SUMMARY OF PRODUCT CHARACTERISTICS

1  NAME OF THE MEDICINAL PRODUCT
ImmuCyst® 81 mg powder for intravesical suspension

2  QUALITATIVE AND QUANTITATIVE COMPOSITION

ImmuCyst® 81 mg is a freeze-dried preparation made from the Connaught substrain of Bacillus Calmette-Guérin (BCG), which is an attenuated strain of Mycobacterium bovis. The bacilli are lyophilised (freeze-dried) and are viable upon reconstitution. The product contains no preservative.

Lyophilisate
BCG Immunotherapy
(Connaught substrain of Bacillus Calmette-Guérin)

Content per Vial
81 mg (dry weight)
Approximately 1.8 to 15.9 x 10^8 Colony Form Units

For a full list of excipients, see section 6.1.

3  PHARMACEUTICAL FORM
Powder for intravesical suspension.

ImmuCyst® 81 mg is a freeze-dried white powder which is free from preservatives.

4  CLINICAL PARTICULARS

4.1  Therapeutic indications
ImmuCyst® 81 mg is indicated for intravesical use in the treatment of primary or recurrent carcinoma in situ (CIS) of the urinary bladder, for the prophylaxis of recurrence of 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.

4.2 Posology and method of administration

Posology

Adults

One dose of ImmuCyst® 81 mg 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 section 4.3) and consists of induction and maintenance therapy.

- The induction therapy schedule consists of one intravesical instillation of
  ImmuCyst® 81mg each week for 6 weeks for a total of 6 doses.
- After a 6 week pause, one intravesical dose should be given each week for 1 to 3
  weeks. Clinical studies have demonstrated that 3 weekly instillations significantly
  increase the complete response rate from 73% to 87% at 6 months, compared
  with no additional treatment given at 3 months. Three weekly instillations should
  definitely be given to patients who still have evidence of bladder cancer.
- Based on clinical studies performed with ImmuCyst® 81 mg, maintenance therapy
  following induction is highly recommended. This consists of one dose given each
  week for 1 to 3 weeks at 6, 12, 18, 24, 30 and 36 months following the initiation
  of induction treatment.

Paediatric population

The safety and efficacy in children have not been established.

Method of Administration

This dose is prepared by reconstituting and diluting the freeze-dried BCG with
sterile, preservative-free saline, to a total of 50 ml instillation volume (see instructions
for use and handling).

A urethral catheter is inserted into the bladder under aseptic conditions. It is
important to note that a sufficient quantity of lubricant is used to reduce the chance of
traumatising the urinary mucosa and therefore the risk of severe complications
including BCG infection and also to reduce the discomfort of the patient. From the
limited evidence, bacteriostatic urethral lubricants have been shown to have an
association with a reduction in the viability of BCG (see section 4.5). As a
precaution, to minimise the amount of lubricant in the bladder, it is recommended that
catheterisation should be performed when the bladder is full. The bladder is drained, rinsing out with the urine any lubricant which may have reached the bladder. The 50 ml suspension of ImmuCyst® 81 mg is instilled slowly by gravity, following which the catheter is withdrawn.

The patient retains the suspension for as long as possible for up to two hours. During the first 15 minutes following instillation, the patient should lie prone. Thereafter, the patient is allowed to be up. At the end of 2 hours, all patients should void in a seated position for environmental safety reasons (see sections 4.4 and 6.6). Unless medically contraindicated patients should be instructed to increase fluid intake in order to flush the bladder in the hours following BCG treatment.

4.3 Contraindications
ImmuCyst® 81 mg is contraindicated for patients:

- with known systemic hypersensitivity reaction to any component (see sections 4.4 and 6.1) of ImmuCyst® 81 mg or after previous administrations of the medicinal product or a medicinal product containing the same substance,
- who have had a biopsy, TUR or traumatic bladder catheterisation (associated with haematuria) in the previous 14 days,
- who are immunosuppressed as a result of malignancies or receiving immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs (see section 4.5), or who are otherwise immunocompromised (including HIV-infected individuals),
- with active tuberculosis, because of the danger of exacerbation or of concomitant systemic BCG infection; active tuberculosis should be ruled out before starting treatment with ImmuCyst® 81 mg,
- with current or previous evidence of a systemic BCG infection (see section 4.4),
- with concurrent febrile illness, urinary tract infection, or macroscopic haematuria; treatment with ImmuCyst® 81 mg should be postponed until their resolution (see sections 4.4 and 6.1).

4.4 Special warnings and precautions for use

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

Special warnings

Systemic BCG Reaction

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 aetiologies 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 (see section 4.8).

Although rare, a systemic BCG reaction is much more likely to occur if ImmuCyst® 81 mg is administered within one week of biopsy, TUR or traumatic bladder catheterisation (associated with haematuria).

Ectopic BCG infection
The risk of these ectopic BCG infections has not been determined but is considered to be very small. 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.

Some male genitourinary tract infections (orchitis/epididymitis) have required orchiectomy.

Immunosuppressive treatments
For patients with a condition that may in future require mandatory immunosuppression (e.g. awaiting organ transplant, myasthenia gravis) the decision to treat with ImmuCyst® 81 mg should be considered carefully.

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

For patients with small bladder capacity, increased risk of bladder contracture should be considered in decisions to treat with ImmuCyst® 81 mg.

If a bacterial urinary tract infection (UTI) occurs during the course of ImmuCyst® 81 mg treatment, ImmuCyst® 81 mg instillation should be withheld until complete resolution of the bacterial UTI for two reasons: (1) the combination of a UTI and BCG- induced cystitis may lead to more severe adverse effects on the genitourinary tract, and (2) BCG bacilli are sensitive to certain antibiotics; antimicrobial administration may therefore diminish the efficacy of ImmuCyst® 81 mg.
ImmuCyst® 81 mg 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.

Intravesicular treatment with ImmuCyst® 81 mg may induce sensitivity to tuberculin purified protein derivative (PPD) which could complicate future interpretations of skin test reactions to tuberculin in the diagnosis of suspected mycobacterial infections. Determination of a patient's reactivity to tuberculin prior to administration of ImmuCyst® 81 mg may therefore be desirable.

**Special precautions for use**

*Contains viable attenuated mycobacteria. Handle as infectious.*

ImmuCyst® 81 mg should be prepared and handled using aseptic technique (see sections 4.2 and 6.6). BCG infections have been reported in health-care workers preparing BCG for administration.

ImmuCyst® 81 mg should not be handled by persons with immune deficiency.

Given the specialised nature of BCG intravesical treatment, ImmuCyst® 81 mg should be administered under the supervision of a qualified physician, such as a urologist, experienced in the use of anti-cancer agents.

Nosocomial infections have been reported in immunosuppressed patients. ImmuCyst® 81 mg should not be handled in areas where parenteral drugs are prepared.

**Serious and Severe Adverse Event Related Precautions**

Care must be taken during administration of intravesicular ImmuCyst® 81 mg not to introduce contaminants into the urinary tract nor to traumatise unduly the urinary mucosa. If the physician believes that the bladder catheterisation has been traumatic (e.g. associated with bleeding), then ImmuCyst® 81 mg should not be administered and there must be a treatment delay of at least 14 days. Subsequent treatment should be resumed as if no interruption in the schedule had occurred.

BCG may persist in the urinary tract for several months after BCG instillations and delayed manifestations of disseminated BCG infection may develop months or years after BCG therapy. Patients who receive immunosuppressive therapy after BCG instillation may be at higher risk of disseminated BCG infection.

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 section 4.8). As standard therapy for BCG infection, treatment with two or more anttymycobacterial 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.

**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® 81 mg 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® 81 mg 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 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® 81 mg. Patients may experience burning with the first void after treatment.

4.5 **Interaction with other medicinal products and other forms of interaction**

**Immunosuppressive Treatments**

Treatment combinations using immunosuppressants and/or radiation interfere with the immune response to ImmuCyst® 81 mg and increase the risk of disseminated BCG infection.

**Antibacterial Drugs**

Antimicrobial therapy for other infections may interfere with the effectiveness of ImmuCyst® 81 mg. Therefore, patients undergoing antimicrobial therapy should be evaluated to assess whether the therapy might diminish the efficacy of ImmuCyst® 81 mg.
Limited in-vitro testing of bacteriostatic lubricants and BCG has shown a reduction in the number of BCG CFU. However, it has been shown in patients that when a bacteriostatic lubricant was used for catheterisation before instillation, the BCG CFU count remained above the required minimum microbial count and there was no significant reduction in the clinical efficacy of BCG therapy.

**Antituberculosis Drugs**

Antituberculosis drugs should not be used prophylactically to prevent the local, irritative side effects of ImmuCyst® 81 mg. There are no data to suggest that the acute, local urinary tract symptoms common with intravesical BCG are due to mycobacterial infection.

**ImmuCyst® 81 mg is not sensitive to pyrazinamide.**

4.6 **Fertility, pregnancy and lactation**

There are no data on the use of ImmuCyst® 81 mg in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). ImmuCyst® 81 mg should not be used during pregnancy unless the clinical condition of the woman requires treatment with ImmuCyst® 81 mg. Women of childbearing potential must use effective contraception during treatment.

It is unknown whether ImmuCyst® 81 mg is excreted in human milk. A risk to the newborns/infants cannot be excluded, in particular if the nursing mother has a systemic BCG infection. Breast-feeding should be discontinued during treatment with ImmuCyst® 81 mg.

4.7 **Effects on ability to drive and use machines**

No studies on the effect on the ability to drive and use machines have been performed.

4.8 **Undesirable effects**

4.8.1 **Summary of the safety profile**

Adverse event information is derived from clinical trials and worldwide post-marketing experience.
Administration of ImmuCyst® 81 mg causes an inflammatory response in the bladder and can provoke signs and symptoms of cystitis (see Table 1). Such reactions may to some degree be taken as evidence that BCG is evoking the desired response, but patients should be carefully monitored for serious adverse events.

Symptoms of bladder irritability are reported in approximately 50% of patients receiving ImmuCyst® 81 mg 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® 81 mg.

Undesirable effects frequencies are presented using the following convention:

- Very common: (≥1/10)
- Common: (≥1/100 and <1/10)
- Uncommon: (≥1/1,000 and <1/100)
- Rare: (≥1/10,000 and <1/1,000)
- Very rare: (<1/10,000), including isolated cases
- Not known: cannot be estimated from the available data.

b. Tabulated list of adverse events

The clinical safety information on ImmuCyst® 81 mg is based on a dataset of 699 patients treated with ImmuCyst® 81 mg in 2 clinical trials. Table 1 below presents the frequencies of adverse events of any severity reported during the induction and maintenance courses of treatment, respectively, in study SWOG 8507 in 587 patients. Footnotes identify the adverse events reported as severe (grade ≥3) at uncommon and common frequency ranking respectively.

Table 1: SWOG Study 8507 – Adverse Reactions

<table>
<thead>
<tr>
<th>Infection and Infestation</th>
<th>Induction</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary Tract Infection</td>
<td>Common</td>
<td>Common*</td>
</tr>
<tr>
<td>Systemic Infection</td>
<td>Uncommon†</td>
<td>Uncommon*</td>
</tr>
<tr>
<td>Pulmonary Infection</td>
<td>Uncommon†</td>
<td>NR</td>
</tr>
<tr>
<td>Infection</td>
<td>Uncommon</td>
<td>NR</td>
</tr>
<tr>
<td>Cystitis</td>
<td>Uncommon</td>
<td>Common*</td>
</tr>
</tbody>
</table>

**Blood and Lymphatic System Disorders**
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Frequency</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaemia</td>
<td>Uncommon</td>
<td>NR</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>Uncommon</td>
<td>NR</td>
</tr>
<tr>
<td>Coagulopathy/Thrombocytopenia</td>
<td>Uncommon†</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td>Common*</td>
<td>Common*</td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Dizziness</td>
<td>Uncommon</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Cardiac Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac (Unclassified)</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>Common*</td>
<td>Common*</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>Uncommon</td>
<td>Common*</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>Uncommon</td>
<td>NR</td>
</tr>
<tr>
<td>Constipation</td>
<td>NR</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Mucositis/Ulcers/Stomatitis</td>
<td>Uncommon</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Hepatobiliary Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver Involvement</td>
<td>Uncommon†</td>
<td>Common</td>
</tr>
<tr>
<td>Granulomatous Hepatitis</td>
<td>Uncommon*</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Skin and Subcutaneous Tissues Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin Rash</td>
<td>Uncommon*</td>
<td>Common</td>
</tr>
<tr>
<td>Hypersensitivity Reaction Skin</td>
<td>NR</td>
<td>Uncommon*</td>
</tr>
<tr>
<td>Skin Abscess</td>
<td>NR</td>
<td>Uncommon</td>
</tr>
<tr>
<td><strong>Musculoskeletal, Connective Tissue and Bone Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthalgia/Myalgia/Arthritis</td>
<td>Uncommon</td>
<td>Common*</td>
</tr>
<tr>
<td><strong>Renal and Urinary Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysuria</td>
<td>Very Common‡</td>
<td>Very Common‡</td>
</tr>
<tr>
<td>Hematuria</td>
<td>Very Common§</td>
<td>Very Common‡</td>
</tr>
<tr>
<td>Urinary Frequency</td>
<td>Very Common‡</td>
<td>Very Common‡</td>
</tr>
<tr>
<td>Urinary Urgency</td>
<td>Common*</td>
<td>Very Common‡</td>
</tr>
<tr>
<td>Bladder Cramps/Pain</td>
<td>Common*</td>
<td>Common‡</td>
</tr>
<tr>
<td>Urinary Incontinence</td>
<td>Uncommon*</td>
<td>Common*</td>
</tr>
<tr>
<td>Adverse Event</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td>---------------------------------------</td>
<td>----------</td>
<td>----------</td>
</tr>
<tr>
<td>Renal Toxicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contracted Bladder</td>
<td>Uncommon*</td>
<td>Common‡</td>
</tr>
<tr>
<td>Ureteral Obstruction</td>
<td>Uncommon*</td>
<td>NR</td>
</tr>
<tr>
<td>Tissue in Urine</td>
<td>NR</td>
<td>Uncommon</td>
</tr>
<tr>
<td><strong>Reproductive System and Breast Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genital Pain</td>
<td>Uncommon</td>
<td>NR</td>
</tr>
<tr>
<td><strong>General Disorders and Administrative Site Conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>Very Common*</td>
<td>Very Common‡</td>
</tr>
<tr>
<td>Malaise</td>
<td>Very Common*</td>
<td>Very Common‡</td>
</tr>
<tr>
<td>Chills</td>
<td>Very Common*</td>
<td>Very Common‡</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Common*</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>

* These events have been reported with a severity grade =3 with an Uncommon frequency rating.
† These events have been reported with a severity grade ≥3 with an Uncommon frequency rating.
‡ These events have been reported with a severity grade =3 with a Common frequency rating.
§ These events have been reported with a severity grade ≥3 with a Common frequency rating.

The same adverse events as shown in Table 1 were also reported during the trial SWOG 8216 in 127 patients, as was the following:

**Musculoskeletal, Connective Tissue and Bone Disorders:**

Flank pain - Uncommon

The following additional adverse events have been spontaneously reported during the post-marketing use of ImmuCyst® 81 mg 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. Their frequency is considered not known.

**Infections and Infestations**

BCG Infection: 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 may persist in the urinary tract for several months after BCG instillations and delayed manifestations of disseminated BCG infection may develop months or years after BCG therapy. Patients who receive immunosuppressive therapy after BCG instillation may be at higher risk of disseminated BCG infection.

BCG infection of 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 choreoretinitis), urinary symptoms (including urethritis), skin rash, alone or in combination (Reiter’s syndrome) have been reported following administration of ImmuCyst® 81 mg. For the reports of Reiter’s syndrome, the risk seems to be more elevated among patients who are positive for HLA-B27.

Renal abscess

**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

**Investigations (Laboratory Tests)**
Abnormal/increased blood creatinine or blood urea nitrogen (BUN)

If a systemic BCG infection 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® 81 mg, the symptoms and signs of the BCG infection, the treatment administered for the reaction, and the response to this treatment.

### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme. Tel: Freephone 0808 100 3352. Website: www.mhra.gov.uk/yellowcard.

### 4.9 Overdose

In case of overdose, patients should be monitored closely (see sections 4.4 and 4.8).

### 5 PHARMACOLOGICAL PROPERTIES

#### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic and Immunomodulating Agents

ATC Code: L03AX03

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.

#### 5.2 Pharmacokinetic properties

Because ImmuCyst® 81 mg contains live mycobacteria, excreted urine may also contain live bacteria (see sections 4.4 and 6.6).
5.3 Preclinical safety data
ImmuCyst® 81 mg administered intravesically induced no serious systemic toxicity in studies in guinea pigs and monkeys. Studies in animals suggest that there is a possibility of a potential for allergenicity to the product.

No animal reproduction studies have been performed. Studies on mutagenicity and carcinogenicity have also not been performed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Monosodium glutamate

6.2 Incompatibilities
In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life
2 years

Reconstituted Product

The product should be used immediately after reconstitution. In the event of a delay between reconstitution and administration, the reconstituted and diluted suspension may be stored, protected from light, for up to 2 hours at a temperature between 2°C and 25°C.

6.4 Special precautions for storage
Store in a refrigerator (2°C - 8°C).

For storage conditions of the reconstituted product, see section 6.3.

At no time should the freeze-dried or reconstituted ImmuCyst® 81 mg be exposed to sunlight, direct or indirect. Exposure to artificial light should be kept to a minimum.
6.5 **Nature and contents of container**

5 ml type 1 amber glass vial sealed with a grey butyl silicone stopper and held closed with an aluminium seal with a blue flip-off plastic top.

Pack of 1

6.6 **Special precautions for disposal**

**Reconstitution of Freeze-Dried Product**

DO NOT REMOVE THE RUBBER STOPPERS FROM THE VIALS. HANDLE AS INFECTIOUS MATERIAL.

The preparation of the ImmuCyst® 81 mg should be done using aseptic technique. A separate area for the preparation of the ImmuCyst® 81 mg suspension is recommended in order to avoid cross contamination (e.g. in a biocontainment cabinet). 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® 81 mg, care should be taken so as to avoid needle stick injuries.

ImmuCyst® 81 mg should not be handled by persons with an immunologic deficiency (see sections 4.3 and 4.4).

ImmuCyst® 81 mg is to be reconstituted only with sterile preservative-free normal saline to ensure proper dispersion of the organisms. For the reconstitution and further dilution of one dose of ImmuCyst® 81 mg, 50ml of sterile preservative-free normal saline are required.

Three options for intravesicular administration are possible:

**Option 1:**

- Using a 5 ml sterile syringe and needle, draw up 3ml of sterile preservative-free saline solution.
- Prepare the surface of the ImmuCyst® 81 mg vial using a suitable antiseptic.
- Using the same syringe and needle, pierce the rubber stopper in the vial of freeze-dried material with the needle.
• Holding the vial of freeze-dried material upright, pull the plunger of the syringe back to the 5 ml marking on the barrel. This will 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. Any reconstituted product, which exhibits flocculation or clumping that cannot be dispersed with gentle shaking should not be used.
• Withdraw the entire contents of the reconstituted material from the vial into the same 5ml 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) with sterile preservative-free normal saline to a final volume of 50 ml for intravesical instillation.

The reconstituted product is then transferred to a bladder syringe.

Option 2:

Following instructions as above except the entire contents from the reconstituted vial is added to a saline bladder irrigation bag instead of a bladder syringe.

Option 3:

Use a 50ml (closed system) saline bladder irrigation bag to reconstitute ImmuCyst® 81 mg and instill the solution as per the manufacturer’s 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® 81 mg instillation should be disinfected with an equal volume of 5% hypochlorite solution (undiluted household bleach) and allowed to stand for 15 minutes before flushing.
MARKETING AUTHORISATION HOLDER

Alliance Pharmaceuticals Limited
Avonbridge House
Bath Road
Chippenham
Wiltshire,
SN15 2BB
UK

MARKETING AUTHORISATION NUMBER(S)

PL 16853/0120

DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19 September 2001

DATE OF REVISION OF THE TEXT

03/10/2016