its effects in patients is unknown. In preliminary clinical models, pentosan polysulfate sodium adhered to the bladder wall mucosal membrane. The drug may act as a buffer to control cell permeability preventing irritating solutes in the urine from reaching the cells.

Food Effects: The effect of food on absorption of pentosan polysulfate sodium is not known. In clinical trials, ELMIRON was administered with water 1 hour before or 2 hours after meals.

Drug-Drug Interactions: Not studied.

CLINICAL TRIALS

ELMIRON was evaluated in two clinical trials for the relief of pain in patients with chronic interstitial cystitis (IC). All patients met the NIH definition of IC based upon the results of cystoscopy, cytology, and biopsy. One blinded, randomized, placebo controlled study evaluated 151 patients (145 women, 5 men, 1 unknown) with a mean age of 44 years (range 18 to 81). Approximately equal numbers of patients received either placebo or ELMIRON 100 mg three times a day for 3 months. Clinical improvement in bladder pain was based upon the patient's own assessment. In this study, 28/74 (38%) of patients who received ELMIRON and 13/74 (18%) of patients who received placebo, showed greater than 50% improvement in bladder pain (p=0.005).

A second clinical trial, the physician's usage study, was a prospectively designed retrospective analysis of 2499 patients who received ELMIRON 300 mg a day without blinding. Of the 2499 patients, 2220 were women, 254 were men, and 25 were of unknown sex. The patients had a mean age of 47 years and 23% were over 60 years of age. By 3 months, 1307 (52%) of the patients had dropped out or were ineligible for analysis, overall, 1192 (48%) received ELMIRON for 3 months; 892 (36%) received ELMIRON for 6 months; and 598 (24%) received ELMIRON for one year.

Patients had unblinded evaluations every 3 months for the patient's rating of overall change in pain in comparison to baseline and for the difference calculated in "pain/discomfort" scores. At baseline, pain/discomfort scores for the original 2499 patients were severe or unbearable in 60%, moderate in 33% and mild or none in 7% of patients. The extent of the patients' pain improvement is shown in Table 1.

At 3 months, 722/2499 (29%) of the patients originally in the study had pain scores that improved by one or two categories. By 6 months, in the 892 patients who continued taking ELMIRON, an additional 116/2499 (5%) of patients had improved pain scores. After 6 months, the percent of patients who reported the first onset of pain relief was less than 1.5% of patients who originally entered in the study (see Table 2).

Table 1: Pain Scores in Reference to Baseline in Open Label Physician's Usage Study (N=2499)¹

Efficacy Parameter	3 months ²	6 months ²
Rating of Overall Change in Pain (Recollection of difference between current pain and baseline pain) ³	N=1161 Median=3 Mean=3.44 CI: (3.37, 3.51)	N=724 Median=4 Mean=3.91 CI: (3.83, 3.99)
Change in Pain/Discomfort Score (Calculated difference in scores at the time point and baseline) ⁴	N=1440 Median=1 Mean=0.51 CI: (0.45, 0.57)	N=904 Median=1 Mean=0.66 CI: (0.61, 0.71)

¹Trial not designed to detect onset of pain relief
²CI = 95% confidence interval
³6-point scale: 1 = worse, 2 = no better, 3 = slightly improved, 4 = moderately improved, 5 = greatly improved, 6 = symptom gone
⁴3-point scale: 1 = none or mild, 2 = moderate, 3 = severe or unbearable

Table 2: Number (%) of Patients with New Relief of Pain/Discomfort¹ in the Open-Label Physician's Usage Study (N=2499)

	at 3 months ² (n=1192)	at 6 months ³ (n=892)
Considering only the patients who continued treatment	722/1192 (61%)	116/892 (13%)
Considering all the patients originally enrolled in the study	722/2499 (29%)	116/2499 (5%)

¹First-time Improvement in pain/discomfort score by 1 or 2 categories
²Number (%) of patients with improvement of pain/discomfort score at 3 months when compared to baseline
³Number (%) of patients without pain/discomfort improvement at 3 months who had improvement at 6 months

INDICATIONS AND USAGE

ELMIRON (pentosan polysulfate sodium) is indicated for the relief of bladder pain or discomfort associated with interstitial cystitis.

CONTRAINDICATIONS

ELMIRON (pentosan polysulfate sodium) is contraindicated in patients with known hypersensitivity to the drug, structurally related compounds, or excipients.

WARNINGS

None.

PRECAUTIONS

General:

ELMIRON (pentosan polysulfate sodium) is a weak anticoagulant (1/15 the activity of heparin). At a daily dose of 300 mg (n = 128), rectal hemorrhage was reported as an adverse event in 6.3% of patients. Bleeding complications of ecchymosis, epistaxis, and gum hemorrhage have been reported (see **ADVERSE REACTIONS**). Patients undergoing invasive procedures or having signs/symptoms of underlying coagulopathy or other increased risk of bleeding (due to other therapies such as coumarin anticoagulants, heparin, t-PA, streptokinase, high dose aspirin, or nonsteroidal anti-inflammatory drugs) should be evaluated for hemorrhage. Patients with diseases such as aneurysms, thrombocytopenia, hemophilia, gastrointestinal ulcerations, polyps, or diverticula should be carefully evaluated before starting ELMIRON.

A similar product that was given subcutaneously, sublingually, or intramuscularly (and not initially metabolized by the liver) is associated with delayed immunoallergic thrombocytopenia with symptoms of thrombosis and hemorrhage. Caution should be exercised when using ELMIRON in patients who have a history of heparin induced thrombocytopenia.

Hepatic Insufficiency: Pentosan polysulfate sodium is desulfated by both the liver and the spleen. The extent to which hepatic insufficiency or splenic disorders may increase the bioavailability of the parent or active metabolites of pentosan polysulfate sodium is not known. Caution should be exercised when using ELMIRON in these patients.

Mildly (<2.5 x normal) elevated transaminase, alkaline phosphatase, γ -glutamyl transpeptidase, and lactic dehydrogenase occurred in 1.2% of patients. The increases usually appeared 3 to 12 months after the start of ELMIRON therapy, and were not associated with jaundice or other clinical signs or symptoms. These abnormalities are usually transient, may remain essentially unchanged, or may rarely progress with continued use. Increases in PTT and PT (<1% for both) or thrombocytopenia (0.2%) were noted.

Alopecia is associated with pentosan polysulfate and with heparin products. In clinical trials of ELMIRON, alopecia could begin within the first 4 weeks of treatment. Ninety-seven percent (97%) of the cases of alopecia reported were alopecia areata, limited to a single area on the scalp.

Information for Patients: Patients should take the drug as prescribed, in the dosage prescribed, and no more frequently than prescribed. Patients should be reminded that ELMIRON has a weak anticoagulant effect. This effect may increase bleeding times.

Laboratory Test Findings: Pentosan polysulfate sodium did not affect prothrombin time (PT) or partial thromboplastin time (PTT) up to 1200 mg per day in 24 healthy male subjects treated for 8 days. Pentosan polysulfate sodium also inhibits the generation of factor Xa in plasma and inhibits thrombin-induced platelet aggregation in human platelet rich plasma *ex vivo*. (See **PRECAUTIONS-Hepatic Insufficiency** Section for additional information.)

Carcinogenicity, Mutagenesis, Impairment of Fertility: Long term carcinogenicity studies of ELMIRON in F344/N rats and B6C3F1 mice have been conducted. In these studies, ELMIRON was orally administered once daily via gavage, 5 days per week, for up to 2 years. The dosages administered to mice were 56, 168 or 504 mg/kg. The dosages administered to rats were 14, 42, or 126 mg/kg for males, and 28, 84, or 252 mg/kg for females. The dosages tested were up to 60 times the maximum recommended human dose (MRHD) in rats, and up to 117 times the MRHD in mice, on a mg/kg basis. The results of these studies in rodents showed no clear evidence of drug-related tumorigenesis or carcinogenic risk.

Pentosan polysulfate sodium was not clastogenic or mutagenic when tested in the mouse micronucleus test or the Ames test (*S. typhimurium*). The effect of pentosan polysulfate sodium on spermatogenesis has not been investigated.

Pregnancy Category B: Reproduction studies have been performed in mice and rats with intravenous daily doses of 15 mg/kg, and in rabbits with 7.5 mg/kg. These doses are 0.42 and 0.14 times the daily oral human doses of ELMIRON when normalized to body surface area. These studies did not reveal evidence of impaired fertility or harm to the fetus from ELMIRON. Direct *in vitro* bathing of cultured mouse embryos with pentosan polysulfate sodium (PPS) at a concentration of 1 mg/mL may cause reversible limb bud abnormalities. Adequate and well controlled studies have not been performed in pregnant women. Because animal studies are not always predictive of human response, this drug should be used in pregnancy only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ELMIRON is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in pediatric patients below the age of 16 years have not been established.

ADVERSE REACTIONS

ELMIRON was evaluated in clinical trials in a total of 2627 patients (2343 women, 262 men, 22 unknown) with a mean age of 47 [range 18 to 88 with 581 (22%) over 60 years of age]. Of the 2627 patients, 128 patients were in a 3 month trial and the remaining 2499 patients were in a long term, unblinded trial.

Deaths occurred in 6/2627 (0.2%) patients who received the drug over a period of 3 to 75 months. The deaths appear to be related to other concurrent illnesses or procedures, except in one patient for whom the cause was not known.

Serious adverse events occurred in 33/2627 (1.3%) patients. Two patients had severe abdominal pain or diarrhea and dehydration that required hospitalization. Because there was not a control group of patients with interstitial cystitis who were concurrently evaluated, it is difficult to determine which events are associated with ELMIRON and which events are associated with concurrent illness, medicine, or other factors.

Adverse Experience In Placebo-Controlled Clinical Trials of ELMIRON 100 mg Three Times a Day for 3 Months		
Body System/ Adverse Experience	ELMIRON n=128	Placebo n=130
CNS Overall Number of Patients*	3	5
Insomnia	1	0
Headache	1	3
Severe Emotional Lability/Depression	2	1
Nystagmus/Dizziness	1	1
Hyperkinesia	1	1
GI Overall Number of Patients*	7	7
Nausea	3	3
Diarrhea	3	6
Dyspepsia	1	0
Jaundice	0	1
Vomiting	0	2
Skin/Allergic Overall Number of Patients*	2	4
Rash	0	2
Pruritus	0	2
Lacrimation	1	1
Rhinitis	1	1
Increased Sweating	1	0
Other Overall Number of Patients*	1	3
Amenorrhea	0	1
Arthralgia	0	1
Vaginitis	1	1
Total Events	17	27
Total Number of Patients Reporting Adverse Events	13	19

* Within a body system, the individual events do not sum to equal overall number of patients because a patient may have more than one event.

The adverse events described below were reported in an unblinded clinical trial of 2499 interstitial cystitis patients treated with ELMIRON. Of the original 2499 patients, 1192 (48%) received ELMIRON for 3 months; 892 (36%) received ELMIRON for 6 months; and 598 (24%) received ELMIRON for one year, 355 (14%) received ELMIRON for 2 years, and 145 (6%) for 4 years.

Frequency (1 to 4%): Alopecia (4%), diarrhea (4%), nausea (4%), headache (3%), rash (3%), dyspepsia (2%), abdominal pain (2%), liver function abnormalities (1%), dizziness (1%).

Frequency (≤1%):

Digestive: Vomiting, mouth ulcer, colitis, esophagitis, gastritis, flatulence, constipation, anorexia, gum hemorrhage.

Hematologic: Anemia, ecchymosis, increased prothrombin time, increased partial thromboplastin time, leukopenia, thrombocytopenia.

Hypersensitive Reactions: Allergic reaction, photosensitivity.

Respiratory System: Pharyngitis, rhinitis, epistaxis, dyspnea.

Skin and Appendages: Pruritus, urticaria.

Special Senses: Conjunctivitis, tinnitus, optic neuritis, amblyopia, retinal hemorrhage.

Post-Marketing Experience:

Rectal Hemorrhage: ELMIRON was evaluated in a randomized, double-blind, parallel group, Phase 4 study conducted in 380 patients with interstitial cystitis dosed for 32 weeks. At a daily dose of 300 mg (n = 128), rectal hemorrhage was reported as an adverse event in 6.3% of patients. The severity of the events was described as "mild" in most patients. Patients in that study who were administered ELMIRON 900 mg daily, a dose higher than the approved dose, experienced a higher incidence of rectal hemorrhage, 15%.

Liver Function Abnormality: A randomized, double-blind, parallel group, phase 2 study was conducted in 100 men (51 ELMIRON and 49 placebo) dosed for 16 weeks. At a daily dose of 900 mg, a dose higher than the approved dose, elevated liver function tests were reported as an adverse event in 11.8% (n = 6) of ELMIRON treated patients and 2% (n = 1) of placebo treated patients.

OVERDOSAGE

Overdose has not been reported. Based upon the pharmacodynamics of the drug, toxicity is likely to be reflected as anticoagulation, bleeding, thrombocytopenia, liver function abnormalities, and gastric distress. (See **CLINICAL PHARMACOLOGY** and **PRECAUTIONS** sections.) At a daily dose of 900 mg for 32 weeks (n = 127) in a clinical trial, rectal hemorrhage was reported as an adverse event in 15% of patients. At a daily dose of ELMIRON 900 mg for 16 weeks in a clinical trial that enrolled 51 patients in the ELMIRON group and 49 in the placebo group, elevated liver function tests were reported as an adverse event in 11.8% of patients in the ELMIRON group and 2% of patients in the placebo group. In the event of acute overdosage, the patient should be given gastric lavage if possible, carefully observed and given symptomatic and supportive treatment.

DOSAGE AND ADMINISTRATION

The recommended dose of ELMIRON is 300 mg/day taken as one 100 mg capsule orally three times daily. The capsules should be taken with water at least 1 hour before meals or 2 hours after meals.

Patients receiving ELMIRON should be reassessed after 3 months. If improvement has not occurred and if limiting adverse events are not present, ELMIRON may be continued for another 3 months.

The clinical value and risks of continued treatment in patients whose pain has not improved by 6 months is not known.

HOW SUPPLIED

ELMIRON® is supplied in white opaque hard gelatin capsules imprinted "BNP7600" containing 100 mg pentosan polysulfate sodium. Supplied in bottles of 100 capsules.

NDC NUMBER 0062-9800-01

STORAGE

Store at controlled room temperature 15°-30°C (59°-86°F).

Rx only

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U.S. Patent #5,180,715

Patient Information

Medication Guide

Questions and Answers About

ELMIRON®

(Generic name = pentosan polysulfate sodium)

Capsules

What is the most important information I should know about ELMIRON?
ELMIRON (pronounced EL ma ron) is used to treat the pain or discomfort of interstitial cystitis (IC). You must take ELMIRON as prescribed by your doctor in the dosage prescribed but no more frequently than prescribed.
ELMIRON is a weak anticoagulant (blood thinner) which may increase bleeding.
Call your doctor if you will be undergoing surgery or will begin taking anticoagulant therapy such as warfarin sodium, heparin, high doses of aspirin, or anti-inflammatory drugs such as ibuprofen.

What is ELMIRON?

ELMIRON is used to treat the pain or discomfort of interstitial cystitis (IC). It is not known exactly how ELMIRON works, but it is not a pain medication like aspirin or acetaminophen and therefore must be taken continuously for relief as prescribed.

Who should not take ELMIRON?

- Patients undergoing surgery should speak with their doctor about when to discontinue ELMIRON prior to surgery.
- ELMIRON should be used during pregnancy only if clearly needed.

What does your doctor need to know?

- If you are taking anticoagulant therapy such as warfarin sodium, heparin, high doses of aspirin, or anti-inflammatory drugs such as ibuprofen.
- If you are pregnant.
- If you have any liver problems.

How should I take ELMIRON?

You should take 1 capsule of ELMIRON by mouth three times a day, with water at least 1 hour before meals or 2 hours after meals. Each capsule contains 100 mg of ELMIRON.

What should I avoid while taking ELMIRON?

Anticoagulant therapy such as warfarin sodium, heparin, high doses of aspirin or anti-inflammatory drugs such as ibuprofen until you speak with your doctor.

What are the most common side effects of ELMIRON?

The most common side effects are hair loss, diarrhea, nausea, blood in the stool, headache, rash, upset stomach, abnormal liver function tests, dizziness and bruising.

Call your doctor if these side effects persist or are bothersome or if there is blood in your stool.

If you suspect that someone may have taken more than the prescribed dose of this medicine, contact your local poison control center or emergency room immediately. This medication was prescribed for your particular condition. Do not use it for another condition or give the drug to others.

This leaflet provides a summary of information about ELMIRON. Medicines are sometimes prescribed for uses other than those listed in a Medication Guide. If you have any questions or concerns, or want more information about ELMIRON, contact your doctor or pharmacist. Your pharmacist also has a longer leaflet about ELMIRON that is written for health professionals that you can ask to read.

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The Medication Guide has been approved by the U.S. Food and Drug Administration.

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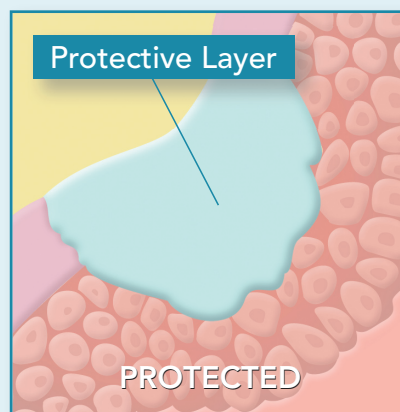
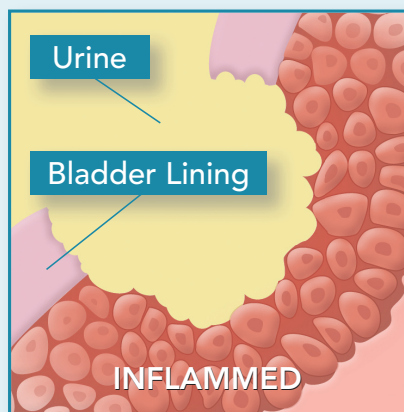
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If you think you have IC, ELMIRON® may offer relief.

ELMIRON® is the only oral medication that's been approved by the FDA for treating the bladder pain or discomfort of IC — and in a clinical study 3 out of 4 patients would recommend it. ELMIRON® is available by prescription only. Ask your doctor if it may be right for you.

IC may be caused by a breakdown of the protective lining of the bladder.



While the exact mechanism of action is unknown, ELMIRON® is believed to adhere to the bladder wall mucosal membrane that insulates the bladder from urine and its irritating substances.

Support, from diagnosis to relief.

Designed especially for new patients on ELMIRON®, our free *Journey to Relief* e-mail support program will provide you with all sorts of tips, resources and money-saving offers to help you along the way. Register at www.OrthoElmiron.com.

ELMIRON® is indicated for the relief of bladder pain or discomfort associated with interstitial cystitis.

Important Safety Information

ELMIRON® has been shown to be generally well tolerated. The most common side effects were blood in stool, diarrhea, nausea, hair loss, headache, rash, upset stomach, abdominal pain, liver function abnormalities and dizziness. When side effects did occur, they were generally mild and usually did not interfere with continuing treatment. Hair loss, when it occurred, was almost always limited to a single area of the scalp, and it grew back when ELMIRON® was discontinued.

ELMIRON® is a weak anticoagulant (blood thinner), which may increase bleeding. Call your doctor if you will be undergoing surgery or will begin taking anticoagulant therapy, such as warfarin, heparin or high doses of aspirin; or anti-inflammatory drugs, such as ibuprofen.

The mechanism of action of ELMIRON® in interstitial cystitis is not fully understood.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

Please see full Product Information on previous page.

Learn more at OrthoElmiron.com

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ELMIRON®
(pentosan polysulfate sodium) 100 mg Capsules