

# Important information please read

Dear Healthcare Professional,

**Re: SUPPLY STATUS: ImmuCyst® BCG Bacillus Calmette-Guerin (BCG) 6.6 - 19.2 x 10000000 CFU powder for injection vial, AUST R 168005**

## Background

Sanofi halted distribution of ImmuCyst (BCG) in April 2012 because the validation of one of the required release tests that confirms the sterility of the product failed to demonstrate an acceptable ability to detect mould and yeast. Additionally, environmental monitoring in the BCG production facility showed an increased level of microorganisms, including mould in the facility. To fully address this situation in consultation with regulatory authorities, Sanofi has decided to renovate the facility and has temporarily suspended production of BCG while renovations are made.

## Alternative Product

Further to the recent shortage of supply of ImmuCyst (BCG) for intravesical administration in the treatment of bladder cancer, Sanofi would like to inform you that we will be supplying a replacement product named TheraCys (BCG). All aspects of TheraCys (BCG), including the active ingredient, excipients and the method and site of manufacture, are identical to ImmuCyst (BCG) with the only exception being the brand name and the packaging. An independent review of the quality of the stock of TheraCys (BCG) was conducted and reviewed by the TGA and concluded that the product was deemed acceptable to be released.

- Further supply of ImmuCyst (BCG) will be interrupted while Sanofi renovates the production facility
- Sanofi will be supplying a replacement product namely TheraCys (BCG), which is identical to ImmuCyst (BCG)
- There is no evidence of contamination in currently released lots of TheraCys (BCG)/ImmuCyst (BCG)

## More about TheraCys (ImmuCyst)

TheraCys (ImmuCyst) is indicated for intravesical use in the treatment of primary and relapsed carcinoma *in situ* (CIS) of the urinary bladder to reduce the frequency of tumour recurrence. It is indicated for the treatment of CIS with or without an association with papillary tumours. TheraCys (ImmuCyst) is not for the treatment of papillary tumours occurring alone. TheraCys (ImmuCyst) is also indicated as a salvage therapy following failure of the urinary bladder to respond to other treatment regimes for CIS. TheraCys (ImmuCyst) is not indicated as an immunizing agent for the prevention of tuberculosis.

TheraCys (ImmuCyst) is contraindicated in concurrent febrile illness, urinary tract infection, or gross haematuria. Treatment with TheraCys (ImmuCyst) should be postponed until their resolution. TheraCys (ImmuCyst) is also contraindicated in:

- Concurrent febrile illness, urinary tract infection, or gross haematuria. Treatment with ImmuCyst (BCG) should be postponed until their resolution.
- Congenital or acquired immune deficiencies, whether due to a concurrent disease (e.g., AIDS, leukaemia, lymphoma) or immunosuppressive therapy (e.g., corticosteroids, cancer therapy [cytotoxic drugs, radiation]) because of the risk of disseminated BCG infection
- Seven to 14 days should elapse before ImmuCyst (BCG) is administered following biopsy, trans-urethral resection or traumatic catheterization
- Other contraindications apply, please consult the Australian ImmuCyst Product Information

## Next Steps

In consultation with the Therapeutic Goods Administration (TGA), it has been determined that the benefits of the product to patients outweigh the risk of potential microbial contamination. To date, there is no evidence of contamination in currently released lots of TheraCys (BCG)/ImmuCyst (BCG) on the market, and there have been no reports of infections that might be caused by contamination in the post marketing adverse event surveillance.

Any case of serious or unexpected adverse reactions in patients receiving TheraCys (ImmuCyst) should be reported to Sanofi Australia or the TGA.

If you would like further information regarding TheraCys (ImmuCyst) please do not hesitate to contact us on the numbers below.

For medical enquiries contact Sanofi Medical Information 1800 818 806  
For enquiries relating to supply contact Sanofi Customer Service 1800 640 791

Sanofi encourages clinicians to discuss this potential issue with their patients to ensure they are able to provide an informed consent.

Yours sincerely

Dr Alex Condoleon  
Medical Director  
Australia & New Zealand

## PRODUCT INFORMATION

### IMMUCYST®

**NAME OF THE MEDICINE**  
Non-proprietary Name

**BCG Immunotherapeutic**  
**DESCRIPTION**

ImmuCyst - BCG Immunotherapeutic (Bacillus Calmette-Guérin/Connaught) is a freeze-dried preparation made from the Connaught substrain of Bacillus Calmette-Guérin, which is an attenuated strain of living bovine tubercle bacillus *Mycobacterium bovis*. The bacilli are lyophilised (freeze-dried) and are viable upon reconstitution. It is produced from a suspension containing viable bacteria of the Connaught strain of Bacillus of Calmette and Guérin (BCG) and formulated to contain 81 mg (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. One dose consists of 81 mg reconstituted material further diluted in 50 mL sterile, preservative-free saline. The reconstituted dose contains  $10.5 \pm 8.7 \times 10^8$  colony forming units (CFU) over the course of its shelf life. ImmuCyst is a white powder.

### 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

**SWOG 8216** ImmuCyst was compared to doxorubicin hydrochloride among patients with either carcinoma *in situ* (CIS) or recurrent papillary tumours of the bladder or both. This trial was a randomised, open-label study conducted in the USA. The randomisation was stratified by the presence or absence of CIS. 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) in 127 patients. Alternatively, 135 patients were randomised to receive doxorubicin intravesically, administered once each week for 5 weeks, with an additional 11 single monthly treatments (total of 16 instillations). Disease free interval was assessed. In addition, response rate was measured in patients with CIS.

## CONSUMER MEDICINE INFORMATION (CMI)

### IMMUCYST® (im-you-sist)

**BCG Immunotherapeutic (BCG im-you-no-thera-pew-tick)**  
**What is in this leaflet**

This leaflet answers some common questions about ImmuCyst.

It does not contain all the available information. It does not take the place of talking to your doctor or pharmacist.

All medicines have risks and benefits. Your doctor has weighed the risks of you being given this medicine against the benefits they expect it will have for you.

**If you have any concerns about being given this medicine, ask your doctor or pharmacist.**

Keep this leaflet with the medicine.

You may need to read it again.

**What ImmuCyst is used for**

ImmuCyst is used to treat some types of cancer that occur on the inside surface of the urinary bladder. The exact way that ImmuCyst works is still not completely known. When instilled into the bladder, ImmuCyst causes an immune reaction in the bladder which causes the body's own cells to help destroy any remaining cancer cells. As with any cancer treatment, ImmuCyst may not be effective in all patients and may not cure your cancer forever.

**Ask your doctor if you have any questions about why it has been prescribed for you.**

This medicine is only available with a doctor's prescription.

This medicine is not addictive.

**Before you are given it**

**When you must not be given it**

**Do not receive ImmuCyst if you have:**

- tuberculosis
- current or history of severe reaction to BCG
- fever
- infection of your urinary tract or bladder
- blood in your urine
- a weak immune system or are taking drugs that weaken your immune system
- had an operation on your bladder within the past 7 to 14 days

**Do not receive ImmuCyst if you are allergic to it or any of the ingredients listed at the end of this leaflet.**

Some symptoms of an allergic reaction include skin rash, itching, shortness of breath or swelling of the face, lips or tongue, which may cause difficulty in swallowing or breathing.

**Do not give ImmuCyst to a child or adolescent.**

There is no experience with its use in children or adolescents under 18 years old.

**Do not receive it if you are pregnant or intend to become pregnant.**

It is not known whether ImmuCyst can affect your developing baby if you are given it during pregnancy.

**Do not receive it if you are breastfeeding or planning to breastfeed.**

It is not known if ImmuCyst passes into breast milk and there is a possibility your baby may be affected.

**Do not receive it after the expiry date (EXP) printed on the carton.**

If you receive it after the expiry date has passed, it may not work as well.

**Do not receive it if the packaging is damaged or shows signs of tampering.**

From published results in the CIS sub-group (n=131) after median follow up of 5.4 years, 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. There was no significant difference in overall survival – ImmuCyst group 59% versus doxorubicin 63%.

**SWOG 8507** This trial was a randomised, open-label study and the randomisation was stratified by the presence or absence of CIS, conducted in the USA. Two treatment regimens of ImmuCyst were compared among similar patients to the SWOG 8216 study. Treatments were administered intravesically with 192 patients randomised to induction only and 192 patients to induction plus maintenance. 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 until 36 months (total of 27 instillations). Median follow-up was 10 years.

From published information, in the sub-group of patients with CIS, the complete response rate was 68% in the induction only group (n=116) and 84% in the induction plus maintenance (n=117) – p = 0.004. There were no recurrence-free or overall survival data for the CIS sub-group.

## INDICATIONS

ImmuCyst is indicated for intravesical use in the treatment of primary and relapse CIS of the urinary bladder to reduce the frequency of tumour recurrence. It is indicated for the treatment of CIS with or without an association with papillary tumours. ImmuCyst is not for the treatment of papillary tumours occurring alone. ImmuCyst is also indicated as a salvage therapy following failure of the urinary bladder to respond to other treatment regimes for CIS.

ImmuCyst is not indicated as an immunizing agent for the prevention of tuberculosis.

## CONTRAINDICATIONS

- Known systemic hypersensitivity reactions to any component (i.e., as defined in **DESCRIPTION** 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 **PRECAUTIONS: Systemic BCG Reaction and Infection**).
- Concurrent febrile illness, urinary tract infection, or gross haematuria. Treatment with ImmuCyst should be postponed until their resolution.
- Congenital or acquired immune deficiencies, whether due to a concurrent disease (e.g., AIDS, leukaemia, lymphoma) or immunosuppressive therapy (e.g., corticosteroids, cancer therapy [cytotoxic drugs, radiation]) because of the risk of disseminated BCG infection (see **PRECAUTIONS: Interactions with Other Medicines**).
- Seven to 14 days should elapse before ImmuCyst is administered following biopsy, trans-urethral resection or traumatic catheterisation.

## PRECAUTIONS

**Local BCG Reaction** Administration of intravesical ImmuCyst causes an inflammatory response in the bladder. Irritative symptoms include dysuria, haematuria and urinary frequency are very common (see **ADVERSE EFFECTS**). Patients with small bladder capacity are at increased risk of bladder contracture and this should be considered in decisions to use ImmuCyst in these patients.

**Systemic BCG Reaction and Infection** A systemic BCG reaction, is a systemic granulomatous illness which may occur (although rarely) subsequent to exposure to BCG. Such reactions may be fatal. Based on clinical experience, systemic BCG reaction may be defined as the presence of any of the following signs (in the absence of other aetiology): fever  $\geq 39.5^{\circ}\text{C}$  for 12 hours or fever  $\geq 38.5^{\circ}\text{C}$  for 48 hours, pneumonitis, hepatitis, other organ dysfunction outside the genitourinary tract with granulomatous inflammation on biopsy, or signs of sepsis including circulatory collapse, acute respiratory distress or disseminated intravascular coagulation.

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". Patients should be monitored for the presence of symptoms and signs of toxicity after each intravesical treatment.

Although rare, a systemic BCG reaction is much more likely if ImmuCyst is administered within one week of a biopsy, transurethral resection or traumatic bladder catheterisation associated with haematuria. Therefore, ImmuCyst treatment should not be given until at least one week after these procedures.

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.

Orchitis and epididymitis caused by BCG may be refractory to antituberculous drug therapy and require orchidectomy.

If a systemic BCG reaction occurs, submit a report 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.

**Treatment of Systemic BCG Reaction and Infection** 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 disease consultation sought. As standard therapy for BCG infection, promptly initiate treatment with two or more antimicrobial agents while diagnostic evaluation, including cultures, is conducted. Use of single antibiotic therapy is not recommended. Negative cultures do not necessarily rule out infection. ImmuCyst is not sensitive to pyrazinamide.

**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.

**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**)

**Before you are given it**

**Tell your doctor if you have allergies to:**

- any of the ingredients listed at the end of this leaflet
- latex
- any other substances, such as foods, preservatives or dyes

**Tell your doctor if you are pregnant or intend to become pregnant.**

Like most medicines of this kind, ImmuCyst is not recommended to be used during pregnancy. Your doctor will discuss the risks and benefits of being given it if you are pregnant.

**Tell your doctor if you are breastfeeding or planning to breastfeed.**

It is not known whether ImmuCyst passes into breast milk. Your doctor will discuss the risks and benefits of being given it if you are breastfeeding or planning to breastfeed.

**Tell your doctor if you have or had any medical conditions, especially the following:**

- tuberculosis or a cough
- an illness with a fever
- an operation to remove a bladder tumour within the past 7 days
- infection of your urinary tract or bladder
- a weak immune system

**Tell your doctor if you plan to have surgery.**

**If you have not told your doctor about any of the above, tell them before you are given ImmuCyst.**

**Taking other medicines**

**Tell your doctor if you are taking any other medicines, including any that you buy without a prescription from your pharmacy, supermarket or health food store.**

Some medicines may interfere with the effect of ImmuCyst. These include:

- medicines that weaken your immune system
- medicines used to treat bacterial infections (antibiotics)
- medicines used to treat tuberculosis

These medicines may be affected by ImmuCyst, or may affect how well it works. ImmuCyst should not be mixed with other medicines.

**How it is given**

ImmuCyst should only be administered by trained professionals, with appropriate handling, in a hospital or clinic environment.

**How much to be given**

**Your doctor will decide what dose of ImmuCyst you will receive.**

Ask your doctor if you want to know more about the dose of ImmuCyst you receive.

**How it is given**

When prepared following recommended instructions, one ImmuCyst treatment is a 53 mL liquid solution. To administer ImmuCyst, your doctor or nurse will insert a tube (a catheter) into your bladder and drain any urine. After the bladder is emptied, the ImmuCyst solution will be slowly run into your bladder via gravity. You must then lie on your sides for 15 minutes each. You will be allowed up for the next hour. At the end of 2 hours, or sooner if you cannot hold the ImmuCyst in your bladder any longer, the ImmuCyst in your bladder can be passed like urine. You may pass the urine using the rubber catheter tube, or if you use the toilet, you must be in a seated position.

**How long it will be given**

ImmuCyst is usually given once a week for 6 weeks. Your doctor will discuss with you whether further doses will be necessary. Some people are given further ImmuCyst treatments over a 2 year period, to help prevent recurrence of disease.

## 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

Adverse effect 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 anti-tuberculous drug therapy can prevent or lessen the irritative symptoms of ImmuCyst.

## Data from Clinical Studies

The adverse reactions which occurred among recipients of ImmuCyst during clinical trials SWOG 8216 and SWOG 8507 are listed in Table 1 and Table 2, respectively.

Data are categorised by MedDRA system organ class and by decreasing frequency.

Table 1: SWOG Study 8216 - Adverse Reactions (n=127)

Adverse Reaction	Percent of Patients	
	Overall Induction Plus Maintenance	(Grade ≥3) (total of 11 instillations)
<b>Infections and infestations</b>		
Cystitis	29%	(0%)
Urinary tract infection	18%	(1%)
<b>Blood and lymphatic system disorders</b>		
Anaemia	21%	(0%)
Leucopenia	5%	(0%)
<b>Metabolism and nutrition disorders</b>		
Anorexia	11%	(0%)
<b>Gastrointestinal disorders</b>		
Nausea/vomiting	16%	(0%)
Diarrhoea	6%	(0%)
<b>Musculoskeletal and connective tissue disorders</b>		
Arthralgia/myalgia/arthritis	7%	(1%)
<b>Renal and urinary disorders</b>		
Dysuria	52%	(4%)
Urinary frequency	40%	(2%)
Haematuria	39%	(7%)
Urinary urgency	18%	(0%)
Renal toxicity (NOS)	10%	(2%)
Urinary incontinence	6%	(0%)
Bladder cramps/pain	6%	(0%)
Contracted bladder	5%	(0%)
<b>Reproductive system and breast disorders</b>		
Genital pain	10%	(0%)
<b>General disorders and administration site conditions</b>		
Malaise	40%	(2%)
Fever	38%	(3%)
Chills	34%	(3%)

The following adverse reactions were reported in <5% of patients:

**Infections and infestations:** local infection, systemic infection, pulmonary infection

**Blood and lymphatic system disorders:** thrombocytopenia, coagulopathy

**Nervous system disorders:** headache, dizziness

**Cardiac disorders:** cardiac (unclassified)

**Gastrointestinal disorders:** abdominal pain, constipation

**Hepatobiliary disorders:** liver involvement

**Skin and subcutaneous tissue disorders:** skin rash

**Musculoskeletal and connective tissue disorders:** flank pain

**Renal and urinary disorders:** tissue in urine, ureteral obstruction

**General disorders and administration site conditions:** fatigue

Table 2: SWOG Study 8507 - Adverse Reactions

Adverse Reaction	Percent of Patients			
	Induction (n=589/589) 6 instillations		Induction + Maintenance (n=248/589) 6+21 instillations	
	Overall	(Grade ≥3)	Overall	(Grade ≥3)
<b>Infections and infestations</b>				
Cystitis	0%	(0%)	29%	(0%)
Urinary tract infection	1%	(0%)	5%	(0%)
<b>Metabolism and nutrition disorders</b>				
Anorexia	3%	(0%)	8%	(0%)
<b>Gastrointestinal disorders</b>				
Nausea/vomiting	3%	(0%)	5%	(1%)
<b>Renal and urinary disorders</b>				
Dysuria	27%	(2%)	48%	(1%)
Haematuria	19%	(4%)	29%	(7%)
Urinary frequency	14%	(2%)	5%	(1%)
Urinary urgency	4%	(0%)	12%	(3%)
Bladder cramps/pain	1%	(0%)	6%	(1%)
<b>Reproductive system and breast disorders</b>				
Genital pain	0%	(0%)	10%	(0%)
<b>General disorders and administration site conditions</b>				
Malaise	17%	(1%)	25%	(2%)
Fever	17%	(0%)	31%	(3%)
Chills	14%	(1%)	32%	(2%)

The following adverse reactions were reported in <5% of patients:

**Infections and infestations:** systemic infection, pulmonary infection

**Blood and lymphatic system disorders:** anaemia, leucopenia, coagulopathy

**Nervous system disorders:** headache

**Cardiac disorders:** cardiac (unclassified)

**Gastrointestinal disorders:** abdominal pain, diarrhoea

**Hepatobiliary disorders:** liver involvement

**Skin and subcutaneous tissue disorders:** skin rash

**Musculoskeletal and connective tissue disorders:** arthralgia, arthritis, myalgia

**Renal and urinary disorders:** contracted bladder, renal toxicity, ureteral obstruction, urinary incontinence

**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 possible to reliably estimate their frequency, or establish a causal relationship to product exposure. Decisions to include these events in labelling 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 categorised by MedDRA system organ class.

## If you receive too much (overdose)

As ImmuCyst is given to you under the supervision of your doctor, it is very unlikely that you will receive too much. However, if you experience any side effects after being given ImmuCyst, tell your doctor or nurse immediately or go to Accident and Emergency at your nearest hospital.

You may need urgent medical attention.

## While you are being given it

### Things you must do

Tell all the doctors, dentists and pharmacists who are treating you that you are being given ImmuCyst. If you are about to be started on any new medicine, tell your doctor and pharmacist that you are being given ImmuCyst.

If you plan to have surgery that needs a general anaesthetic, tell your doctor or dentist that you are being given this medicine.

If you become pregnant while you are being given this medicine, tell your doctor immediately.

### Things you must not do

Do not receive this medicine to treat any other complaints.

### Things to be careful of

It is important that for 6 hours following your ImmuCyst treatment, you go to the toilet in a seated position. This is because ImmuCyst is prepared from bacteria and is still able to cause infection in some people.

Any urine you pass in these 6 hours must be disinfected with bleach (such as 'White King'). This can be done by adding an equal amount of bleach to the urine and leaving it for 15 minutes in the toilet bowl before flushing.

Be careful driving or operating machinery until you know how ImmuCyst affects you.

There have been no studies on the effects of ImmuCyst on the ability to drive or operate machines.

## Side effects

All medicines have some unwanted side effects. Sometimes they are serious, but most of the time they are not. Your doctor has weighed the risks of using this medicine against the benefits they expect it will have for you.

Do not be alarmed by this list of possible side effects.

You may not experience any of them.

Tell your doctor as soon as possible if you do not feel well while you are being given ImmuCyst.

It helps most people with bladder cancer, but it may have unwanted side effects in a few people.

Tell your doctor if you have any of the following for longer than 48 hours after treatment, or they increase in severity:

- pain or burning when passing urine
- fever, chills or tiredness
- cough and flu-like symptoms

Tell your doctor immediately if you notice any of the following:

- blood in the urine or a need to urinate frequently
- joint pain
- pain, irritation or redness of the eyes
- cough
- skin rash
- feeling of nausea and vomiting
- diarrhoea or loss of appetite
- genital pain or swelling of the male sex organs

If any of the following happen, tell your doctor immediately, or go to Accident and Emergency at your nearest hospital:

- swelling of the face, lips, mouth or throat, which may cause difficulty in swallowing or breathing.

## 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 on aneurysms and prosthetic devices (including arterial grafts, cardiac devices and artificial joints) has also been reported.

Joint symptoms (arthritis, arthralgia), ocular symptoms (including conjunctivitis, uveitis, iritis, keratitis, granulomatous chorioretinitis), 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.

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 disorders

Flu like symptoms (rare)

## Investigations

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

## DOSE 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.

Each dose (1 reconstituted vial) is further diluted in an additional 50 mL of sterile, preservative-free saline for a total of 53 mL (see below). A urethral catheter is inserted into the bladder under aseptic conditions, the bladder drained and then 53 mL suspension of ImmuCyst is instilled slowly by gravity following which the catheter is withdrawn.

Intravesical treatment of the urinary bladder should begin 7 to 14 days after biopsy or transurethral resection. A dose of 1 vial of ImmuCyst is instilled into the bladder once weekly for 6 weeks (induction therapy).

It is of utmost importance that care 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.

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 hygienic safety reasons. Unless medically contraindicated, patients should be instructed to increase fluid intake in order to flush the bladder in the hours following BCG treatment.

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.

Based on clinical studies performed with ImmuCyst, maintenance therapy following induction is recommended. Global clinical practice guidelines consider maintenance therapy for at least one year as the standard of care.

## Handling Precautions

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

The preparation of the ImmuCyst suspension 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 stopper from the vial.

Prepare the surface of the ImmuCyst vial using a suitable antiseptic.

Reconstitute and dilute immediately prior to use.

Using a 5 mL sterile syringe and needle, draw up 3 mL of sterile, preservative-free saline solution.

Using the same syringe and needle, pierce the rubber stopper on 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 instillation into the bladder.

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

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

If there is an avoidable delay between reconstitution and administration, this delay should not exceed 2 hours at a temperature between 2°C - 25°C.

## 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

Not documented.

The Poisons Information Centre, telephone number 131126, should be contacted for advice on the management of an overdose.

## PRESENTATION AND STORAGE CONDITIONS

ImmuCyst is supplied in packages containing 1 vial of the freeze-dried ImmuCyst containing 10.5 ± 8.7 x 10<sup>8</sup> 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.

ImmuCyst has a shelf life of 24 months (from the date of initiation of the viability [CFU] test).

## NAME AND ADDRESS OF THE SPONSOR

sanofi-aventis australia pty ltd

12-24 Talavera Road

Macquarie Park

NSW 2113

Australia

## POISON SCHEDULE OF THE MEDICINE

S4

## DATE OF APPROVAL

Date of TGA approval: 11 February 2010

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- hives
- fainting
- yellowing of the skin and eyes (jaundice)

These are very serious side effects. If you have them, you may have had a serious allergic reaction to ImmuCyst. You may need urgent medical attention or hospitalisation.

These side effects are very rare.

Tell your doctor if you notice anything else that is making you feel unwell.

Other side effects not listed above may occur in some consumers.

Ask your doctor to answer any questions you may have.

## After being given it

If you have any queries about any aspect of your medicine, or any questions regarding the information in this leaflet, discuss them with your doctor.

## Storage

ImmuCyst must be stored at 2°C - 8°C.

The best place is in the bottom of your refrigerator. ImmuCyst will be damaged and will not work if it gets too warm, is put into your freezer or is exposed to light.

ImmuCyst must stay sealed in its original pack until your doctor or nurse is ready to prepare it for use. It must not be opened in the sunlight.

## Disposal

If your doctor tells you to stop using ImmuCyst, or the medicine has passed its expiry date, return any unused medicine to your pharmacist.

## Product description

### What it looks like

One ImmuCyst pack contains one vial.

### Ingredients

Active Ingredient: Each dose (one vial) of ImmuCyst contains between 1.8 - 19.2 x 10<sup>8</sup> bacteria of the Connaught strain of Bacillus of Calmette and Guérin (BCG).

### Inactive Ingredients:

ImmuCyst also contains monosodium glutamate (MSG).

### Manufacturer/Sponsor

ImmuCyst is supplied in Australia by:

sanofi-aventis australia pty ltd

12-24 Talavera Road

Macquarie Park

NSW 2113

ImmuCyst is supplied in New Zealand by:

sanofi-aventis new zealand limited

Level 8, James and Wells Tower

56 Cawley Street

Ellerslie

Auckland

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