PACIS®
BCG, Live
(For Intravesical Use)

For the treatment of carcinoma *in situ* (CIS) of the urinary bladder.

WARNING

PACIS® contains live, attenuated mycobacteria. Because of the potential risk for transmission, it should be prepared, handled and disposed of as a biohazardous material (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

BCG infections have been reported in health care workers, primarily from exposures resulting from accidental needle sticks or skin lacerations during the preparation of BCG for administration. Nosocomial infections have been reported in immunosuppressed patients receiving parenteral drugs that were prepared in areas in which BCG was prepared. BCG is capable of dissemination when administered by the intravesical route, and serious infections, including fatal infections, have been reported in patients receiving intravesical BCG (see WARNINGS, PRECAUTIONS and ADVERSE REACTIONS).

DESCRIPTION

PACIS® BCG, Live (for intravesical use), is a lyophilized preparation of an attenuated strain of *Mycobacterium bovis* (Bacillus Calmette-Guérin [BCG], substrain Montreal) which has been grown on glycerinized potato medium followed by further passages on Sauton medium. After harvesting by filtration, the mycobacteria are resuspended in a 15% (w/v) lactose solution, filled into ampules, and lyophilized.

Montreal substrain BCG originates from a BCG culture given to Dr. Armand Frappier by Dr. C. Guérin in 1937. This substrain was maintained by passaging until 1973, when the current primary and secondary seed lots were laid down. PACIS ® has also been known as "the Armand-Frappier strain of BCG."

PACIS® is formulated to contain 120 mg semi-solid dry weight (2.4 to 12 x 10^8 colony-forming units [C.F.U.]) per ampule of BCG. The potency of PACIS® is determined by colony counts derived from a serial passage assay using Dubos medium.

This product contains no preservatives. Each vial of PACIS® is ready to use following reconstitution with sterile, preservative-free saline (0.9% Sodium Chloride Injection USP).

CLINICAL PHARMACOLOGY

Carcinoma *in situ* (CIS) of the urinary bladder is a superficial neoplasm that is considered to be an aggressive precursor of invasive transitional cell carcinoma. Areas of CIS that cannot be resected are treated by a variety of methods, especially intravesical therapy.[1,2] The mechanism of action of PACIS® in treatment of CIS is unknown; however, the available evidence suggests that intravesical BCG is a form of immunotherapy.[3] Intravesical BCG appears to induce tumor regression through a number of specific and non-specific actions. It promotes a local inflammatory reaction with histiocytic and leukocytic infiltration in the urinary bladder that is apparently associated with an elimination or reduction of superficial cancerous lesions. Studies have reported that the anti-tumor activity of BCG may require a thymus-dependent immune response, and that T-lymphocyte-mediated mechanisms play an essential role.[3]

Intravesical Use for Carcinoma *in Situ* of the Urinary Bladder

Two studies provide data on the efficacy of PACIS® in patients with CIS. The first is the original randomized study of BCG for the treatment of superficial bladder cancer, which was initiated in 1978. The second is a contemporary series of patients treated with PACIS® under the Canadian Emergency Drug Release Program (EDR) from 1988 to 1992.

The randomized trial was a single-center study which randomized a total of 88 patients with superficial bladder cancer to six weekly instillations of PACIS®, or observation only, after transurethral resection (TUR) of all bladder tumors. Patients were evaluated at three(3), six(6) and nine(9) months. The primary endpoint for the analysis of activity was the number of patients who were disease-free at both the six(6)- and nine(9)-month evaluations. A complete response (CR) required a negative cystoscopy, cytology and biopsy, and an improvement in irritative symptoms, if present initially.

Sixty-six CIS patients, with or without concurrent papillary tumors, were identified: 38 in the observation-only arm and 28 in the PACIS® arm. Eleven patients in the PACIS® arm (39%) and three patients in the control arm (8%) were disease-free at the six(6)- and nine(9)-month evaluations (Table 1). This difference was statistically significant ($p = 0.005$ by a two-sided Fisher's Exact Test).

Table 1

RESPONSE OF PATIENTS WITH CARCINOMA *IN SITU* TO PACIS® OR OBSERVATION

	Study Arm		
Parameter	**PACIS® N = 28**	**Observation N = 38**	**p-value**
Disease-Free at 6 & 9 Months	**11 (39%)**	**3 (8%)**	**0.005**
95% Confidence Interval (CI)	**22%, 59%**	**2%, 22%**	**—**

A retrospective, long-term follow-up was conducted, and worsening-free and overall survival were analyzed (Table 2). Worsening disease was defined as "... *an abandonment of intravesical therapy strategies and/or direct evidence of stage T2 or higher disease.*" The Kaplan-Meier estimates of two-year worsening-free survival for the PACIS® and observation arms were 74% and 54%, respectively. The Kaplan-Meier estimates of five-year overall survival for the PACIS® and observation arms were 89% and 72%, respectively. These differences were not statistically significant.

Table 2

ESTIMATED LONG-TERM SURVIVAL IN PATIENTS WITH CARCINOMA IN SITU FOLLOWING PACIS ® OR OBSERVATION

Parameter	Study Arm: PACIS® N = 27	Study Arm: Observation N = 37	p-value
2-year Worsening-Free Survival	74%	54%	0.09
95% CI	59%, 93%	40%, 73%	—
5-year Overall Survival	89%	72%	0.08
95% CI	78%, 100%	59%, 89%	—

Additional supportive data have been obtained for seventeen patients treated under the Emergency Drug Request Program (EDR). Responses were seen in 15 patients (88%) (Table 3). In these patients, the median worsening-free survival was 48 months, and the median overall survival was 67 months. However, the number of events do not allow for a stable estimate of long-term outcomes.

Table 3

SEVENTEEN CIS PATIENTS TREATED UNDER THE CANADIAN EDR PROGRAM

Parameter	Result	95% CI
Disease-Free Response	15 (88%)	64%, 99%
2-Year Worsening-Free Survival	76%	59%, 99%
5-Year Overall Survival	53%	28%, 98%

INDICATIONS AND USAGE

PACIS® is indicated for intravesical use in the treatment of carcinoma *in situ* (CIS) in the absence of an associated invasive cancer of the bladder in the following situations: 1) primary treatment of CIS with or without papillary tumors after TUR, 2) secondary treatment of CIS in patients failing to respond or relapsing after intravesical therapy with other agents, 3) primary or secondary treatment of CIS for patients with medical contraindications to radical surgery. PACIS® is not indicated for the prevention of papillary tumors after TUR or for the treatment of papillary tumors occurring alone.

CONTRAINDICATIONS

PACIS® should not be used in immunosuppressed patients or persons with congenital or acquired immune deficiencies, whether due to concurrent disease (e.g., AIDS, leukemia, lymphoma) or cancer therapy (e.g., cytotoxic drugs, radiation), or in patients receiving steroids at immunosuppressive doses, or other immunosuppressive therapies (e.g. corticosteroids), because of the possibility of establishing a systemic BCG infection.

Treatment should be postponed until resolution of a concurrent febrile illness, urinary tract infection or gross hematuria. Seven to fourteen days should elapse before administering PACIS® following biopsy, TUR or traumatic catheterization.

PACIS® should not be administered to persons with active tuberculosis. A positive Mantoux test is a contraindication only if there is evidence of an active tuberculosis infection.

WARNINGS

PACIS® is not a vaccine for the prevention of cancer. It should not be administered as an immunizing agent for the prevention of tuberculosis.

PACIS® is an infectious agent. Physicians using this product should be familiar with the literature on the prevention and treatment of BCG-related complications, and should be prepared in such emergencies to contact an infectious disease specialist with experience in treating the infectious complications of intravesical BCG. The treatment of the infectious complications of BCG requires long-term, multiple-drug antibiotic therapy. Special culture media are required for mycobacteria, and physicians administering intravesical BCG should have these media readily available.

Instillation of PACIS® onto a bleeding mucosa may promote systemic BCG infection. Treatment should be postponed for at least one week following TUR, biopsy, traumatic catheterization or gross hematuria.

Deaths have been reported as a result of systemic BCG infection and sepsis. Patients should be monitored for the presence of symptoms and signs of toxicity after each intravesical treatment. Febrile episodes with flu-like symptoms lasting more than 72 hours, fever $\geq 103^{\circ}F$, systemic manifestations increasing in intensity with repeated instillations, or persistent abnormalities of liver function tests suggest BCG infection and may require antituberculous therapy. Local symptoms (prostatitis,

epididymitis, orchitis) lasting more than two to three days may also suggest active infection (see Management of Serious BCG Complications subsection for Warnings).

There are currently no data on the effectiveness of intravesical instillation of PACIS® in the treatment of invasive bladder cancer, and PACIS® is not recommended for these patients.

The use of PACIS® may cause tuberculin sensitivity. Since this is a valuable aid in the diagnosis of tuberculosis, it may therefore be advisable to determine the tuberculin reactivity by PPD skin testing prior to administration of PACIS®.

Intravesical instillations should be postponed during antibiotic treatment since antimicrobial therapy may interfere with the effectiveness of PACIS® (see DRUG INTERACTIONS). PACIS® should not be used in individuals with concurrent infection.

Small bladder capacity has been associated with an increased risk of severe local reactions and should be considered in decisions to treat with PACIS®.

Management of serious BCG Complications: The acute, localized, irritative toxicities of PACIS® may be accompanied by systemic manifestations consistent with a "flu-like" syndrome. Systemic adverse effects of one to two days' duration (e.g., malaise, fever and chills) often reflect hypersensitivity reactions which can be treated with antihistamines. However, **symptoms such as fever of $\geq$ 101.3°F (38.5°C) or acute localized inflammation such as epididymitis, prostatitis, or orchitis persisting longer than two to three days suggest active infection, and an evaluation for serious infectious complications should be considered.**

PACIS® is sensitive to the most commonly used antituberculous agents (isoniazid, rifampin and ethambutol). PACIS® is also sensitive to clofazimine, cycloserine, ethionamide, para-aminosalicylic acid, rifabutin and thiacetazone. **PACIS® is not sensitive to pyrazinamide.**

In patients who develop persistent fever or experience an acute febrile illness consistent with severe sepsis syndrome, two or more antimycobacterial agents should be administered while diagnostic evaluation, including cultures, is conducted. **BCG treatment should be discontinued**. Physicians using this product should be familiar with the literature on prevention, diagnosis, and treatment of BCG-related complications and, when appropriate, should consult an infectious disease specialist or other physician with experience in the diagnosis and treatment of mycobacterial infections.

PRECAUTIONS

General: PACIS® contains live mycobacteria and should be prepared and handled using aseptic technique (see Preparation of the Agent section). To avoid cross-contamination, parenteral drugs should not be prepared in areas where BCG has been in use. Nosocomial infections have been reported in immunosuppressed patients receiving parenteral drugs that were prepared in areas in which BCG was prepared[5]. All equipment, supplies and receptacles in contact with PACIS® should be handled and disposed of as biohazardous.

Precautions should be taken, particularly in common preparation areas, to avoid cross-contamination of parenteral products with BCG.

The possibility of allergic reactions should be assessed. PACIS® administration should not be attempted in individuals with severe immune deficiency disease. PACIS® should be administered with caution to persons in groups at high risk for HIV infection. PACIS® should be avoided in asymptomatic carriers with a positive HIV serology.

Care should be taken during intravesical administration to avoid introducing contaminants into the urinary tract or traumatizing unduly the urinary mucosa. Seven to fourteen days should elapse before PACIS® is administered following TUR, biopsy or traumatic catheterization.

Laboratory Tests: The use of PACIS® might cause tuberculin sensitivity. It is advisable to determine tuberculin reactivity of patients receiving PACIS® by PPD skin testing before treatment is initiated.

Information for Patients: PACIS® is retained in the bladder for two hours and then voided. At the end of treatment all patients should void in a seated position to avoid splashing of urine. Urine voided during the 6 hours after instillation must be disinfected with an equal volume of 5% sodium hypochlorite solution (undiluted household bleach) and allowed to stand for 15 minutes before flushing. Patients should be instructed to increase fluid intake in order to "flush" the bladder in the hours following BCG treatment. Patients may experience burning with the first void after treatment.

Patients should be attentive to side effects, such as fever, chills, malaise, flu-like symptoms or increased fatigue. If the patient experiences severe urinary side effects (e.g., burning or pain on urination, urgency, frequency of urination, blood in the urine), joint pain, cough or skin rash, the physician should be notified immediately.

Drug Interaction: Drug combinations containing immunosuppressants and/or bone marrow depressants and/or radiation interfere with the development of the immune response and should not be used in combination with PACIS®.

Antimicrobial therapy for other infections may interfere with the effectiveness of PACIS®.

There are no data to suggest that the acute, local urinary tract toxicity common with BCG is due to mycobacterial infection, and **antituberculosis drugs (e.g. isoniazid) should not be used to prevent or treat the local irritative toxicities of PACIS®.**

Carcinogenesis, Mutagenesis, Impairment of Fertility: PACIS® has not been evaluated for carcinogenic or mutagenic potential, or for impairment of fertility.

Pregnancy Category C: Animal reproduction studies have not been conducted with PACIS®. It is also not known whether PACIS® can cause fetal harm when administered to a pregnant woman or if it can affect reproductive capacity. PACIS® should not be given to a pregnant woman except when clearly needed. Women should be advised not to become pregnant while on therapy.

Nursing Mothers: It is not known whether PACIS® is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions from PACIS® in

nursing infants, it is advisable to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness of PACIS® for the treatment of carcinoma *in situ* of the urinary bladder in pediatric patients have not been established.

Geriatric Use: While no specific studies on geriatric patients have been performed with PACIS, more than 1/3 of the patients included in the original randomized study of BCG used to generate Tables 1 and 2 were 65 years of age or older. In addition, more than 2/3 of the patients in the Canadian EDR program used to generate Table 3 were 65 years of age or older.

ADVERSE REACTIONS

Symptoms of bladder irritability, related to the inflammatory response induced, are reported by the majority of patients receiving intravesical BCG therapy. The symptoms typically begin 4 to 6 hours after instillation and last 24 to 72 hours.[4] The irritative side effects are usually seen following the third instillation, and tend to increase in severity after each administration. These irritative effects can usually be managed symptomatically with pyridium, propantheline bromide or oxybutinin chloride, and acetaminophen or ibuprofen. The mechanism of action of the irritative side effects has not been studied, but is most consistent with an immunological mechanism. There is no evidence that dose reduction or therapy with an antituberculous drug can prevent or lessen the irritative toxicity of PACIS®.

Flu-like symptoms (malaise, fever and chills) may accompany the localized irritative toxicities and often reflect hypersensitivity reactions that can be treated symptomatically with antihistamines.

Although uncommon, serious infectious complications of intravesical BCG have been reported. The most serious infectious complication of BCG is disseminated sepsis with associated mortality. In addition, *M. bovis* infections have been reported in lung, liver, bone, bone marrow, kidney, regional lymph nodes and prostate in patients who have received intravesical BCG. Some male genitourinary tract infections (orchitis/epididymitis) have been resistant to multiple-drug antituberculous therapy and required orchiectomy.

If a patient develops persistent fever or experiences an acute febrile illness consistent with BCG infection, BCG treatment should be discontinued and the patient immediately evaluated and treated for systemic infection (see Warnings).

Physicians using this product should be familiar with the literature on prevention, diagnosis and treatment of BCG-related complications, and when appropriate, should consult an infectious disease specialist or other physician with experience in the diagnosis and treatment of mycobacterial infections.

The following adverse reactions were reported in 292 patients receiving PACIS® (Table 4).

Table 4

ADVERSE REACTIONS REPORTED IN 292 PATIENTS RECEIVING PACIS®

	All Grades		Grade ≥ 3	
	1st Course Only		All Courses	
Adverse Reactions	**N**	**%**	**N**	**%**
Dysuria/Cystitis	176	60%	27	9%
Urgency/Frequency	102	35%	21	7%
Hematuria	99	34%	18	6%
Fever	38	13%	2	1%
Flu-Like Syndrome	36	12%	4	1%
Other Genitourinary Symptoms	35	12%	3	1%
Nocturia	32	11%	0	---
Urinary Incontinence	21	7%	1	<1%
Urinary Retention	17	6%	4	1%
Abdominal Pain	16	5%	2	1%
Urinary Tract Infection	15	5%	3	1%
Diarrhea/GI	10	3%	1	<1%
Local Pain	8	3%	3	1%
Foreign Material In Urine	7	2%	1	<1%
Irritative Bladder symptoms	6	2%	0	---
Not Otherwise Specified	5	2%	1	<1%
Chills	4	1%	0	-
BCG Systemic Infection	1	<1%	3	1%

OVERDOSAGE

Overdosage occurs if more than one ampule of PACIS® is administered per instillation. If overdosage occurs, the patient should be closely monitored for signs of active local or systemic BCG infection. For acute local or systemic reactions suggesting active infection, an infectious disease specialist experienced in BCG complications should be consulted.

DOSAGE AND ADMINISTRATION

Intravesical treatment with PACIS® should begin between 7 to 14 days after biopsy or TUR. After use, all equipment should be sterilized or disposed of properly, as with any other biohazardous waste (see PRECAUTIONS). **PACIS® should not be injected subcutaneously or intravenously.**

Preparation of the Agent. The preparation of PACIS® suspension should be done using sterile technique. If the preparation cannot be performed in a biocontainment hood, the pharmacist or individual responsible for mixing the agent should wear gloves, mask and gown to avoid inadvertent exposure to broken skin or inhalation of BCG organisms. Precautions should be taken, particularly in common preparation areas, to avoid cross-contamination of parenteral products with PACIS®. PACIS® should not be handled by persons with an immunologic deficiency. Draw 1 mL of sterile diluent (preservative-free 0.9% Sodium Chloride Injection USP) at 4°C to 25°C (39°F to 77°F), into a small syringe and add to *one ampule* of PACIS® to resuspend. Leave them in contact for about 1 minute. Then mix the suspension by withdrawing it into the syringe and expelling it gently back into the ampule 2 or 3 times. Avoid the production of foam: Do not shake. At no time should the reconstituted product be exposed to sunlight, direct or indirect. Exposure to artificial light should be kept to a minimum. Dilute the reconstituted product in an additional 49 mL of saline diluent, bringing the total volume to 50 mL. The suspended PACIS® should be used immediately after preparation. Discard after two hours.

Treatment and Schedule. Patients should not drink fluids for 4 hours before treatment, and should empty their bladder prior to PACIS® administration. PACIS® is instilled into the bladder slowly by gravity flow, via the catheter. DO NOT FORCE the flow of PACIS®. The PACIS® is retained in the bladder for two hours and then voided. Patients unable to retain the suspension for two hours should be allowed to void sooner, if necessary. Ideally, during the first hour following instillation, the patient should lie for 15 minutes each in the prone and supine positions and also on each side. The patient is then allowed to be up but should retain the suspension for another 60 minutes for a total of two hours. Patients should be instructed to drink enough liquid after treatment to maintain adequate hydration. The recommended induction course of PACIS® therapy is a single dose of 120 mg instilled into the bladder once weekly for six weeks. This schedule may be repeated if tumor remission has not been achieved and if the clinical circumstances warrant. The use of maintenance PACIS® has not been studied.

HOW SUPPLIED

PACIS® (Bacillus Calmette-Guérin [BCG], substrain Montreal) is supplied as a single-dose ampule of 120 mg (semi-dry weight) lyophilized BCG (2.4 to 12 x 10^8 C.F.U./ampule).

STORAGE

PACIS® should be kept in a refrigerator at a temperature between 2°C and 8°C (35°F and 46°F). PACIS® should not be used after the expiration date marked on the ampule. The product should be used immediately after reconstitution. **At no time should the lyophilized or reconstituted PACIS® be exposed to sunlight, direct or indirect.**

REFERENCES

1. Herr HW: Intravesical therapy. A critical review. Urol Clinics No Amer 1987;14: 399-404.

2. Catalona WJ, Dresner SM, Haaff EO: Management of Superficial Bladder Cancer. In: Genitourinary Cancer. DG Skinner and G Lieskovsky (eds.), Philadelphia: WB Saunders, 1988, pp. 281-294.

3. Ratliff TL: Mechanisms of action of intravesical BCG for bladder cancer. Prog Clin Biol Res 1989; 310: 107-122.

4. Lamm DL, Steg A, Boccon-Gibod L, et al: Complications of bacillus Calmette-Guérin immunotherapy: Review of 2602 patients and comparison of chemotherapy complications. EORTC Genitourinary Group Monograph 6: BCG in Superficial Bladder Cancer. Alan R. Liss, Inc., New York, NY 1989; pp. 335-355.

5. Stone MM, Vannier AM, Storch SK, et al: Brief report, Meningitis due to iatrogenic BCG infection in two immunocompromised children. N. England J. Med 1995; 333-561-563.

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