BCG LIVE (INTRAVESICAL)

WARNING
TheraCys® [BCG Live (Intravesical)] contains live, attenuated mycobacteria. Because of the potential risk for transmission, it should be prepared, handled, and disposed of as a biohazard material (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

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

DESCRIPTION
TheraCys®- BCG Live (Intravesical) is a freeze-dried preparation made from the Connaught strain of Bacillus Calmette and Guérin, which is an attenuated strain of Mycobacterium bovis.

The BCG organisms in the product are grown on media containing potatoes, glycerine, asparagine, citric acid, potassium phosphate, magnesium sulfate, ferric ammonium citrate, calcium chloride, copper sulfate and zinc sulfate. Monosodium glutamate is added to the BCG organisms prior to freeze-drying.

Each vial of TheraCys® contains 81 mg of freeze-dried BCG. Prior to use, each vial is reconstituted with the accompanying diluent (3 mL), which contains sodium chloride, sodium phosphate and Tween 80. Neither the freeze-dried BCG nor the diluent contain preservative.

One dose of TheraCys® consists of one 81 mg vial of reconstituted material further diluted in 50 mL sterile, preservative-free saline.

The BCG organisms are viable upon reconstitution. In vitro potency is determined by an assay of the number of colonies grown on solid medium. The reconstituted product contains 10.5 ± 8.7 x 10⁸ colony forming units (CFU) per vial when resuspended in the diluent provided.

CLINICAL PHARMACOLOGY
BCG Live (Intravesical) promotes a local acute inflammatory and sub-acute granulomatous reaction with macrophage and lymphocyte infiltration in the urothelium and lamina propria of the urinary bladder. The exact mechanism of action is unknown, but the anti-tumor effect appears to be T-lymphocyte-dependent.

CLINICAL STUDIES
In a multicenter randomized clinical trial conducted by the Southwest Oncology Group (SWOG), TheraCys® was compared to doxorubicin hydrochloride (Adriamycin®) in patients with carcinoma in situ (CIS) of the urinary bladder, recurrent Ta/T1 papillary tumors of the urinary bladder, or both. Patients were stratified by the presence or absence of CIS, and analyzed separately. All papillary tumors were completely resected prior to study entry. The study endpoints were disease-free survival and 2-year disease-free survival. TheraCys® was administered intravesically weekly 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 over 2 years). The initial treatment with doxorubicin was given within 3 days of TUR, followed by 4 weekly treatments and then by 11 monthly treatments (total of 16 instillations over 1 year). Cytology and cystoscopy were obtained every 3 months for 2 years. A total of 285 patients were randomized: 142 to treatment with doxorubicin (69 CIS and 73 non-CIS) and 143 to treatment with TheraCys® (70 CIS and 73 non-CIS). An intent-to-treat analysis was performed.

For patients with CIS, the complete response rate (i.e., negative biopsies and urine cytology) within 6 months of the initiation of treatment was 33% with doxorubicin and 71% with TheraCys® (p<0.001, Fisher’s Exact Test). The probability of being disease-free at 2 years was 23% with doxorubicin and 51% with TheraCys® (p<0.001, Z Test). The median disease-free survival was 4.9 months for doxorubicin and 30 months for TheraCys® (p<0.001, Log Rank Test).

For patients with Ta/T1 papillary tumors only, the 2-year disease-free survival was 29% with doxorubicin and 50% with TheraCys® (p=0.008, Z Test). The median disease-free survival was 10.5 months with doxorubicin and 22.5 months with TheraCys® (p=0.001, Log Rank Test).

The results are summarized in Table 1.
INDICATIONS AND USAGE
TheraCys® is indicated for the treatment and prophylaxis of carcinoma in situ (CIS) of the urinary bladder, and for the prophylaxis of primary or recurrent stage Ta and/or T1 papillary tumors following transurethral resection (TUR). TheraCys® is not recommended for stage TaG1 papillary tumors, unless they are judged to be at high risk of tumor recurrence. TheraCys® is not indicated as an immunizing agent for the prevention of tuberculosis.

CONTRAINDICATIONS
TheraCys® should not be used in immunosuppressed patients or persons with congenital or acquired immune deficiencies, whether due to concurrent disease (e.g., AIDS, leukemia, lymphoma), cancer therapy (e.g., cytotoxic drugs, radiation), or immunosuppressive therapy (e.g., corticosteroids).

Treatment should be postponed until resolution of a concurrent febrile illness, urinary tract infection, or gross hematuria. Seven to 14 days should elapse before BCG is administered following biopsy, TUR, or traumatic catheterization.

TheraCys® should not be administered to persons with active tuberculosis. Active tuberculosis should be ruled out in individuals who are PPD positive before starting treatment with TheraCys®.

WARNINGS
TheraCys® is not a vaccine for the prevention of cancer.

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

Intravesical instillation of TheraCys® into a patient with an actively bleeding urinary mucosa may promote systemic BCG infection. Treatment should be postponed for at least 1 week following transurethral resection, biopsy, traumatic catheterization, or gross hematuria.

Deaths have been reported as a result of systemic BCG infection and sepsis. Patients should be monitored for the presence of symptoms and signs of toxicity after each intravesical treatment. Febrile episodes with flu-like symptoms lasting more than 72 hours, fever ≥103°F (39.4°C), systemic manifestations increasing in intensity with repeated instillations, or persistent abnormalities of liver function tests suggest systemic BCG infection and may require antituberculous therapy. Local symptoms (prostatitis, epididymitis, orchitis) lasting more than 2-3 days may also suggest active infection (See Management of Serious BCG Complications subsection of Warnings). The use of TheraCys® may cause tuberculin sensitivity. Since this is a valuable aid in the diagnosis of tuberculosis, it may be advisable to determine the tuberculin reactivity by PPD skin testing before treatment.

Intravesical instillations of BCG should be postponed during treatment with antibiotics, since antimicrobial therapy may interfere with the effectiveness of TheraCys® (see DRUG INTERACTIONS). TheraCys® should not be used in individuals with concurrent infections.

Small bladder capacity has been associated with increased risk of severe local reactions and should be considered in deciding to use TheraCys® therapy.

BCG infection of aneurysms and prosthetic devices (including arterial grafts, cardiac devices, and artificial joints) have been reported following intravesical administration of BCG. 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 an ectopic BCG infection in patients with pre-existing arterial aneurysms or prosthetic devices of any kind.

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

Management of Serious BCG Complications.
Acute, localized irritative toxicities of TheraCys® may be accompanied by systemic manifestations, consistent with a “flu-like” syndrome. Systemic adverse effects of 1-2 days' duration such as malaise, fever, and chills often reflect hypersensitivity reactions. However, symptoms such as fever of ≥101.3°F (38.5°C), or acute localized inflammation such as epididymitis, prostatitis, or orchitis persisting longer than 2-3 days suggest active infection, and evaluation for serious infectious complications should be considered.

In patients who develop persistent fever or experience an acute febrile illness consistent with BCG infection, two or more antimycobacterial agents should be administered while diagnostic evaluation, including cultures, is conducted. BCG treatment should be discontinued. Negative cultures do not necessarily rule out infection. Physicians using this product should be familiar with the literature on prevention, diagnosis, and treatment of BCG-related complications and, when appropriate, should consult an infectious disease specialist or other physician with experience in the diagnosis and treatment of mycobacterial infections.

### Table No. 1: SWOG Study 8216 – Efficacy

<table>
<thead>
<tr>
<th></th>
<th>Carcinoma in situ</th>
<th>TheraCys®</th>
<th>Ta/T1 Papillary Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Doxorubicin</td>
<td>TheraCys®</td>
<td>Doxorubicin</td>
</tr>
<tr>
<td>N=69</td>
<td></td>
<td>N=70</td>
<td>N=73</td>
</tr>
<tr>
<td>Complete Response</td>
<td>23 (33%)</td>
<td>50 (71%)</td>
<td>–</td>
</tr>
<tr>
<td>Median Disease-free Survival†</td>
<td>4.9 Months</td>
<td>30 Months</td>
<td>10.5 Months</td>
</tr>
<tr>
<td>2-Year Disease-free Survival†</td>
<td>23%</td>
<td>51%</td>
<td>29%</td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td>(15%, 35%)</td>
<td>(41%, 65%)</td>
<td>(20%, 41%)</td>
</tr>
</tbody>
</table>

† Based upon Kaplan-Meier estimates.
TheraCys® is sensitive to the most commonly used antituberculous agents (isoniazid, rifampin and ethambutol). TheraCys® is not sensitive to pyrazinamide.

PRECAUTIONS

General
TheraCys® contains live mycobacteria and should be prepared and handled using aseptic technique (See Preparation of Agent subsection of Dosage and Administration). BCG infections have been reported in health-care workers preparing BCG for administration. Needle stick injuries should be avoided during the handling and mixing of TheraCys®. Nosocomial infections have been reported in immunosuppressed patients receiving parenteral drugs which were prepared in areas in which BCG was prepared. BCG is capable of dissemination when administered by intravesical route and serious infections, including fatal infections, have been reported in patients receiving intravesical BCG. Care should be taken not to traumatize the urinary tract or to introduce contaminants into the urinary system. Seven to 14 days should elapse before TheraCys® is administered following TUR, biopsy, or traumatic catheterization. TheraCys® should be administered with caution to persons in groups at high risk for HIV infection. The use of TheraCys® may cause tuberculin sensitivity. It may therefore be advisable to determine the tuberculin reactivity by PPD skin testing before treatment.

Information For Patients
TheraCys® is retained in the bladder for 2 hours and then voided. Patients should void while seated in order to avoid splashing of urine. For the 6 hours after treatment, voided urine should be disinfected for 15 minutes with an equal volume of household bleach before flushing. Patients should be instructed to increase fluid intake in order to “flush” the bladder in the hours following BCG treatment. Patients may experience burning with the first void after treatment.

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

Drug Interaction
Drug combinations containing immunosuppressants and/or bone marrow depressants and/or radiation interfere with the development of the immune response and should not be used in combination with TheraCys®. Antimicrobial therapy for other infections may interfere with the effectiveness of TheraCys®. There are no data to suggest that the acute, local urinary tract toxicity common with BCG is due to mycobacterial infection, and antituberculosis drugs (e.g., isoniazid) should not be used to prevent or treat the local, irritative toxicities of TheraCys®.

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

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

Nursing Mothers
It is not known whether TheraCys® is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions from TheraCys® in nursing infants, it is advisable to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use
Safety and effectiveness of TheraCys® for the treatment of superficial bladder cancer in pediatric patients have not been established.

ADVERSE EVENTS
Symptoms of bladder irritability, related to the inflammatory response induced, are reported in approximately 50% of patients receiving TheraCys® (refer to Table No. 2). The symptoms typically begin 4-6 hours after instillation and last 24-72 hours. The irritative side effects are usually seen following the third instillation, and tend to increase in severity after each administration. The irritative bladder adverse effects can usually be managed symptomatically with products such as pyridium, propantheline bromide, oxybutynin chloride and acetaminophen. 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 toxicity of TheraCys®.

The “flu-like” symptoms (malaise, fever, and chills) which may accompany the localized, irritative toxicities often reflect hypersensitivity reactions which can be treated symptomatically. Antihistamines have also been used.

Adverse reactions to TheraCys® tend to be progressive in frequency and severity with subsequent instillation. Delay or postponement of treatment may or may not reduce the severity of a reaction during subsequent instillation.

Ocular symptoms (including uveitis, conjunctivitis, iritis, keratitis, granulomatous choreoretinitis) alone, or in combination with joint symptoms (arthritis or arthralgia), urinary symptoms and/or skin rash, have been reported following administration of intravesical BCG. The risk appears to be elevated among patients who are positive for HLA-B27. Although uncommon, serious infectious complications of intravesical BCG have been reported. The most serious infectious complication of BCG is disseminated sepsis with associated mortality. In addition, M. bovis infections have been reported in lung, liver, bone, bone marrow, kidney, regional lymph nodes, and prostate in patients who have received intravesical BCG. Some male genitourinary tract infections (orchitis/epididymitis) have been refractory to multiple drug antituberculous therapy and required orchietomy.
If a patient develops persistent fever or experiences an acute febrile illness consistent with BCG infection, BCG treatment should be discontinued and the patient immediately evaluated and treated for BCG infection (See Warnings).

In SWOG Study 8216, 112 patients received TheraCys®. The incidence of adverse reactions associated with intravesical TheraCys® is given below.

### Table No. 2: SWOG Study 8216 – Toxicity

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Percent of Patients</th>
<th>Adverse Event</th>
<th>Percent of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall (Grade ≥3)</td>
<td></td>
<td>Overall (Grade ≥3)</td>
</tr>
<tr>
<td>Dysuria</td>
<td>52% (4%)</td>
<td>Arthralgia/Myalgia</td>
<td>7% (1%)</td>
</tr>
<tr>
<td>Urinary Frequency</td>
<td>40% (2%)</td>
<td>Urinary Incontinence</td>
<td>6% (0%)</td>
</tr>
<tr>
<td>Malaise</td>
<td>40% (2%)</td>
<td>Cramps/Pain</td>
<td>6% (0%)</td>
</tr>
<tr>
<td>Hematuria</td>
<td>39% (7%)</td>
<td>Diarrhea</td>
<td>6% (0%)</td>
</tr>
<tr>
<td>Fever (&gt;38°C)</td>
<td>38% (3%)</td>
<td>Contracted Bladder</td>
<td>5% (0%)</td>
</tr>
<tr>
<td>Chills</td>
<td>34% (3%)</td>
<td>Leukopenia</td>
<td>5% (0%)</td>
</tr>
<tr>
<td>Cystitis</td>
<td>29% (0%)</td>
<td>Coagulopathy</td>
<td>3% (0%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>21% (0%)</td>
<td>Abdominal Pain</td>
<td>3% (0%)</td>
</tr>
<tr>
<td>Urinary Tract Infection</td>
<td>18% (1%)</td>
<td>Liver Involvement</td>
<td>3% (0%)</td>
</tr>
<tr>
<td>Urgency</td>
<td>18% (0%)</td>
<td>Systemic Infection</td>
<td>3% (0%)</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>16% (0%)</td>
<td>Pulmonary Infection</td>
<td>3% (0%)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>11% (0%)</td>
<td>Cardiac (Unclassified)</td>
<td>3% (0%)</td>
</tr>
<tr>
<td>Renal Toxicity (NOS)</td>
<td>10% (2%)</td>
<td>Headache</td>
<td>2% (0%)</td>
</tr>
<tr>
<td>Genital Pain</td>
<td>10% (0%)</td>
<td>Skin Rash</td>
<td>2% (0%)</td>
</tr>
</tbody>
</table>

The following adverse events were reported in ≤1% of patients: tissue in urine, local infection, constipation, dizziness, fatigue, thrombocytopenia, and flank pain.

In this study, local irritative symptoms were more common with TheraCys® than with doxorubicin; however, grade ≥3 irritative toxicity was similar, occurring in ~2-7% of patients. Systemic symptoms (fever, chills, malaise, etc.) were also more common with TheraCys®. Overall, grade ≥3 toxicities were seen in 26 patients (23%) treated with TheraCys® and 25 patients (21%) treated with doxorubicin. “Systemic infection” was reported to occur in three patients treated with TheraCys® (one grade 2 and two grade 3) and one patient treated with doxorubicin (grade 2). In four patients, treatment was discontinued because of toxicity (two with irritative symptoms, one with severe hematuria, and one with possible BCG infection). In addition, six patients refused further treatment because of severe local toxicity and/or chills. Six of these ten patients received TheraCys®. Table 3 compares the common adverse events reported in SWOG Study 8216.

### Table No. 3: SWOG Study 8216 – Comparative Toxicity

<table>
<thead>
<tr>
<th>Study Arm</th>
<th>TheraCys® (N=112)</th>
<th>Doxorubicin (N=119)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade ≥3</td>
</tr>
<tr>
<td>Dysuria</td>
<td>58 (52%)</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>Frequency</td>
<td>45 (40%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Malaise</td>
<td>45 (40%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Hematuria</td>
<td>44 (39%)</td>
<td>8 (7%)</td>
</tr>
<tr>
<td>Fever (&gt;38°C)</td>
<td>43 (38%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Chills</td>
<td>38 (34%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Cystitis</td>
<td>33 (29%)</td>
<td>0</td>
</tr>
<tr>
<td>Urgency</td>
<td>20 (18%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>18 (16%)</td>
<td>0</td>
</tr>
<tr>
<td>Bladder Cramps/Pain</td>
<td>7 (6%)</td>
<td>0</td>
</tr>
</tbody>
</table>

### Reporting of Adverse Reactions

Patients should be encouraged to report all adverse events after treatment with TheraCys®. Adverse events should be reported by health care providers to MEDWATCH (call 1-800-FDA-1088). Physicians, physician assistants, nurses and pharmacists should report adverse occurrences temporally related to the administration of the product to the Director of Medical Affairs, Aventis Pasteur Inc., Discovery Drive, Swiftwater PA 18370 or call 1-800-822-2463.

### OVERDOSAGE

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

One dose of TheraCys® [BCG Live (Intravesical)] consists of the intravesical instillation of 81 mg (dry weight) BCG. This dose is prepared by reconstituting the vial containing freeze-dried BCG with the contents of the vial containing diluent. The vial of reconstituted BCG is further diluted in 50 mL of sterile, preservative-free saline, for a total of 53 mL instillation volume (see reconstitution instructions).

Do not inject subcutaneously or intravenously.

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

The patient retains the suspension for as long as possible for a total of 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 safety reasons. Patients should be instructed to maintain adequate hydration.

Preparation of Agent

The preparation of the TheraCys® suspension should be done using aseptic technique. To avoid cross-contamination, parenteral drugs should not be prepared in areas where BCG has been prepared. A separate area for the preparation of the TheraCys® suspension is recommended. All equipment, supplies and receptacles in contact with TheraCys® should be handled and disposed of as biohazardous. The pharmacist or individual responsible for mixing the agent should wear gloves and eye protection, and take precautions to avoid contact of BCG with broken skin. If the preparation cannot be performed in a biocontainment hood, then a mask and gown may be worn to avoid inhalation of BCG organisms and inadvertent exposure to broken skin.

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

Do not remove the rubber stopper from the vial.

Apply a sterile piece of cotton moistened with a suitable antiseptic to the surface of the rubber stoppers of the vial of diluent and vial of TheraCys®. Reconstitute the freeze-dried material with the total 3 mL volume of diluent. 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 (approximately 3 mL) of the reconstituted material into the syringe.

TheraCys® should be reconstituted only with the diluent provided to ensure proper dispersion of the organisms.

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

TheraCys® should be used immediately after reconstitution. However, if there is an unavoidable delay between reconstitution and administration, this delay must not exceed 2 hours. Any reconstituted product which exhibits flocculation or clumping that cannot be dispersed with gentle shaking should not be used.

Treatment Schedule

Intravesical treatment of the urinary bladder should begin 7 to 14 days after biopsy or transurethral resection, and consists of induction and maintenance therapy. For the induction therapy, one dose of TheraCys® is administered each week for 6 consecutive weeks. Induction therapy should be followed by maintenance therapy, consisting of one dose given 3, 6, 12, 18, and 24 months following the initial dose.

HOW SUPPLIED

TheraCys® is supplied in packages containing one vial of the freeze-dried product, containing 81 mg (dry weight) (10.5 ± 8.7 x 10⁸ CFU) and one vial containing 3 mL of diluent - Product No. 49281-880-01.

STORAGE

TheraCys® [BCG Live (Intravesical)] and the accompanying diluent should be kept in a refrigerator at a temperature between 2°– 8°C (35°– 46°F). It should not be used after the expiration date marked on the vial, otherwise it may be inactive.

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

REFERENCES


Product Information as of October 1999.

Manufactured by: Aventis Pasteur Limited
Toronto, Ontario, Canada

Distributed by: Aventis Pasteur Inc.
Swiftwater PA 18370 USA

Printed in Canada

Aventis Pasteur