PRODUCT MONOGRAPH

ImmuCyst®

Bacillus Calmette-Guérin (BCG), substrain Connaught

Powder for suspension for intravesical use

81 mg

ANTINEOPLASTIC

ATC Code: L03AX03

Sanofi Pasteur Limited
Toronto, Ontario, Canada

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ImmuCyst®

Bacillus Calmette-Guérin (BCG), substrain Connaught

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Non-medicinal Ingredients
Intravesical Instillation	Powder for suspension: 81 mg (dry weight) equivalent to $10.5 \pm 8.7 \times 10^8$ colony forming units (CFU)	Monosodium glutamate *For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING*

DESCRIPTION

ImmuCyst® [Bacillus Calmette-Guérin (BCG), substrain Connaught] is a freeze-dried preparation made from the Connaught substrain of Bacillus Calmette-Guérin, which is an attenuated strain of *Mycobacterium bovis* for treatment of non-muscle invasive bladder cancer (Ta/T1 papillary tumours and CIS). (1)

The BCG organisms are viable upon reconstitution. The reconstituted product contains $10.5 \pm 8.7 \times 10^8$ colony-forming units (CFU) per instillation dose.

INDICATIONS AND CLINICAL USE

ImmuCyst® is indicated for intravesical use in the treatment of primary or recurrent carcinoma *in situ* (CIS) of the urinary bladder, for prophylaxis of recurrence of CIS of the urinary bladder and for prophylaxis following transurethral resection (TUR) of primary or recurrent stage Ta and/or T1 papillary tumours, or any combination thereof, regardless of antecedent intravesical treatment. (1)

ImmuCyst® is not indicated as an immunizing agent for the prevention of tuberculosis. (1)

CONTRAINDICATIONS

- Known systemic hypersensitivity reaction to any component (see DESCRIPTION and WARNINGS AND PRECAUTIONS) of ImmuCyst® or after previous administration of the medicinal product or a medicinal product containing the same substances.
- Active tuberculosis. Active tuberculosis should be ruled out before starting treatment with ImmuCyst®.
- Current symptoms or previous history of systemic BCG reaction. (See WARNINGS AND PRECAUTIONS.)
- Concurrent febrile illness, urinary tract infection, or gross hematuria. Treatment with ImmuCyst® should be postponed until their resolution. (See WARNINGS AND PRECAUTIONS, Serious and Severe Adverse Events Related Precautions.)
- Congenital or acquired immune deficiencies, whether due to concurrent disease (e.g., AIDS, leukemia and lymphoma) or immunosuppressive therapy (e.g., corticosteroids, cancer therapy [cytotoxic drugs, radiation]) (see DRUG INTERACTIONS, Drug-Drug Interactions) because of the risk of disseminated BCG infection.
- A minimum of 14 days should elapse before ImmuCyst® is administered following biopsy, TUR or traumatic catheterization. (2)

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Systemic BCG Reactions

A systemic BCG reaction, which may be fatal, is a systemic granulomatous illness, which may occur (although rarely) subsequent to exposure to BCG.

Because it is usually difficult to isolate BCG organisms from affected organs, it is often unclear to what extent such a reaction is caused by an infectious process versus an inflammatory hypersensitivity reaction, hence the term "systemic BCG reaction".

Based on past clinical experience with intravesical BCG, "systemic BCG reaction" may be defined as the presence of any of the following signs, if no other etiologies for such signs are detectable: fever ≥39.5°C for 12 hours; fever ≥38.5°C for 48 hours; pneumonitis; hepatitis; other organ dysfunction outside of the genitourinary tract with granulomatous inflammation on biopsy; or the classical signs of sepsis, including circulatory collapse, acute respiratory distress and disseminated intravascular coagulation. (3) (See ADVERSE REACTIONS.)

Although rare, a systemic BCG reaction is much more likely to occur if ImmuCyst® is administered within 14 days of biopsy, TUR or traumatic bladder catheterization (associated with hematuria).

General

For intravesical instillation only. Do not inject subcutaneously, intradermally or intravenously.

Advice for Patients

Fever, chills, malaise, flu-like symptoms, increased fatigue or an increase in urinary symptoms, (such as burning or pain on urination) can occur. However, patients should be advised to notify their physicians if any of these symptoms last more than 48 hours or increase in severity. Patients should also notify their physicians if they experience any of the following: an increase in urinary symptoms (such as urgency, frequency of urination, blood in urine), joint pain, eye complaints (such as pain, irritation or redness), cough, skin rash, jaundice, nausea or vomiting.

Because ImmuCyst® contains live mycobacteria, excreted urine may also contain live bacteria. Patients should be advised on appropriate infection control procedures to protect family and close contacts from infection. Patients living with or in close quarters to persons who are immunocompromised (on chemotherapy, etc.) should exercise special caution to avoid inadvertently transmitting BCG infection to such susceptible persons. ImmuCyst® is retained in the bladder for as long as possible up to 2 hours and then voided. To avoid transmission of BCG to others, for 6 hours after treatment patients should void while seated to avoid splashing of urine. Urine voided during this time should be disinfected with an equal volume of household bleach for 15 minutes before flushing or disposal. Unless medically contraindicated, patients should be instructed to increase fluid intake to “flush” the bladder for several hours following treatment with ImmuCyst®. Patients may experience burning with the first void after treatment.

Handling Precautions

Handle as infectious. ImmuCyst® contains live attenuated mycobacteria and should be prepared and handled using aseptic technique. (See DOSAGE AND ADMINISTRATION, Reconstitution of Freeze-Dried Product.) BCG infections have been reported in health-care workers preparing BCG for administration.

Nosocomial infections have been reported in immunosuppressed patients receiving parenteral drugs, which were prepared in areas in which BCG was prepared. (4) (5)

Carcinogenesis and Mutagenesis

Mutagenesis and carcinogenesis studies have not been conducted with ImmuCyst® in animals or in humans. Results from clinical trials do not indicate any increased potential for mutagenesis or carcinogenesis although that was not specifically monitored.

Cardiovascular

The risk of ectopic BCG infections has not been determined but is considered to be very small. BCG infection of aneurysms, arterial grafts and cardiac devices can also occur. The benefits of BCG therapy must be carefully weighed against the possibility of ectopic BCG infection in patients with arterial aneurysms or prosthetic devices of any kind.

Genitourinary

Some male genitourinary tract infections (orchitis/epididymitis) have been refractory to multiple drug antimycobacterial therapy and required orchiectomy.

If a bacterial urinary tract infection (UTI) occurs during the course of ImmuCyst® treatment, ImmuCyst® instillation should be withheld until complete resolution of the bacterial UTI, since the combination of a UTI and BCG-induced cystitis may lead to more severe adverse effects on the genitourinary tract; moreover, because BCG bacilli are sensitive to a wide variety of antibiotics; (6) antimicrobial administration may diminish the efficacy of ImmuCyst®.

Hypersensitivity

Acute allergic reaction has been very rarely reported following intradermal injection of BCG vaccine for the prevention of tuberculosis and therefore should be taken into consideration when administering ImmuCyst®.

The stopper of the vial for this product contains natural latex rubber , which may cause allergic reactions.

Immune

For patients with a condition that may in the future require mandatory immunosuppression (e.g., awaiting organ transplant, myasthenia gravis) the decision to treat with ImmuCyst® should be considered carefully.

Treatments using immunosuppressants and/or radiation interfere with the immune response to ImmuCyst® and increase the risk of disseminated BCG infection. (2)

Because of the risk of BCG infection, ImmuCyst® 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), cancer therapy (e.g., cytotoxic drugs, radiation), or immunosuppressive therapy (e.g., corticosteroids).

Intravesical treatment with ImmuCyst® may induce a positive response to purified protein derivative (PPD). (See DRUG INTERACTIONS.) Determination of a patient's reactivity to PPD should be conducted before administration of ImmuCyst®.

ImmuCyst® should not be handled by persons with an immunologic deficiency.

Peri-operative Considerations

A minimum of 14 days should elapse before ImmuCyst® is administered following biopsy, TUR or traumatic catheterization. There should be no evidence of hematuria prior to instillation of ImmuCyst®.

Sensitivity/Resistance

ImmuCyst® is not sensitive to pyrazinamide. (7)

Serious and Severe Adverse Events Related Precautions

To prevent serious infections, avoid trauma and/or introduction of contaminants to the urinary tract, a minimum of 14 days should elapse before ImmuCyst® is administered following traumatic catheterization. (See CONTRAINDICATIONS.) The treatment schedule should subsequently be resumed as if no interruption in treatment had occurred.

Patients should be monitored for the presence of symptoms and signs of toxicity after each intravesical treatment. If a patient develops persistent fever or experiences an acute febrile illness consistent with BCG infection, BCG instillations should be permanently discontinued, the patient immediately evaluated and treated for BCG infection and an infectious diseases consultation sought. (See CONTRAINDICATIONS.) As standard therapy for BCG infection, treatment with two or more antimycobacterial agents must be initiated promptly while diagnostic evaluation, including cultures, is conducted. Use of single antibiotic therapy is not recommended. Negative cultures do not necessarily rule out infection.

Special Populations

ImmuCyst® is not recommended for prophylactic treatment following TUR of stage TaG1 papillary tumours unless they are judged to be at high risk of tumour recurrence.

In patients with small bladder capacity, increased risk of bladder contracture should be considered in decisions to treat with ImmuCyst®.

Patients undergoing antimicrobial therapy for other infections should be evaluated to assess whether the therapy might diminish the efficacy of ImmuCyst®. (See DRUG INTERACTIONS, Drug-Drug Interactions.)

Pregnant Women

Animal reproduction studies have not been conducted with ImmuCyst®. It is also not known whether ImmuCyst® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. ImmuCyst® should be given to a pregnant woman only if clearly needed. Women should be advised not to become pregnant while on therapy. (1)

Nursing Women

It is not known whether ImmuCyst® can be excreted in human milk. Because many medicinal products are excreted in human milk and because of the potential for serious adverse reactions from ImmuCyst® in nursing infants, it is advisable to discontinue breastfeeding if the mother's condition requires treatment with ImmuCyst®. (1)

Pediatrics

Safety and effectiveness of therapy with ImmuCyst® in pediatric patients has not been established. Therefore, ImmuCyst® should not be used in pediatric patients.

ADVERSE REACTIONS

Adverse event information is derived from clinical trials and worldwide post-marketing experience.

Administration of ImmuCyst® causes an inflammatory response in the bladder and can provoke signs and symptoms of cystitis. (See Table 1 and Table 2.) Such reactions may to some degree be taken as evidence that BCG is evoking the desired response, but careful patient monitoring is required.

Symptoms of bladder irritability are reported in approximately 50% of patients receiving ImmuCyst® and typically begin a few hours after instillation and last 6 - 48 hours. The symptoms are usually seen following the third instillation and tend to increase in severity after each administration. 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 antituberculous drug therapy can prevent or lessen the irritative symptoms of ImmuCyst®. (1) (3)

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse drug reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rules.

Description of Data Sources

The adverse reactions which occurred among recipients of ImmuCyst® during clinical trials SWOG 8216 and SWOG 8507 (see ACTION AND CLINICAL PHARMACOLOGY) are listed in Table 1 and Table 2.

Data are categorized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and by decreasing frequency.

Table 1: SWOG Study 8216 - Adverse Reactions (n = 112)

Adverse Reaction	Percent of Patients Overall Induction Plus Maintenance	Percent of Patients (Grade ≥3) (Total of 11 Instillations)
Infections and Infestations		
Cystitis	29.5%	(0.0%)
Urinary Tract Infection	17.9%	(0.0%)
Pulmonary Infection	2.7%	(0.0%)
Systemic Infection	2.7%	(1.8%)
Infection	0.9%	(0.9%)
Blood and Lymphatic System Disorders		
Anemia	20.5%	(0.0%)
Leukopenia	5.4%	(0.0%)
Coagulopathy/Thrombocytopenia	0.9%	(0.0%)
Metabolism and Nutrition Disorders		
Anorexia	10.7%	(0.0%)
Nervous System Disorders		
Headache	1.8%	(0.0%)
Dizziness	0.9%	(0.0%)
Cardiac Disorders		
Cardiac (Unclassified)	2.7%	(0.0%)
Gastrointestinal Disorders		
Nausea/Vomiting	16.1%	(0.0%)
Diarrhea	6.3%	(0.0%)
Abdominal Pain	2.7%	(0.0%)
Constipation	0.9%	(0.0%)
Hepatobiliary Disorders		
Liver Involvement	2.7%	(0.0%)
Skin and Subcutaneous Tissue Disorders		
Skin Rash	1.8%	(0.0%)

Musculoskeletal and Connective Tissue and Bone Disorders		
Arthralgia/Myalgia/Arthritis	7.1%	(0.9%)
Flank Pain	0.9%	(0.0%)
Renal and Urinary Disorders		
Dysuria	51.8%	(3.6%)
Urinary Frequency	40.2%	(1.8%)
Hematuria	39.3%	(7.1%)
Urinary Urgency	17.9%	(0.9%)
Renal Toxicity (NOS)	9.8%	(1.8%)
Urinary Incontinence	6.3%	(0.0%)
Bladder Cramps/Pain	6.3%	(0.0%)
Contracted Bladder	5.4%	(0.9%)
Tissue in Urine	0.9%	(0.0%)
Ureteral Obstruction	0.9%	(0.0%)
Reproductive System and Breast Disorders		
Genital Pain	9.8%	(0.0%)
General Disorders and Administration Site Conditions		
Malaise	40.2%	(1.8%)
Fever	38.4%	(2.7%)
Chills	33.9%	(2.7%)
Fatigue	0.9%	(0.0%)

Table 2: SWOG Study 8507 - Adverse Reactions

Adverse Reaction	**Percent of Patients**			
	Induction (n = 587/587) 6 Instillations		**Induction + Maintenance (n = 247/587) 6 + 21 Instillations**	
	Overall	**(Grade ≥3)**	**Overall**	**(Grade ≥3)**
Infections and Infestations				
Urinary Tract Infection	1.0%	(0.0%)	4.5%	(0.4%)
Systemic Infection	0.9%	(0.5%)	0.4%	(0.4%)
Pulmonary Infection	0.5%	(0.2%)	NR*	NR
Infection	0.3%	(0.0%)	NR	NR
Cystitis	0.2%	(0.0%)	2.0%	(0.4%)
Blood and Lymphatic Disorders				
Anemia	0.7%	(0.0%)	NR	NR
Leukopenia	0.3%	(0.0%)	NR	NR
Coagulopathy/Thrombocytopenia	0.2%	(0.2%)	NR	NR
Metabolism and Nutrition Disorders				
Anorexia	4.6%	(0.3%)	7.7%	(0.4%)
Nervous System Disorders				
Headache	0.3%	(0.0%)	0.4%	(0.0%)
Dizziness	0.2%	(0.0%)	NR	NR

Cardiac Disorders				
Cardiac (Unclassified)	0.3%	(0.0%)	1.2%	(0.0%)
Gastrointestinal Disorders				
Nausea/Vomiting	2.6%	(0.3%)	4.9%	(0.8%)
Diarrhea	0.9%	(0.0%)	1.2%	(0.4%)
Abdominal Pain	0.3%	(0.0%)	NR	NR
Constipation	NR	NR	0.8%	(0.0%)
Mucositis/Ulcers/Stomatitis	0.2%	(0.0%)	NR	NR
Hepatobiliary Disorders				
Liver Involvement	0.3%	(0.2%)	2.0%	(0.0%)
Granulomatous Hepatitis	0.2%	(0.2%)	NR	NR
Skin and Subcutaneous Tissue Disorders				
Skin Rash	0.7%	(0.3%)	1.2%	(0.0%)
Hypersensitivity Reaction Skin	NR	NR	0.4%	(0.4%)
Skin Abscess	NR	NR	0.4%	(0.0%)
Musculoskeletal and Connective Tissue Disorders				
Arthralgia/Myalgia/Arthritis	0.3%	(0.0%)	1.2%	(0.4%)
Renal and Urinary Disorders				
Dysuria	26.4%	(1.7%)	45.8%	(8.9%)
Hematuria	18.6%	(3.6%)	28.3%	(7.3%)
Urinary Frequency	14.1%	(1.7%)	34.0%	(7.3%)
Urinary Urgency	3.2%	(0.3%)	12.2%	(2.8%)
Bladder Cramps/Pain	1.4%	(0.3%)	3.6%	(1.2%)
Urinary Incontinence	0.9%	(0.3%)	2.0%	(0.8%)
Renal Toxicity	0.9%	(0.0%)	0.8%	(0.0%)
Contracted Bladder	0.5%	(0.2%)	3.6%	(2.0%)
Ureteral Obstruction	0.2%	(0.2%)	NR	NR
Tissue in Urine	NR	NR	0.8%	(0.0%)
Reproductive System and Breast Disorders				
Genital Pain	0.3%	(0.0%)	NR	NR
General Disorders and Administration Site Conditions				
Fever	17.2%	(0.3%)	31.12%	(2.0%)
Malaise	16.7%	(0.7%)	24.7%	(2.0%)
Chills	14.1%	(0.9%)	31.6%	(2.0%)
Fatigue	1.0%	(0.3%)	0.8%	(0.0%)

* NR = Not Reported

Data from Post-Marketing Experience

The following additional adverse events have been spontaneously reported during the post-marketing use of ImmuCyst® worldwide. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to product exposure. Decisions to include these events in labeling were based on one or more of the following factors: 1) severity of the event, 2) frequency of reporting or 3) strength of causal connection to ImmuCyst®.

Data are categorized by MedDRA system organ class.

Infections and Infestations

BCG Infection (rare): BCG is capable of dissemination when administered by the intravesical route. Serious infections, including sepsis with associated mortality, have been reported. BCG infections have also been reported in eye, lung, liver, bone, bone marrow, kidney, regional lymph nodes, peritoneum, genitourinary tract (orchitis/epididymitis) and prostate (e.g., granulomatous prostatitis).

BCG infection of aneurysms and prosthetic devices (including arterial grafts, cardiac devices and artificial joints) has also been reported. (8) (9)

Joint symptoms (arthritis, arthralgia), ocular symptoms (including conjunctivitis, uveitis, iritis, keratitis, granulomatous choreoretinitis), urinary symptoms (including urethritis), skin rash, alone or in combination (Reiter's syndrome), have been reported following administration of ImmuCyst®. For the reports of Reiter's syndrome, the risk seems to be more elevated among patients who are positive for HLA-B27. (10)

Renal abscess (very rare).

Respiratory, Thoracic and Mediastinal Disorders

Pneumonia, interstitial lung disease.

Skin and Subcutaneous Tissue Disorders

Erythema nodosum.

Renal and Urinary Disorders

Renal failure, pyelonephritis, nephritis (including tubulointerstitial nephritis, interstitial nephritis and glomerulonephritis).

Urinary retention (including bladder tamponade and feeling of residual urine).

General Disorders and Administration Site Conditions

Flu like symptoms (rare).

Investigations (Laboratory Tests)

Abnormal/increased blood creatinine or blood urea nitrogen (BUN).

Physicians, nurses and pharmacists should report any adverse reaction related to the administration of the product to the appropriate health authorities in accordance with local requirements and to the Global Pharmacovigilance Department, Sanofi Pasteur Limited, 1755 Steeles Avenue West, Toronto, ON, M2R 3T4 Canada. 1-888-621-1146 (phone) or 416-667-2435 (fax). The report should include details of the treatment history with ImmuCyst®, relevant medical history, the symptoms and signs of the adverse reaction, the treatment administered for the reaction and the response to such treatment.

DRUG INTERACTIONS

Serious Drug Interactions

Immunosuppressive Treatments

Treatment combinations using immunosuppressants and/or radiation interfere with the immune response to ImmuCyst® and increase the risk of disseminated BCG infection. (See WARNINGS AND PRECAUTIONS.) (2)

Drug-Drug Interactions

Intravesical treatment with ImmuCyst® may induce a positive response to PPD, which may complicate future interpretations of skin test reactions to PPD when used to diagnose suspected mycobacterial infections. Determination of a patient's reactivity to PPD should be conducted before administration of ImmuCyst®.

Antibacterial Drugs

Antimicrobial therapy for other infections may interfere with the effectiveness of ImmuCyst®. (6) Patients undergoing antimicrobial therapy should be evaluated to assess whether the therapy might diminish the efficacy of ImmuCyst®.

Antituberculosis Drugs

Antituberculosis drugs should not be used prophylactically to prevent the local, irritative side effects of ImmuCyst®. There are no data to suggest that the acute, local urinary tract symptoms common with intravesical BCG are due to mycobacterial infection.

ImmuCyst® is not sensitive to pyrazinamide. (7)

DOSAGE AND ADMINISTRATION

Recommended Dose

One dose of ImmuCyst® consists of the intravesical instillation of 81 mg BCG.

Intravesical treatment of the urinary bladder should begin a minimum of 14 days after biopsy or TUR (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS) and consists of induction and maintenance therapy.

- The induction therapy schedule consists of one intravesical instillation of ImmuCyst® each week for 6 weeks for a total of 6 doses.
- Based on clinical studies performed with ImmuCyst®, maintenance therapy following induction is highly recommended. After a 6-week pause, one intravesical dose should be given each week for 1 to 3 weeks. Then, one dose should be given each week for 1 to 3 weeks at 6, 12, 18, 24, 30 and 36 months following the initiation of induction treatment.

Reconstitution of Freeze-Dried Product

The preparation of ImmuCyst® should be done using **aseptic technique**. A separate area for the preparation of the ImmuCyst® suspension is recommended in order to avoid cross contamination. The person responsible for mixing the agent should wear gloves, eye protection, a mask and gown to avoid inhalation of BCG organisms and inadvertent exposure of broken skin to BCG organisms.

When handling and reconstituting ImmuCyst®, care should be taken so as to avoid needle stick injuries.

ImmuCyst® should not be handled by persons with an immunologic deficiency. (See WARNINGS AND PRECAUTIONS.)

Do not remove the rubber stopper from the vial.

Prepare the surface of the ImmuCyst® and diluent (if provided) vials using a suitable antiseptic.

Presentation with diluent: Using a 5 mL sterile syringe and needle, draw into the syringe a volume of air equal to the volume of diluent in the vial. Pierce the center of the rubber stopper in the vial containing diluent with the sterile needle of the syringe, invert the vial and slowly inject into it the air contained in the syringe. Keeping the point of the needle immersed in the diluent, withdraw into the syringe 3.0 mL of

diluent for the 81 mg vial presentation. Then, holding the syringe-plunger steady, withdraw the needle from the vial.

Presentation without diluent: Using a 5 mL sterile syringe and needle, draw up 3 mL of sterile preservative-free saline solution.

For both presentations: Using the same syringe and needle, pierce the rubber stopper in the vial of freeze-dried material with the needle. Hold the vial of freeze-dried material upright and pull the plunger of the syringe back to create a mild vacuum in the vial. Release the plunger and allow the vacuum to pull the saline from the syringe into the vial of freeze-dried material. After all the saline has passed into the freeze-dried material, remove the needle and syringe.

Shake the vial gently until a fine, even suspension results. Avoid foaming since this will prevent withdrawal of the proper dose. Withdraw the entire contents of the reconstituted material from the vial into the same 5 mL syringe. Return the vial to an upright position before removing the syringe from the vial.

Further dilute the reconstituted material from the vial (1 dose) in an additional 50 mL of sterile, preservative-free saline to a final volume of 53 mL for intravesical instillation.

Any reconstituted product which exhibits flocculation or clumping that cannot be dispersed with gentle shaking should not be used.

Administration

For intravesical instillation only. Do not inject subcutaneously or intravenously.

This dose is prepared by reconstituting 1 vial containing 81 mg freeze-dried BCG with 3 mL of diluent or with 3 mL of sterile, preservative-free saline. The reconstituted BCG is further diluted in 50 mL of sterile, preservative-free saline, for a total of 53 mL instillation volume. (See WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION, Reconstitution of Freeze-Dried Product.)

A urethral catheter is inserted into the bladder under **aseptic conditions,** the bladder is drained and then the 53 mL suspension of ImmuCyst® is instilled slowly by gravity, following which the catheter is withdrawn.

The patient retains the suspension for as long as possible up to two hours. The patient should lie prone for the first 15 minutes following instillation. Thereafter, the patient is allowed to be up. At two hours after the instillation, all patients should void in a seated position for hygienic safety reasons. (See WARNINGS AND PRECAUTIONS and SPECIAL HANDLING INSTRUCTIONS.) Unless medically contraindicated, patients should be instructed to increase fluid intake in order to flush the bladder in the hours following BCG treatment.

OVERDOSAGE

Not documented.

ACTION AND CLINICAL PHARMACOLOGY

Pharmacodynamics

When administered intravesically as a cancer therapy, BCG promotes a local acute inflammatory and sub-acute granulomatous reaction with macrophage and leukocyte infiltration in the urothelium and lamina propria of the urinary bladder. (11) (12) The local inflammatory effects are associated with an elimination or reduction of non-muscle invasive cancerous tumours of the urinary bladder (Ta/T1 papillary tumours and CIS). The exact mechanism of action is unknown, but the anti-tumour effect appears to be T-lymphocyte dependent. (12) (13)

Pharmacokinetics

Because ImmuCyst® contains live mycobacteria, excreted urine may also contain live bacteria. (See WARNINGS AND PRECAUTIONS and SPECIAL HANDLING INSTRUCTIONS.)

STORAGE AND STABILITY

ImmuCyst® should be stored at 2° to 8°C (35° to 46°F) (i.e., in a refrigerator). It should not be used after the expiration date marked on the vial, otherwise it may be inactive.

At no time should the freeze-dried ImmuCyst® be exposed to direct or indirect sunlight. Exposure to artificial light should also be kept to a minimum.

Reconstituted Product

Once reconstituted, the product should be used immediately.

Reconstituted product should not be exposed to direct or indirect sunlight. Exposure to artificial light should also be kept to a minimum.

If there is an unavoidable delay between reconstitution and administration, this delay should not exceed 2 hours at a temperature between 2° to 25°C (35° to 77°F).

Any reconstituted product, which exhibits flocculation or clumping that cannot be dispersed with gentle shaking, should not be used.

SPECIAL HANDLING INSTRUCTIONS

Instructions for Disposal

Unused product, packaging and all equipment and materials used for instillation of the product (e.g., syringes, catheters) should be placed immediately in a container for biohazardous materials and disposed of according to local requirements applicable to biohazardous materials.

Urine voided during the 6-hour period following ImmuCyst® instillation should be disinfected with an equal volume of 5% hypochlorite solution (undiluted household bleach) and allowed to stand for 15 minutes before flushing. (See WARNINGS AND PRECAUTIONS.)

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms

ImmuCyst® is supplied as a sterile lyophilized white powder in a vial containing 81 mg. If provided, the diluent is a sterile clear colourless solution supplied in a vial containing 3 mL.

Composition

Active Ingredients:

Bacillus Calmette-Guérin (BCG), substrain Connaught	81 mg

Other Ingredients:

Excipient

Monosodium glutamate	150 mg (5% w/v)

Diluent (if provided)**:**

Sodium chloride	25.5 mg (0.85% w/v)
Disodium hydrogen phosphate	7.5 mg (0.25% w/v)
Sodium dihydrogen phosphate	1.7 mg (0.06% w/v)
Polysorbate 80	0.75 mg (0.025% w/v)
Water for injection	up to 3 mL

No preservative is added.

Packaging:

ImmuCyst® is supplied in a package containing either:

- one 81 mg vial of BCG with one 3 mL vial diluent
- one 81 mg vial of BCG

ImmuCyst® is supplied in an amber Type 1 glass vial and the diluent (if provided) is supplied in a clear Type 1 glass vial. The stopper for both vials contains natural latex rubber.

Vaccine Information Service: 1-888-621-1146 or 416-667-2779.
Business Hours: 8 a.m. to 5 p.m. Eastern Time Monday to Friday.
Full product monograph available on request or visit us at www.sanofipasteur.ca

Product information as of January 2010.

Manufactured by:
Sanofi Pasteur Limited
Toronto, Ontario, Canada

R11-0110 Canada

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Product Characteristics

ImmuCyst® [Bacillus Calmette-Guérin (BCG), substrain Connaught] is prepared from a culture of the Connaught strain of Bacillus Calmette-Guérin (BCG), which is an attenuated strain of living bovine tubercle bacillus, *Mycobacterium bovis.* The bacilli are lyophilized and are viable upon reconstitution.

The reconstituted product contains $10.5 \pm 8.7 \times 10^8$ colony-forming units (CFU) per instillation dose when resuspended. (1)

ImmuCyst® is supplied in a single vial containing 81 mg of BCG with a 3 mL vial of diluent (if provided). The product and the diluent (if provided) contain no preservative. One dose consists of one 81 mg vial of reconstituted material further diluted in 50 mL sterile, preservative-free saline.

CLINICAL TRIALS

Study Demographics and Trial Design

Table 3: Summary of Patient Demographics for Clinical Trials

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
SWOG 8216	Randomized	81 mg intravesically	127	65-68	male
SWOG 8507	Randomized	81 mg intravesically	389	62-73	male & female

Clinical studies have proven the effectiveness of ImmuCyst® for patients with non-muscle invasive bladder cancer at the Carcinoma *in situ* (CIS), Ta and T1 stages, including two multicentre controlled, randomized trials.

In the first study SWOG 8216, ImmuCyst® was compared to doxorubicin hydrochloride (Adriamycin®) among patients with either CIS or recurrent papillary tumours or both. (14) ImmuCyst® was administered intravesically once each week for 6 weeks, with an additional single instillation at 3, 6, 12, 18 and 24 months following the initiation of treatment (total of 11 instillations). Doxorubicin was administered once each week for 5 weeks, with an additional 11 single monthly treatments.

For patients with CIS, the complete response rate (i.e., negative biopsies and urine cytology) within 6 months of the initiation of treatment was 70% with ImmuCyst® versus 34% with doxorubicin ($p < 0.001$); the probability of being disease-free (i.e., having no evidence of bladder cancer) at 5 years was 45% (n = 64 patients) and 18% (n = 67 patients), respectively ($p < 0.001$ by proportional hazards regression model); and among complete responders, the median time to treatment failure was 39 months versus 5.1 months, respectively. Among patients with papillary tumours (Ta or T1) without CIS, the probability of being disease-free at 5 years was 37% (n = 63 patients) with ImmuCyst® versus 17% (n = 68 patients) with doxorubicin ($p = 0.015$ by proportional hazards regression model). (14)

In the second study SWOG 8507, two treatment regimens of ImmuCyst® were compared among similar patients to the first study. (15) (16) The initial study report covered a median follow-up period of 3.2 years (1992), (15) and a recent analysis reported a total of ten years of median follow-up data (2000). (16) A 6-

week induction course alone (total of 6 instillations) was compared to a more intensive regimen consisting of the following: an induction course of one treatment each week for 6 weeks; after a 6-week pause, another treatment each week for 3 weeks; and then maintenance therapy consisting of one instillation each week for 3 weeks at 6 months after the initiation of the induction course and then every 6 months for 36 months (total of 27 instillations from the start of therapy).

Comparing the maintenance regimen to the no-maintenance regimen (i.e., 6-week induction course only), the following results were found: the five-year survival was 78% in the no-maintenance compared to 83% in the maintenance arm (p = 0.08).

The overall five-year recurrence free survival was 41% in the no-maintenance group and 60% in the maintenance group (p <0.0001). The recurrence free survival in the 3-week maintenance group (n = 192 patients) was found to be twice as long as (77 versus 36 months) for the no-maintenance group (n = 192 patients). Among a total of 278 eligible patients with CIS, the complete response rate was increased from expected 68% to 84%. The between arm difference for the overall rate of CIS response was significant at p = 0.004. Among the patients with papillary tumours (Ta or T1) without CIS, the median recurrence free survival was 78 months in the maintenance group (n = 128 patients) and 28 months in the no-maintenance group (n = 126 patients).

This study provides evidence that the 3-week, 3-year BCG maintenance schedule provides superior protection from disease recurrence and improves long-term survival. (15) (16)

TABLE 1: COMPARATIVE STUDIES ON EFFICACY OF IMMUCYST®: TREATMENT REGIMENS AND COMPLETE RESPONSE RATES

Treatment Arm	TREATMENT REGIMEN																	RESULTS		
	Number of Weekly Instillations at Time (in Months) Commencing with the First Instillation i.e., Time 0 = Time of First Instillation.																Total No. of Instil-lations	CIS Patients with Complete Response		
	0	2	3	4	5	6	7	8	9	10	11	12	18	24	30	36		n	%	p
ImmuCyst® versus Doxorubicin[4]	6	-	1	-	-	1	-	-	-	-	-	1	1	1	-	-	11	64	70	p < 0.001*
	5	1	1	1	1	1	1	1	1	1	1	1	-	-	-	-	16	67	34	
ImmuCyst® Maintenance versus ImmuCyst® Induction Only[6]	6	-	3	-	-	3	-	-	-	-	-	3	3	3	3	3	27	97	84	p = 0.004
	6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	6	79	68	

* within 6 Months of Initiation of Treatment

PHARMACOLOGY

When administered intravesically as a cancer therapy, BCG promotes a local acute inflammatory and sub-acute granulomatous reaction with macrophage and leukocyte infiltration in the urothelium and lamina

propria of the urinary bladder. (11) (12) The local inflammatory effects are associated with an elimination or reduction of non-muscle invasive cancerous tumours of the urinary bladder (Ta/T1 papillary tumours and CIS). The exact mechanism of action is unknown, but the anti-tumour effect appears to be T-lymphocyte dependent. (12) (13)

General Discussion of BCG Therapy for Bladder Cancer

CIS of the Urinary Bladder

CIS may occur either alone or in association with papillary tumours, particularly those of higher grade. CIS may be multifocal and may be also associated with multifocal pre-malignant dysplastic lesions. While transurethral resection (TUR) is the primary treatment for CIS, it is often not curative: some lesions may be either undetectable or unresectable or both. Furthermore, even with curative TUR, CIS is associated with a high incidence of recurrence and of recurrence of higher-stage lesions, including cancer invasive of the muscle layer of the urinary bladder (stage T2 or higher). Intravesical ImmuCyst® [Bacillus Calmette-Guérin (BCG), substrain Connaught] has been studied and established as both an alternative to radical surgical treatment for CIS and as prophylaxis for recurrence of CIS.

Papillary Tumours of the Urinary Bladder

While TUR is the primary treatment of non-muscle invasive papillary tumours (Ta/T1 tumours), these tumours have a tendency to recur and to progress. This is particularly true when there are two or more co-existing papillary tumours, when there has already been a recurrence of such tumours, or when there is co-existing CIS. In these circumstances, ImmuCyst® has been shown to increase significantly the time to recurrence when administered intravesically for prophylactic purposes following TUR.

TOXICOLOGY

Data from animal studies do not suggest any special hazards other than those already reported from human studies. (1)

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References List

1 Data on File at Sanofi Pasteur Limited.

2 Koya, MP, et al. Complications of Intravesical Therapy for Urothelial Cancer of the Bladder. J Urol 2006;175:2004-10.

3 Lamm DL, et al. Incidence and treatment of complication of bacillus Calmette-Guérin intravesical therapy in superficial bladder cancer. J Urol 1992;147:596-600.

4 Waecker NJ, et al. Nosocomial transmission of Mycobacterium bovis bacille Calmette-Guérin to children receiving cancer therapy and to their health care providers. Clin Infect Dis 2000;30:356-62.

5 Stone MM, et al. Brief report: meningitis due to iatrogenic BCG infection in two immunocompromised children. N Engl J Med 1995;333:561-3.

6 Durek C, et al. Interference of modern antibacterials with bacillus Calmette-Guérin viability. J Urol 1999;162:1959-62.

7 van der Meijden APM, et al. The possible influence of antibiotics on results of bacillus Calmette-Guérin intravesical therapy for superficial bladder cancer. J Urol 1991;146:444-6.

8 Wolf YG, et al. Infection of a ruptured aortic aneurysm and an aortic graph with bacillus Calmette-Guérin after intravesical administration for bladder cancer. J Vasc Surg 1995;22:80-4.

9 Stone D. Mycobacterium bovis infection of an implantable defibrillator following intravesical therapy with bacille Calmette-Guérin. Clin Inf Dis 1993;16:825-6.

10 Wittes RC, et al. Characterization of BCG-associated sterile arthritis and Reiter's syndrome. New Delhi, India; 10th International Congress of Immunology. 1998. p. 1245-9.

11 Mikkelsen DJ, Ratliff TL. Mechanisms of action of intravesical bacillus Calmette-Guérin for bladder cancer. In: Urologic Oncology. 1989:195-211.

12 O'Donnell MA, DeWolf WC. BCG immunotherapy for superficial bladder cancer. New prospects for an old warhorse. Surg Oncol Clin North Amer 1995;4:189-202.

13 Prescott S, et al. Intravesical Evans strain BCG therapy: quantitative immunohistochemical analysis of the immune response within the bladder wall. J Urol 1992;147:1636-42.

14 Lamm DL, et al. A randomized trial of intravesical doxorubicin and immunotherapy with bacille Calmette-Guérin for transitional-cell carcinoma of the bladder. N Engl J Med 1991;325:1205-19.

15 Lamm DL, et al. Maintenance BCG immunotherapy of superficial bladder cancer: a randomized prospective Southwest Oncology Group study. J Urol 1992;147:247A.

16 Lamm DL, et al. Maintenance bacillus Calmette-Guérin immunotherapy for recurrent Ta, T1 and carcinoma in situ transitional cell carcinoma of the bladder. A randomized Southwest Oncology Group study. J Urol 2000;163(4):1124-9.

IMPORTANT: PLEASE READ BEFORE TAKING THIS MEDICATION

PART III: CONSUMER INFORMATION
ImmuCyst®

Bacillus Calmette-Guérin (BCG), substrain Connaught

This leaflet is Part III of a three-part "Product Monograph" published when ImmuCyst® was approved for sale in Canada. It gives Consumers information about ImmuCyst®. Because this is a summary, it does not tell you everything about the medication. Contact your doctor or pharmacist if you have any questions about this product.

ABOUT THIS MEDICATION

What the medication is used for:

ImmuCyst® is used to treat cancerous growths (tumours) on the surface of the bladder. ImmuCyst® also prevents the growth of new tumours.

What it does:

ImmuCyst® works by stimulating your body's immune system to fight against bladder tumours. This form of treatment is called immunotherapy. Research has shown that immunotherapy is a more effective treatment than chemotherapy in fighting the growth of bladder tumours.

When it should not be used:

- If you get a bacterial urinary tract infection (UTI) while you are taking ImmuCyst® or if you have large amounts of blood in your urine, your doctor may stop the treatment.
- The effects of ImmuCyst® on pregnancy are not known. Female patients should use birth control while on ImmuCyst®. Tell your doctor immediately if you think you may be pregnant.
- Women should not breastfeed while on ImmuCyst®.
- Do not use ImmuCyst® if you are allergic to any ingredient in the product.
- People who have active tuberculosis (TB) should not have this treatment.
- People who have any form of immune deficiency should not have this treatment. Immune deficiency may result from diseases (such as AIDS, leukemia and lymphoma) or from treatments that suppress the immune system (such as corticosteroid or cancer therapy that includes cytotoxic drugs or radiation).
- If you have a bladder operation, you should wait a minimum of 14 days before starting to take ImmuCyst®.

What the medicinal ingredient is:

ImmuCyst® is a freeze-dried preparation made from weakened bacteria called *Mycobacterium bovis*. The BCG organisms are alive but weakened.

What the important non-medicinal ingredients are:

Monosodium glutamate: 150 mg

The non-medicinal ingredients of the diluent (if provided) are:
Sodium chloride
Disodium hydrogen phosphate
Sodium dihydrogen phosphate
Polysorbate 80
Sterile water for injection

For a full listing of non-medicinal ingredients see Part 1 of the Product Monograph.

What dosage forms it comes in:

Every vial contains 81 mg (dry weight) of BCG powder. The powder must be mixed with saline. A health-care provider will give you the medication through a catheter (a tube) inserted into your bladder.

Serious Warnings and Precautions

Systemic BCG Reactions

A systemic BCG reaction is a general body illness caused by spread of BCG beyond the bladder or an unusual reaction of your body to BCG within your bladder. This reaction is rare but may occur after ImmuCyst® treatment.

Contact your doctor if you have any of the following symptoms, after having an ImmuCyst® treatment:

- fever higher than 39.5°C for 12 hours
- fever higher than 38.5°C for 48 hours
- difficulty breathing
- skin or eyes turning yellow
- unusual bleeding or bruising

WARNINGS AND PRECAUTIONS

Before you use ImmuCyst® talk to your doctor or pharmacist if you:

- have blood in your urine or a urinary tract infection,
- have had a treatment or a disease (such as AIDS) that weakens your immune system,
- have had radiation therapy for cancer,
- are pregnant, breast feeding or intending to become pregnant during therapy,
- have a major medical or surgical procedure scheduled during or shortly after ImmuCyst® treatment,
- have any allergies to the ingredients in ImmuCyst®.

INTERACTIONS WITH THIS MEDICATION

Treatment using immunosuppressants and/or radiation interfere with the body's response to ImmuCyst®. They also increase the risk of side effects from the medication.

Antibiotic therapy used for other infections may interfere with the effectiveness of ImmuCyst®.

Treatment with ImmuCyst® may cause a positive tuberculosis skin test. The results of a skin test for tuberculosis **any** time after treatment with ImmuCyst® may show that you have tuberculosis even if you don't. If you need a TB skin test, it should be done before you start treatment with ImmuCyst®.

PROPER USE OF THIS MEDICATION

Before Your Treatment

- Tell your doctor about any medications you take regularly. Certain drugs affect how ImmuCyst® works (e.g., some antibiotics, medications that may suppress your bone marrow or immune system and/or radiation).
- Do not drink fluids for at least 2 hours before your treatment so that your bladder will be empty.
- You will have to go to your doctor's office or the hospital for treatment with ImmuCyst®. The treatment does not take a long time, but you should take the day off because of the things you need to do after your treatment.

Things to Know About Your Treatment

When will you have it?

- Your treatment should begin about 2 weeks after biopsy or transurethral resection.
- For the first course of treatment, you will get one dose of ImmuCyst® into your bladder once-a-week for 6 weeks.
- If your doctor prescribes maintenance treatments, you will continue with one dose per week for 3 weeks after six weeks have gone by since you completed your first course of treatment. After six months have passed since you began your first course of treatment, you will have one dose per week for 1 to 3 weeks every 6 months. Your doctor will decide how long you will need maintenance treatment.

What will they do?

- Your doctor or nurse will place a catheter (tube) into your bladder. If there is any urine in your bladder it will be drained through the catheter.
- The doctor or nurse will attach a container of ImmuCyst® solution to the catheter. The solution will run into your bladder. This process is called instillation.
- When all the solution is in your bladder, the catheter will be removed.

What do you have to do?

- Be sure to lie on your stomach for the first 15 minutes after the catheter is removed. After that, you can get up and move around. This will make sure ImmuCyst® has completely covered the inside of your bladder.
- You must hold the ImmuCyst® inside your bladder for as long as possible, up to 2 hours. After 2 hours, you can empty your bladder.

After Your Treatment

- Unless your doctor tells you not to, you should drink lots of liquids for the next 24 hours. Try to drink at least twelve 250 mL (8 oz.) glasses of liquid per day. Urinate frequently.
- Because ImmuCyst® may be infectious; you should disinfect the urine in the toilet before you flush. To do this, pour one cup of pure undiluted bleach into the toilet bowl every time you urinate. Leave bleach in the toilet bowl for 15 minutes before flushing. You should do this every time you urinate for the first 6 hours after treatment.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Some people have unpleasant side effects during their treatment with ImmuCyst®. However, the side effects are usually easy to manage. On your treatment days, they may be worse but they will get better in a few days. It is important for you to stay on ImmuCyst® for the whole treatment time. Completing the treatment helps to prevent the tumour from coming back.

Please talk to your doctor about any side effects that you feel may prevent you from finishing the treatment.

The most common side effects include:

- flu-like symptoms: fever, chills, headaches, and muscle aches
- frequent or painful urination
- urination at night
- traces of blood in your urine.

To help you manage these side effects, get plenty of bed rest, drink lots of liquids and take acetaminophen or ASA for any pain and fever. If you are concerned about your symptoms, contact your doctor.

This is not a complete list of side effects. Contact your doctor or pharmacist if you have any unexpected side effects while taking ImmuCyst®.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

If you experience the following symptoms, contact your doctor or get emergency help immediately:

- any sign of an **ALLERGIC REACTION**, which includes difficulty breathing, shortness of breath, wheezing, rash or hives and/or swelling of the face, or
- any sign of a **BCG INFECTION** which includes cough, high fever for more than 12 hours (greater than 39.5°C) or a fever (greater than 38.5°C) which lasts longer than two days.

If you notice the following symptoms, please see your doctor as soon as possible:

- yellow eyes or skin
- white or grey-coloured stools
- fever with chills, headache, muscle or joint pain that is not relieved by acetaminophen or ASA and lasts for more than 2 days
- severe pain or excessive urinating
- eye problems
- blood in urine

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:
toll-free telephone: 866-234-2345
toll-free fax: 866-678-6789
By email: cadrmp@hc-sd.gc.ca

By regular mail:
National AR Centre
Marketed Health Products Safety and Effectiveness Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa, ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

HOW TO STORE IT

ImmuCyst® should be stored at 2º to 8ºC by your health-care provider.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: www.sanofipasteur.ca or by contacting the sponsor,

Sanofi Pasteur Limited
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