

DATA SHEET

IMMUCYST®

NAME OF THE MEDICINE

ImmuCyst

Non-proprietary Name

BCG Immunotherapeutic

DESCRIPTION

ImmuCyst - BCG Immunotherapeutic (Bacillus Calmette-Guérin/Connaught) is a freeze dried preparation of an attenuated strain of *Mycobacterium bovis*. It is produced from a suspension containing viable bacteria of the Connaught strain of Bacillus of Calmette and Guérin (BCG) and formulated to contain 81mg (dry weight) of BCG and 150 mg monosodium glutamate. This product contains no preservative.

Each vial of ImmuCyst is reconstituted with 3 mL of sterile, preservative-free saline solution.

PHARMACOLOGY

Pharmacodynamics

When administered into the bladder 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. The local inflammatory effects are associated with an elimination or reduction of non-muscle invasive cancerous lesions of the urinary bladder. The exact mechanism of action is unknown, but the anti-tumour effect appears to be T-lymphocyte dependent.

Pharmacokinetics

As ImmuCyst contains live mycobacteria, excreted urine may also contain live bacteria.

CLINICAL TRIALS

In a controlled multicentre study ImmuCyst was compared to doxorubicin hydrochloride (Adriamycin) in the treatment of CIS of the urinary bladder. Among the 54 patients receiving ImmuCyst, 74% had a complete response with an estimated median time to treatment failure (recurrence, progression or death) of 48.2 months compared to 42% complete response and 5.9 months to treatment failure for Adriamycin. Prior treatment with other agents did not adversely affect the response to ImmuCyst.

Table 1: Response of patients with carcinoma *in situ* to treatment with ImmuCyst or Adriamycin

	ImmuCyst (n=54)	Adriamycin (n=60)
Complete Response	74%*	42%*
No Response	11%	10%
Increasing Disease	13%	42%
No evaluation	2%	7%
TOTAL	100%	100%

* Difference is statistically significant (p<0.01)

Table 2: Time to recurrence, progression or death: Time to Treatment Failure (TTF)

	At Risk	Failures	Median TTF
ImmuCyst	54	27	48.2 months*
Adriamycin	60	46	5.9 months*

* Difference is statistically significant (p<0.01 stratified logrank)

Table 3: Prior versus no prior treatment

Treatment	Response rate	Median TTF (# events/N)
Prior treatment and ImmuCyst	81%	Not reached (11/26)
Prior treatment and Adriamycin	53%	7 months (22/30)
No prior treatment and ImmuCyst	68%	32.8 months (16/28)
No prior treatment and Adriamycin	30%	3.7 months (24/30)

No survival advantage for ImmuCyst therapy over that for Adriamycin has been demonstrated.

INDICATIONS

ImmuCyst (BCG Immunotherapeutic) is indicated for intravesical use in the treatment and prophylaxis of primary or recurrent carcinoma-in-situ (CIS) of the urinary bladder, and for the 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.

CONTRAINDICATIONS

- Known systemic hypersensitivity reactions to any component (i.e. as defined in **DESCRIPTION** and **PRECAUTIONS**) of ImmuCyst or after previous administration of the medicinal product or a medicinal product containing the same substances.
- 7 to 14 days should elapse before ImmuCyst is administered following biopsy, TUR or traumatic catheterisations.
- Patients receiving immunosuppressive therapy and/or radiation or those with compromised immune systems should not receive ImmuCyst due to the risk of overwhelming systemic infection.
- Congenital or acquired immune deficiencies, whether due to a concurrent disease (eg. AIDS, leukaemia, lymphoma) or immunosuppressive therapy (eg. corticosteroids, cancer therapy [cytotoxic drugs, radiation, etc]) because of the risk of disseminated BCG infection (see **PRECAUTIONS: Interactions with other Medicines**).
- Patients with urinary tract infection are at increased risk of disseminated BCG infections or increased severity of bladder infection and therefore should not receive ImmuCyst treatment until resolution of the concurrent illness. ImmuCyst should not be administered to patients with current or previous evidence of systemic BCG reaction (see Warnings and Suggested Guidelines for the Management of Adverse Reactions Associated with ImmuCyst Therapy).
- Patients with active tuberculosis should not receive ImmuCyst because of the danger of exacerbation or of concomitant systemic BCG reaction.
- Prior to treatment with ImmuCyst a mantoux test should be performed. If this is positive, ImmuCyst is contraindicated only if there is evidence of active BCG infection.
- ImmuCyst should not be administered to patients with fever unless the cause of the fever is determined and evaluated. If due to an infection, ImmuCyst should be withheld until it subsides.

PRECAUTIONS

For instillation into the bladder only. Do not inject subcutaneously or intravenously.

Local BCG Reaction

Administration of intravesical ImmuCyst causes an inflammatory response in the bladder and has been associated with haematuria, urinary frequency, dysuria and bacterial urinary tract infection. Careful monitoring of urinary status is required. Local irritative symptoms of the bladder and flu-like symptoms are common.

Systemic BCG Reaction and Infection

A systemic BCG reaction, which may be fatal, is a systemic granulomatous illness which may occur (although rarely) subsequent to exposure to BCG. However, because it is usually difficult to isolate BCG organisms from affected organs, it is often unclear to what extent such a reaction is due to an infectious process versus an inflammatory hypersensitivity reaction: hence the term "systemic 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 etiologies for such signs are detectable: fever $>39.5^{\circ}\text{C}$ for >12 hours; fever $>38.5^{\circ}\text{C}$ 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. Although rare, a systemic BCG reaction is much more likely to occur if BCG is administered within one week of either transurethral resection or traumatic bladder catheterisation that was associated with haematuria.

One case of systemic BCG reaction has been reported in a patient with a prosthetic aortic valve and a prior history of bacterial endocarditis; it is unknown whether these constitute risk factors for a systemic BCG reaction. Two fatalities have been reported with the use of ImmuCyst, both associated with systemic BCG reaction. One was associated with intravesical instillation in spite of traumatic catheterisation in a patient with antecedent alcoholic liver disease. The second case may have been related to continued BCG treatment of a patient with an unrecognised systemic BCG reaction. The appropriate treatment of systemic BCG reaction is discussed in 'Suggested Guidelines for the Management of Adverse Reactions Associated with ImmuCyst Therapy'.

Systemic adverse reactions have included nausea, diarrhoea, anaemia, leucopaenia, prostatitis and ureteral obstruction. Deaths have been reported following intravesical administration of ImmuCyst. If systemic BCG infection is suspected the patient should be immediately treated with fast acting anti-tuberculosis antibiotic therapy following consultation with an infectious disease specialist. ImmuCyst therapy should be withheld upon any suspicion of systemic infection.

Bacterial Urinary Tract Infection

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, 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 rubber latex, which may cause allergic reactions.

Information 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.

As 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. ImmuCyst is retained in the bladder for as long as possible up to two 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.

Use in Pregnancy (Category B2)

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

Use in Lactation

It is not known whether ImmuCyst can be excreted in human milk. As 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.

Paediatric Use

Safety and effectiveness of ImmuCyst for CIS in children have not been established. Therefore ImmuCyst should not be used in paediatric patients.

Use in Special Populations

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

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.

Other Information

Patients undergoing antimicrobial therapy for other infections should be evaluated to assess whether the therapy will obviate the effects of ImmuCyst actions.

Intravesical treatment with ImmuCyst may induce a sensitivity to tuberculin which could complicate future interpretations of skin test reactions to tuberculin.

ImmuCyst is not a vaccine to prevent cancer.

ImmuCyst contains viable attenuated mycobacteria and should be handled as infectious. All equipment and materials used during instillation of ImmuCyst should be disposed of as biohazardous waste.

It is recommended that intravesical ImmuCyst not be administered any sooner than one week following transurethral resection.

Care must be taken during administration of intravesical ImmuCyst not to introduce contaminants into the urinary tract or to traumatise unduly the urinary mucosa. If the physician believes that the bladder catheterisation has been traumatic, then ImmuCyst should not be administered and there must be a treatment delay of at least one week. Subsequent treatment should be resumed as if no interruption in the schedule had occurred.

Interactions with other Medicines

This medicinal product must not be mixed with other vaccine or medicinal products.

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 **CONTRAINDICATIONS**).

Antibacterial drugs

Antimicrobial therapy for other infections may interfere with the effectiveness of ImmuCyst. Therefore 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.

Effect on Laboratory Tests

Intravesical treatment with ImmuCyst may induce a sensitivity response to Tuberculosis Purified Protein Derivative (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.

Driving a Vehicle or Performing Other Hazardous Tasks

No studies on the effects on the ability to drive or use machines have been performed.

ADVERSE EFFECTS

Table 4 summarises the suggested guidelines for the treatment of adverse reactions.

If there is any suspicion of active BCG infection the opinion of an infectious diseases specialist should be sought immediately.

The most common local adverse reactions reported following the intravesical instillation of ImmuCyst include: dysuria, urinary frequency, haematuria, cystitis, urgency, urinary tract infection, urinary incontinence and cramps/pain.

Symptoms usually begin 2 to 4 hours after instillation and persist for 24 to 72 hours.

Systemic reactions usually last for 1-3 days after each intravesical instillation, the most common of these are as follows: malaise, fever (>38°C), chills, anaemia, nausea/vomiting, anorexia, myalgia/arthritis/arthritis, diarrhoea, leucopenia, renal toxicity and genital pain. Granulomatous prostatitis, epididymo-orchitis, disseminated intravascular coagulation, abdominal pain and renal abscess have been reported. Fatalities have been reported with the use of ImmuCyst after traumatic catheterisation or in the presence of urinary infection.

Irritative vesical side effects associated with ImmuCyst administration can be managed symptomatically, for example with propantheline bromide and paracetamol.

Skin rashes, arthralgias and migratory arthritis are rare, and are considered to be strictly allergic reactions.

Systemic infection as a result of the spread of BCG organisms has occasionally occurred with intravesical ImmuCyst administration.

BCG organisms, including the Connaught strain, are susceptible to all currently used anti-tuberculosis drugs, with the exception of pyrazinamide. Accordingly, for more serious reactions other than the systemic BCG reactions described in Warnings, for example, severe urinary tract adverse events or allergic reactions, isoniazid with or without rifampicin should be administered for 3-6 months. If a systemic BCG reaction occurs, an Infectious Disease consultation should be sought. ImmuCyst should be permanently discontinued, and triple anti-tuberculosis therapy should be initiated promptly and continued for 6 months. Commonly this will comprise isoniazid (300mg daily), rifampicin (600 mg daily) and ethambutol (1000 mg daily). In the presence of signs of septic shock as a manifestation of a systemic BCG reaction, the addition of short term corticosteroids, (e.g. prednisolone, 40 mg daily), has been shown to be beneficial both in five patients, and in an animal model and should therefore be considered.

If a systemic BCG reaction has occurred, a report should be submitted to both the manufacturer and the appropriate health authorities. The report should include details of the treatment history with ImmuCyst, the symptoms and signs of the BCG reaction, the treatment administered for the reaction, and the response to such treatment.

Table 4: Suggested Guidelines for the Management of Adverse Reactions Associated With ImmuCyst

Symptom, Sign or Syndrome	Treatment
1. Irritative bladder symptoms <48 hours duration.	Symptomatic treatment.
2. Irritative bladder symptoms ≥48 hours duration.	Symptomatic treatment; postpone next ImmuCyst treatment until complete resolution. If complete resolution has not occurred within one week, administer isoniazid (INH), 300mg daily until complete resolution.
3. Concomitant bacterial UTI.	Postpone next ImmuCyst treatment until completion of anti-microbial therapy and negative urine culture.
4. Other genitourinary tract adverse events: symptomatic granulomatous prostatitis, epididymo-orchitis, ureteral obstruction, or renal abscess.	Discontinue ImmuCyst. Administer INH, 300mg daily and rifampin, 600mg daily, for 3-6 months.
5. Fever <38.5°C of <48 hours duration.	Symptomatic treatment with acetaminophen (paracetamol).
6. Skin rash, arthralgias, or migratory arthritis.	Anti-histamines or non-steroidal anti-inflammatories. If no response, discontinue ImmuCyst and administer INH, 300mg daily for 3 months.
7. Systemic BCG reaction (as defined in 'Warnings') without signs of septic shock.	Discontinue ImmuCyst. Seek an Infectious Disease Consultation. Administer triple-drug anti-tuberculous therapy for 6 months.
8. Systemic BCG reaction (as defined in 'Warnings') with signs of septic shock.	As for (7). Consider addition of short-term high-dose systemic corticosteroids.

DOSAGE AND ADMINISTRATION

For instillation into the bladder only. Do not inject subcutaneously or intravenously.

One dose of ImmuCyst consists of instillation into the bladder of 81 mg BCG.

It is of most importance that care be taken during treatment to avoid trauma to the urinary tract or the introduction of contaminants.

Adults and Elderly

Intravesical treatment and prophylaxis for CIS of the urinary bladder should begin between 7 to 14 days after biopsy or transurethral resection of this procedure is done. A dose of 1 vial of ImmuCyst is instilled into the bladder once weekly for 6 weeks (induction therapy). Each dose (1 reconstituted vial) is further diluted in an additional 50ml sterile, preservative-free saline for a total of 53ml (see below). A urethral catheter is inserted into the bladder under aseptic conditions, the bladder drained and then 53ml suspension of ImmuCyst is instilled slowly by gravity following which the catheter is withdrawn. During the first hour following instillation, the patient should lie for 15 minutes on each side. The patient is then allowed to be up but retains the suspension for another 60 minutes for a total of two hours. All patients may not be able to retain the suspension for the 2 hours and should be instructed to void in less time if necessary. At the end of 2 hours all patients should void in a seated position for safety reasons. Patients should be instructed to maintain adequate hydration.

The exact number of instillations necessary to achieve an optimum response remains unknown. Most patients who respond will do so with six to twelve instillations.

In a group of 54 patients with CIS who had a 74% response rate to ImmuCyst treatment, additional treatments were given at 3, 6, 12, 18 and 24 months. Maintenance treatments at these times may be indicated for some patients, depending on the physician's judgement. Factors to be considered in reaching this decision include the number of tumour foci and the rate of tumour recurrence.

Handling Precautions

ImmuCyst contains viable attenuated mycobacteria and should be handled as infectious.

The preparation of the ImmuCyst should be done using aseptic techniques. 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. BCG infections have been reported in healthcare 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.

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.

Reconstitution of freeze-dried product and withdrawal from rubber stoppered vial

Do not remove the rubber stoppers from the vials.

Reconstitute and dilute immediately prior to use.

ImmuCyst should be reconstituted with saline solution. Inject 3 mL of sterile, preservative-free saline solution into the vial of freeze dried ImmuCyst. Withdraw the entire contents of the reconstituted material from the vial into a syringe.

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

The product should be used immediately after reconstitution. Any reconstituted product which exhibits flocculation or clumping that cannot be dispersed gently by shaking, should not be used.

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.

OVERDOSAGE

Overdosage occurs if more than 1 vial of ImmuCyst is administered per instillation. The patient should be closely monitored for signs of systemic infection and treated with anti-tuberculous treatment if necessary.

PRESENTATION AND STORAGE CONDITIONS

ImmuCyst is supplied in packages containing 1 vial of the freeze dried ImmuCyst containing $6.6-19.2 \times 10^8$ CFU/vial.

ImmuCyst is presented as a type 1 amber glass vial, with a butyl (10.3% latex) stopper and an aluminium seal fitted with a plastic flip-top button. ImmuCyst should be kept in a refrigerator at a temperature between 2°C - 8° C.

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

It should not be used after the expiration date marked on the vial, otherwise it may be inactive.

MEDICINE CLASSIFICATION

Prescription Medicine

NAME AND ADDRESS OF THE SPONSOR

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DATE OF PREPARATION

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