

PRODUCT MONOGRAPH

 OncoTICE[®]

Bacillus Calmette-Guérin (BCG), Strain TICE[®]

Powder for Solution and after dilution and reconstitution contains $1-8 \times 10^8$ Colony Forming Units (CFU) equivalent to approximately 50 mg wet weight.

Antineoplastic Agent for Bladder Instillation

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Bacillus Calmette-Guérin (BCG), Strain TICE®

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravesicular	Powder for solution; 50 mg wet weight equivalent to approximately 1 to 8 x 10 ⁸ colony forming units (CFU) of TICE® BCG/vial	Not applicable <i>For a complete listing see Dosage Forms, Composition and Packaging section</i>

DESCRIPTION

OncoTICE®, [Bacillus Calmette-Guérin (BCG), strain TICE®], is a freeze-dried preparation containing Bacillus Calmette and Guérin (BCG), strain TICE® which is a live, attenuated strain of *Mycobacterium bovis*. The culture medium from which the freeze-dried cake is prepared has the following relative composition: lactose 150 grams, Sauton medium 250 mL and water 750 mL. The freeze-dried BCG preparation is delivered in vials, each containing 1 to 8 x 10⁸ colony forming units (CFU) of TICE® BCG which is equivalent to approximately 50 mg wet weight. No preservatives have been added.

INDICATIONS AND CLINICAL USE

OncoTICE® (Bacillus Calmette-Guérin (BCG), Strain TICE®) is indicated for treatment of primary or relapsing flat urothelial cell carcinoma *in situ* (CIS) of the urinary bladder, and as an adjuvant therapy after TUR of a primary or relapsing superficial papillary urothelial cell carcinoma of the bladder stage T_A (grade 2 or 3) or T₁ (grade 1, 2, or 3). It is only recommended for stage T_A grade 1 papillary tumors, when there is judged to be a high risk of tumor recurrence.

OncoTICE® is not indicated for the treatment of invasive bladder cancer. It is not recommended for papillary tumors of stages higher than T₁.

Geriatrics:

OncoTICE[®] can be used in geriatric patients (see *DOSAGE AND ADMINISTRATION*, *WARNINGS AND PRECAUTIONS* and *CLINICAL TRIALS*).

Pediatrics (< 18 years of age):

No studies with OncoTICE[®] have been performed in pediatric patients

CONTRAINDICATIONS

- OncoTICE[®] is not indicated for the treatment of invasive bladder cancer.
- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the *DOSAGE FORMS, COMPOSITION AND PACKAGING* section of the product monograph.
- OncoTICE[®] should not be used in patients with impaired immune response irrespective of whether this impairment is congenital or caused by disease, drugs, or other therapy.
- OncoTICE[®] should be avoided in patients with a positive HIV serology.
- OncoTICE[®] is contraindicated during pregnancy and lactation (see *WARNINGS AND PRECAUTIONS*).
- Clinical evidence of existing active tuberculosis should be ruled out in individuals who are purified protein derivative (PPD) positive before starting treatment with OncoTICE[®].
- OncoTICE[®] should not be used concomitantly with antituberculosis drugs like streptomycin, para-amino-salicylic acid (PAS), isoniazid (INH), rifampicin and ethambutol because a potential loss of the antitumor activity of BCG may result.
- In patients with urinary tract infections, therapy with OncoTICE[®] should be postponed or interrupted until the bacterial culture from urine becomes negative and the therapy with antibiotics and/or urinary antiseptics is stopped.
- In case of gross hematuria, OncoTICE[®] therapy should be stopped or postponed until the hematuria has been successfully treated or has resolved.

WARNINGS AND PRECAUTIONS**General**

OncoTICE[®] should not be administered intravenously, subcutaneously or intramuscularly.

OncoTICE[®] is not for oral or intradermal use.

OncoTICE[®] is not a vaccine for the prevention of cancer, or for the prevention of tuberculosis.

Physicians that use 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, when appropriate, infectious disease specialists with experience in treating the infectious complications of intravesical BCG. The treatment of infectious complications of BCG requires long term, multiple-drug antibiotic therapy.

OncoTICE[®] contains live, potentially pathogenic bacteria. Reconstitution, preparation of the OncoTICE[®] suspension for instillation and administration should be performed under aseptic conditions. Unused OncoTICE[®] and all equipment, supplies, and receptacles in contact with OncoTICE[®] should be handled and disposed of as biohazardous.

Patients should be monitored for the presence of symptoms of systemic BCG infection and for signs of toxicity after each intravesical treatment as death has been reported as a result of systemic BCG infections and sepsis.

In order to protect the partner, the patient should be recommended to either refrain from intercourse within one week after OncoTICE[®] instillation, or to use a condom.

Transurethral resection (TUR):

When used as an adjuvant therapy after TUR of a superficial urothelial cell carcinoma of the bladder (See *INDICATIONS AND CLINICAL USE*), treatment with OncoTICE[®] should be started between 10 and 15 days after performing the TUR. Treatment should not be started until mucosal lesions after TUR have healed.

Genitourinary

Care should be taken not to traumatize the urinary tract. Seven to 14 days should elapse before OncoTICE[®] is administered following TUR, biopsy, or traumatic catheterization.

Traumatic catheterization or other injuries to the urethra or bladder mucosa can promote systemic BCG infection. Delaying OncoTICE[®] administration should be considered in such patients until mucosal damage has healed.

Sensitivity

The use of OncoTICE[®] may sensitize patients to tuberculin resulting in a positive reaction to PPD, therefore determination of tuberculin reactivity by PPD skin testing should be performed before starting the treatment with OncoTICE[®].

Special Populations

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

Nursing Women: It is not known whether OncoTICE[®] is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions from OncoTICE[®] in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatrics (< 18 years of age): Safety and effectiveness of OncoTICE[®] for the treatment of superficial bladder cancer in children have not been established.

Geriatrics:

OncoTICE[®] can be used in geriatric patients (see *DOSAGE AND ADMINISTRATION*, *WARNINGS AND PRECAUTIONS* and *CLINICAL TRIALS*).

Monitoring and Laboratory Tests

In patients with known risk factors for HIV infection, it is recommended to perform adequate HIV assays prior to therapy.

Before the first intravesical instillation of OncoTICE[®], a Mantoux test (PPD) should be performed. In the event that this test is positive, the intravesical instillation of OncoTICE[®] is contraindicated only if there is supplementary medical evidence for an active tuberculosis infection.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Adverse reactions are often localized to the bladder but may be accompanied by systemic manifestations.

Toxicity and side-effects appear to be directly related to the cumulative CFU count of BCG administered with the various instillations. Approximately 90% of patients develop local irritative symptoms in the bladder. Pollakiuria and dysuria are reported very frequently. The cystitis and typical inflammatory reactions (granulomas) which occur in the mucosa of the bladder after instillation of BCG, and which cause these symptoms, may be an essential part of the anti-tumor activity of the BCG. In most cases, the symptoms disappear within two days after instillation and the cystitis does not require treatment. During maintenance treatment with BCG, the symptoms of cystitis may be more pronounced and prolonged. Generally there are no long-term urinary complications.

Irritative bladder adverse effects associated with OncoTICE[®] administration have been managed symptomatically with pyridium, propantheline bromide or oxybutinin chloride, and acetaminophen or ibuprofen.

Also commonly observed is malaise, a low to medium grade fever and/or influenza-like symptoms (fever, rigors, malaise and myalgia) which may accompany the localized, irritative

toxicities that often reflect hypersensitivity reactions and can be treated symptomatically. These symptoms usually appear within 4 hours after instillation and last for 24 to 48 hours. Fever higher than 39°C typically resolves within 24 to 48 hours when treated with antipyretics (preferably paracetamol) and fluids. However, it is frequently not possible to distinguish these uncomplicated febrile reactions from early systemic BCG infections. Therefore, it is recommended that fever above 39.0 °C that does not resolve within 12 hours despite antipyretic therapy must be considered as systemic BCG-infection, necessitating clinical confirmatory diagnosis and treatment. *see WARNINGS AND PRECAUTIONS – GENERAL.*

Systemic adverse effects such as malaise, fever, and chills may reflect hypersensitivity reactions and can be treated with antihistamines. The “flu-like” syndrome of 1-2 day’s duration that frequently accompanies OncoTICE® administration should be treated symptomatically. Systemic BCG infections could be due to traumatic catheterization, bladder perforation or premature BCG instillation after extensive TUR of a superficial carcinoma of the bladder. *see WARNINGS AND PRECAUTIONS – GENITOURINARY.* These systemic infections may be manifested by pneumonitis, hepatitis, cytopenia, infective aneurysm and/or sepsis after a period of fever and malaise during which symptoms progressively increase.

Patients with manifest symptoms of therapy-induced BCG infections should be adequately treated with anti-tuberculous agents following regular treatment schedules used for tuberculosis infections: when systemic infection is present, the triple drug therapy (isoniazid-rifampicin-ethambutol) with or without cycloserine is given first for several weeks and is followed by therapy with isoniazid and rifampicin; rifampicin plus isoniazid are given when there are signs of an active BCG infection without systemic involvement. In these cases, further instillations of OncoTICE® are contra-indicated.

Deaths have been reported as a result of systemic BCG infections and sepsis. There have been two cases of nephrogenic adenoma, a benign lesion of bladder epithelium, associated with intravesical BCG therapy.

In general, the adverse effects of BCG therapy in bladder carcinoma have been of short duration and moderate morbidity. The side effects of intravesical OncoTICE® therapy are generally mild and transient.

Clinical Trial Adverse Drug Reactions

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

A summary of the incidence and severity of adverse effects observed in a study of 674 patients with superficial bladder cancer, treated intravesically with OncoTICE[®] is presented in Table 1 below. The adverse events reported in other studies have been similar.

TABLE 1

<u>Local Adverse Effects</u>	<u>Incidence (%)</u>	<u>Severe (%)</u>
Dysuria	59.5	10.7
Urinary Frequency	40.4	7.4
Hematuria	26.0	7.4
Cystitis	5.9	1.9
Urgency	5.8	1.3
Nocturia	4.5	0.6
Cramps/pain	4.0	0.9
Urinary Incontinence	2.4	---
Urinary Debris	2.2	0.4
Genital Inflammation/Abscess	1.8	0.4
Urinary Tract Infection	1.5	0.9
Urethritis	1.2	---
Pyuria	0.7	0.1
Epididymitis/Prostatitis	0.3	---
Urinary Obstruction	0.3	---
Contracted Bladder	0.2	---
Orchitis	0.2	---
<u>Systemic Adverse Effects</u>	<u>Incidence (%)</u>	<u>Severe (%)</u>
Fever	19.9	7.6
Malaise/Fatigue	7.4	---
Shaking Chills	3.3	1.0
Nausea/Vomiting	3.0	0.3
Arthritis/Myalgia	2.7	0.4
Headache/Dizziness	2.4	---
Anorexia/Weight Loss	2.2	0.1
Allergic	2.1	0.4
Cardiac	1.9	1.3
Respiratory (Unclassified)	1.6	0.2
Abdominal Pain	1.5	0.6
Anemia	1.3	0.4
Diarrhea	1.2	0.1
Pneumonitis	1.2	0.6
Gastrointestinal (Unclassified)	1.0	---
Neurologic	0.9	0.3
Rash	0.6	0.2
BCG Sepsis	0.4	0.4
Coagulopathy	0.3	0.3
Leukopenia	0.3	---
Thrombocytopenia	0.3	---

Hepatic Granuloma	0.2	0.2
Hepatitis	0.2	0.2

Flu-like syndrome (which includes fever, shaking chills, malaise and myalgia) had an incidence of 33.2% of which 9.0% were severe.

Severe was ECOG Grade 3 or 4

Post-Market Adverse Drug Reactions

The following adverse reactions (Table 2) are reported from the post-market surveillance as serious and unexpected. This information is based on experience and clinical data published.

TABLE 2

Occurrence	MedDRA System Organ Class	Preferred terms
Rare (>1/10,000, <1/1,000)	Respiratory, thoracic and mediastinal disorders	Cough
	Reproductive system and breast disorders	Epididymitis
Very rare (<1/10,000)	Infections and infestations	Pharyngitis, orchitis, Reiter's syndrome, Lupus vulgaris
	Blood and lymphatic system disorders	Lymphadenopathy
	Metabolism and nutrition disorders	Anorexia
	Psychiatric disorders	Confusional state
	Nervous system disorders	Dizziness, dysaesthesia ¹ , hyperaesthesia ¹ , paresthesia, somnolence, headache, hypertonia, neuralgia ¹
	Eye disorders	Conjunctivitis
	Ear and labyrinth disorders	Vertigo ¹
	Vascular disorders	Hypotension
	Respiratory, thoracic and mediastinal disorders	Bronchitis, dyspnea, rhinitis
	Gastrointestinal disorders	Dyspepsia ¹ , flatulence ¹
	Skin and subcutaneous tissue disorders	Alopecia, hyperhidrosis
	Musculoskeletal and connective tissue disorders	Back pain
	Renal and urinary disorders	Renal failure acute
	Reproductive system and breast disorders	Balanoposthitis, prostatitis, vulvovaginal discomfort ¹
	General disorders and administration site conditions	Chest pain, edema peripheral, granuloma ²
Investigations	Prostatic specific antigen increased, weight decreased	

1 Only isolated cases reported during post-marketing surveillance

2 Granuloma NOS has been observed in various organs including the aorta, bladder, epididymis, gastrointestinal tract, kidney, liver, lungs, lymph nodes, peritoneum, prostate

DRUG INTERACTIONS

Overview

Immunosuppressants and/or bone marrow depressants and/or radiation may interfere with the development of the immune response and thus with the anti-tumour efficacy and should, therefore, not be used in combination with OncoTICE®.

Drug-Drug Interactions

OncoTICE® is sensitive to most antibiotics and, in particular, to the routinely used anti-tuberculous agents, like streptomycin, para-aminosalicylic acid (PAS), isoniazid (INH), rifampicin and ethambutol except for pyrazinamide. Therefore, the anti-tumour activity of OncoTICE® may be decreased by concomitant therapy with antibiotics. If a patient is being treated with antibiotic it is recommended to postpone the intravesical instillation until the end of the antibiotic treatment (see also *CONTRAINDICATIONS*).

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with drug-herb have not been established.

Drug-Laboratory Interactions

No data has been established.

Drug-Lifestyle Interactions

Based on the pharmacodynamic profile of OncoTICE®, it is assumed that the product will not affect the ability to drive and to use machines.

DOSAGE AND ADMINISTRATION

Dosing Considerations

For each instillation, the contents of one vial of OncoTICE®, [Bacillus Calmette-Guérin (BCG), strain TICE®], reconstituted and diluted as indicated, are instilled into the urinary bladder.

OncoTICE® must not be administered intravenously, subcutaneously or intramuscularly.

Induction treatment:

Weekly instillation with OncoTICE® for 6 consecutive weeks.

Maintenance treatment:

Additional instillations of OncoTICE® at week 8 and 12 and monthly from months 4 to 12.

Missed Dose

No data established.

Administration

Insert a catheter via the urethra into the bladder and drain the bladder completely. Connect the 50 mL syringe containing the prepared OncoTICE[®] suspension to the catheter, and instill the suspension into the bladder.

After instillation, remove the catheter.

The instilled OncoTICE[®] suspension must remain in the bladder for a period of 2 hours. After two hours, have the patient void the instilled suspension in a sitting position.

Note: The patient is not allowed to ingest any fluid during a period of 4 hours prior to instillation, or during the time that the OncoTICE[®] suspension remains in the bladder after instillation (2 hrs).

If a spill or contamination occurs, area should be cleaned by covering the area with paper towels soaked with tuberculocidal disinfectant for at least 10 minutes. Wastes should be treated as biohazardous and disposed of accordingly (*see SPECIAL HANDLING INSTRUCTIONS*).

Perform the following procedures under aseptic conditions:

Reconstitution-Suspension for Bladder Instillation

Add 1 mL of a sterile, pyrogen-free and preservative-free physiological saline solution by means of a sterile syringe and allow standing for a few minutes. Then gently swirl the vial until a homogeneous suspension is obtained. (Caution: avoid forceful agitation).

Preparation of the solution for instillation:

Transfer the suspension from the vial into a sterile 50 mL syringe. Rinse the vial with another 1 mL of sterile, pyrogen-free and preservative-free physiological saline. Add the rinse fluid to the suspension in the 50 mL syringe. Finally dilute the contents of this syringe (1 mL OncoTICE[®] suspension + 1 mL rinse fluid) by adding sterile, pyrogen-free and preservative-free physiological saline solution up to a total volume of 50 mL. Mix the suspension carefully.

Note: The suspension must not be filtered.

This suspension is now ready for instillation; it contains a total of 1 to 8 x 10⁸ CFU of TICE BCG.

Incompatibilities

OncoTICE[®] is incompatible with hypotonic and hypertonic solutions. OncoTICE[®] should be mixed with physiological saline as described above under *Reconstitution*. Other incompatibility studies have not been performed.

OVERDOSAGE

Overdosage occurs if more than one vial of OncoTICE[®], is administered per instillation. The patient should be closely monitored for signs of systemic BCG infection and treated with anti-tuberculous medication (*see ADVERSE REACTIONS section*).

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

It has anti-tumor activity, but the exact mechanism of action is not known. Study data suggest that an active nonspecific immune response takes place. BCG invokes a local inflammatory response involving a variety of immune cells, such as macrophages, natural killer cells and T cells.

Pharmacodynamics

OncoTICE[®] is an immunostimulating agent (ATC code L 03AX03).

Pharmacokinetics

For the treatment and recurrence prophylaxis of bladder cancer, the attachment of BCG to the bladder wall after voiding has been shown to be important. This allows a targeted pharmacological effect at the site of application. It is known that Tice BCG can bind specifically to fibronectin in the bladder wall. However, most instilled OncoTICE[®] will be excreted with the first urine void two hours after the instillation.

STORAGE AND STABILITY

Intact OncoTICE[®] vials containing freeze-dried BCG, must be stored at 2 – 8° C and protected from light. The expiry date indicated on the label of the vials only applies if the vials are stored under these conditions.

The reconstituted solution for bladder instillation can be stored for up to **2 hours** when refrigerated at 2 – 8° C and protected from light. Unused solution should be discarded after **2 hours**.

SPECIAL HANDLING INSTRUCTIONS

OncoTICE[®] contains live attenuated mycobacteria. Reconstitution, preparation of the OncoTICE[®] suspension for instillation and administration should be performed under aseptic conditions.

Spillage of OncoTICE[®] suspension may cause TICE BCG contamination. Any spilled OncoTICE[®] suspension should be cleaned by covering the area with paper towels soaked with

tuberculocidal disinfectant for at least 10 minutes. Unused OncoTICE[®] and all equipment, supplies, and receptacles in contact with OncoTICE[®] should be handled and disposed of as bio-hazardous.

Accidental exposure to OncoTICE[®] could occur through self-innoculation, by dermal exposure through an open wound or by ingestion of OncoTICE[®] suspension. OncoTICE[®] exposure should not produce significant adverse health outcomes in healthy individuals. However, in case of suspected, accidental self-innoculation, PPD skin testing is advised at the time of the accident and six weeks later to detect skin test conversion.

DOSAGE FORMS, COMPOSITION AND PACKAGING

OncoTICE[®], [Bacillus Calmette-Guérin (BCG), strain TICE[®]], is supplied as a freeze-dried preparation in 2 mL vials; each vial contains 1 to 8×10^8 CFU of TICE BCG which is equivalent to approximately 50 mg wet weight. It is supplied in boxes containing 1 vial per box.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

OncoTICE[®], [Bacillus Calmette-Guérin (BCG), strain TICE[®]], is a freeze-dried preparation containing Bacillus Calmette and Guérin (BCG), strain TICE[®] which is a live, attenuated strain of *Mycobacterium bovis*. The culture medium from which the freeze-dried cake is prepared has the following relative composition: lactose 150 grams, Sauton medium 250 mL and water 750 mL.

The freeze-dried BCG preparation is delivered in vials, each containing 1 to 8×10^8 colony forming units (CFU) of TICE BCG which is equivalent to approximately 50 mg wet weight. No preservatives have been added.

CLINICAL TRIALS

To evaluate the efficacy of intravesical administration of BCG Bacillus Calmette-Guérin (BCG), strain TICE[®] in the treatment of carcinoma *in situ*, patients were identified who had been treated with BCG, Strain TICE[®] under 6 different studies in which the most important shared aspect was the use of an induction plus maintenance schedule. Patients received BCG, Strain TICE[®] (50 mg; 1 to 8×10^8 CFU) intravesically, once weekly for at least 6 weeks and once monthly thereafter for up to 12 months. A longer maintenance was given in some cases. The study population consisted of 153 patients, 132 males, 19 females, and 2 unidentified as to gender. Thirty patients lacking baseline documentation of CIS and 4 patients lost to follow-up were not evaluable for treatment response. Therefore, 119 patients were available for efficacy evaluation. The mean age was 69 years (range: 38-97 years). There were 2 categories of clinical response: (1) Complete Histological Response (CR), defined as complete resolution of carcinoma *in situ* documented by cystoscopy and cytology, with or without biopsy; and (2) Complete Clinical Response Without Cytology (CRNC), defined as an apparent complete disappearance of tumor upon cystoscopy. The results of a 1987 analysis of the evaluable patients are shown in **Table 3**.

TABLE 3: The Response of Patients With CIS Bladder Cancer in 6 Studies

	Entered	Evaluable	CR	CRNC	Overall response
No. (%) of patients	153	119 (78%)	54 (46%)	36 (30%)	90 (76%)

A 1989 update of these data is presented in **Table 4**. The median duration of follow-up was 47 months.

TABLE 4: Follow-up Response of Patients With CIS Bladder Cancer in 6 Studies - 1989 Status of 90 Responders (CR or CRNC)

Response	1987/CR n=54	1987/CRNC n=36	1987 Response n=90	Percent
CR	30	15	45	50
CRNC	0	0	0	0
Unrelated death	6	6	12	13
Failure	18	15	33	37

There was no significant difference in response rates between patients with or without prior intravesical chemotherapy. The median duration of response, calculated from the Kaplan-Meier curve as median time to recurrence, is estimated at 4 years or greater. The incidence of cystectomy for 90 patients who achieved a complete response (CR or CRNC) was 11%. The median time to cystectomy in patients who achieved a complete response (CR or CRNC) exceeded 74 months.

The efficacy of intravesical BCG, Strain TICE[®] in preventing the recurrence of a T_AT₁ bladder cancer after complete transurethral resection of all papillary tumors was evaluated in 2 open-label, randomized phase III clinical trials. Initial diagnosis of patients included in the studies was determined by cystoscopic biopsies. One was conducted by the Southwestern Oncology Group (SWOG) in patients at high risk of recurrence. High risk was defined as 2 occurrences of tumor within 56 weeks, any stage T1 tumor, or 3 or more tumors presenting simultaneously. The second study was conducted at the Nijmegen University Hospital; Nijmegen, The Netherlands. In this study patients were not selected for high risk of recurrence. In both studies treatment was initiated between 1 and 2 weeks after transurethral resection (TUR).

In the SWOG trial (study 8795) patients were randomized to BCG, Strain TICE[®] or mitomycin C (MMC). Both drugs were given intravesically weekly for 6 weeks, at 8 and 12 weeks, and then monthly for a total treatment duration of 1 year. Cystoscopy and urinary cytology were performed every 3 months for 2 years. Patients with progressive disease or residual or recurrent disease at or after the 6 month follow-up were removed from the study and were classified as treatment failures.

A total of 469 patients was entered into the study: 237 to the BCG, Strain TICE[®] arm and 232 to the MMC arm. Twenty-two patients were subsequently found to be ineligible, and 66 patients had concurrent CIS, and were analyzed separately. Four patients were lost to follow-up, leaving 191 evaluable patients in the BCG, Strain TICE[®] arm and 186 in the MMC arm. Of the patients, 84% were male and 16% were female. The average age of these patients was 65 years old.

The Kaplan-Meier estimates of 2-year disease-free survival are shown in **Table 5**. The difference in disease-free survival time between the 2 groups was statistically significant by the log rank test

($P=0.03$). The 95% confidence interval of the difference in 2-year disease-free survival was 12% \pm 10%. No statistically significant differences between the groups were noted in time to tumor progression, tumor invasion, or overall survival.

TABLE 5: Results of SWOG Study 8795

	BCG, Strain TICE[®] Arm N=191	MMC Arm N=186
Estimated disease-free survival at 2 years	57%	45%
95% Confidence Interval (CI)	(50%, 65%)	(38%, 53%)

In the Nijmegen study, the efficacy of 3 treatments was compared: BCG, Strain TICE[®], *Rijksinstituut voor Volksgezondheid en Milieuhygiene* substrain BCG (BCG-RIVM), and MMC.

BCG, Strain TICE[®] and BCG-RIVM were given intravesically weekly for 6 weeks. In contrast to the SWOG study, maintenance BCG was not given. Mitomycin C was given intravesically weekly for 4 weeks and then monthly for a total duration of treatment of 6 months. Cystoscopy and urinary cytology were performed every 3 months until recurrence.

A total of 469 patients was enrolled and randomized. Thirty-two patients were not evaluable, 17 were ineligible, 15 were withdrawn before treatment, and 50 had concurrent CIS and were analyzed separately, leaving 387 evaluable patients: 117 in the BCG, Strain TICE[®] arm, 134 in the BCG-RIVM arm, and 136 in the MMC arm. Twenty-eight patients (24%) in the BCG, Strain TICE[®] arm, 32 patients (24%) in the BCG-RIVM arm, and 24 patients (18%) in the MMC arm had T_AG1 tumors. The median duration of follow-up was 22 months (range: 3-54 months).

The Kaplan-Meier estimates of 2-year disease-free survival are shown in **Table 6**. The differences in disease-free survival among the 3 arms were not statistically significant by the log-rank test ($P=0.08$).

TABLE 6: Results of Nijmegen Study

	BCG, Strain TICE[®] Arm N=117	BCG-RIVM Arm N=134	MMC Arm N=136
Estimated disease-free survival at 2 years	53%	62%	64%
95% Confidence Interval (CI)	(44%, 64%)	(53%, 72%)	(55%, 74%)

In both the SWOG 8795 study and the Nijmegen study, acute toxicity was more common, and usually more severe with BCG, Strain TICE[®] than with MMC.

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PART III: CONSUMER INFORMATION

OncoTICE[®],
Bacillus Calmette-Guérin (BCG), strain TICE[®]

This leaflet is part III of a three-part "Product Monograph" published when OncoTICE[®] was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about OncoTICE[®]. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

OncoTICE[®] contains something called 'BCG' ('Bacillus Calmette-Guérin' strain TICE[®]). This is a bacterium which has been specially altered, so that it can be used as a medicine.

OncoTICE[®] is used to treat bladder cancer. It is also used to prevent bladder cancer from coming back after bladder surgery.

What it does:

OncoTICE[®] belongs to the group of medicines called immunostimulants. These medicines stimulate certain parts of the immune system and thereby invoke a local inflammatory response

When it should not be used:

- If you are hypersensitive (allergic) to Bacillus Calmette-Guérin (BCG) strain TICE[®] or any of the other ingredients of OncoTICE[®].
- If you have invasive bladder cancer.
- If you suffer from active tuberculosis.
- If you are being treated with anti-tuberculosis drugs.
- If you are HIV-positive.
- If you suffer from an impaired immune system (reduced immunity against infectious diseases), irrespective of the cause.
- If you are pregnant or breastfeeding.
- If you have blood in your urine.
- If you have a urinary tract infection. If you suffer from cystitis (inflammation of the bladder), you will first receive a course of antibiotics before treatment with OncoTICE[®] starts. Treatment with antibiotics needs to be finished before treatment with OncoTICE[®] is started.

What the medicinal ingredient is:

The medicinal ingredient in OncoTICE[®], is Bacillus Calmette-Guérin (BCG), strain TICE[®].

What the important nonmedicinal ingredients are:

Nonmedicinal ingredients are lactose 150 grams and Sauton medium (lactose, asparagine, citric acid (E330), potassium phosphate, magnesium sulfate, iron ammonium citrate, glycerol (E422), ammonium hydroxide (E527), zinc formate).

What dosage forms it comes in:

OncoTICE[®] is supplied as a freeze-dried preparation in 2 mL vials; each vial contains 1 to 8 x 10⁸ CFU of TICE BCG which is equivalent to approximately 50 mg wet weight. It is supplied in boxes containing 1 vial per box.

WARNINGS AND PRECAUTIONS

BEFORE you use OncoTICE[®] talk to your doctor or pharmacist:

Before the first intravesical instillation of OncoTICE[®], your doctor will probably perform a skin test (Mantoux test) to investigate if you have an active tuberculosis infection.

- If a skin test (Mantoux test) is performed after treatment with OncoTICE[®], it may be positive.
- When the bladder wall or ureter is damaged during catheterization, treatment will need to be postponed until the lesion is healed.
- It is important that infection with the HIV virus is excluded. It may be necessary that a blood sample is taken to test for HIV. Your doctor might also ask if there are any risk factors, such as unsafe sex, use of dirty needles if you are a drug user and blood transfusions.
- To protect your partner from transmission of the BCG bacteria, it is advisable to refrain from sexual intercourse during the week following treatment with OncoTICE[®]. If you use a condom you can have intercourse, on condition that the condom is used correctly, and does not tear.
- If you are pregnant. OncoTICE[®] should not be given during pregnancy.
- If you are breastfeeding. OncoTICE[®] should not be given to breastfeeding mothers.

There is no warning that your ability to drive or operate machines will be affected.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with OncoTICE[®] include:

- Antibiotics
- Medicines for tuberculosis
- Medicines which suppress the immune system (immune suppressants)
- Medicines which suppress the production of bone marrow cells (bone marrow suppressants)
- Radiation therapy

If you are using any of these medicines or are undergoing one of these therapies, your doctor will probably postpone the treatment until you have stopped this treatment.

PROPER USE OF THIS MEDICATION

OncoTICE[®] will always be given by a healthcare professional.

Usual dose:

OncoTICE® is usually given once a week for 6 weeks followed by additional doses of OncoTICE® as part of your 'maintenance treatment'. Your doctor will talk to you about this.

Before it is given

- Do not drink any liquid the 4 hours before OncoTICE® is given to you.
- You will be asked to pass water immediately before OncoTICE® is given to you.

Being given your medicine

- First your genital area will be cleaned with a sterile solution.
- A nurse will then pass a small flexible tube into your bladder. This will remove any urine that is still in your bladder.
- OncoTICE® is then run into your bladder through this tube. This will only take a few minutes.
- The tube will then be removed.

After it has been given

- OncoTICE® will be left in your bladder for 2 hours.
- Do not drink any liquid for 2 hours after you have been given OncoTICE®.
- After 2 hours you will be asked to pass water, to empty your bladder. You should do this while sitting down to avoid splashing your urine around the toilet.

During the next 6 hours

- If you need to pass water again, also do this while sitting down.
- Every time you pass water, add two cups of household bleach to the toilet.
- Leave the bleach and urine to stand in the toilet for 15 minutes before flushing.

Overdose:

OncoTICE® is made up from a standard bottle by your doctor, pharmacist or nurse. It is unlikely that you will receive too much OncoTICE®. If you do have too much, your doctor will check carefully to see whether you have BCG infection. If necessary you will need to have treatment for tuberculosis.

Missed Dose:

No data established

- Severe urinary side effects such as burning or pain on urination, urgency, frequency of urination, blood in urine
- An increase in urinary symptoms (such as urgency, frequency of urination, blood in urine)
- Joint pain
- Cough
- Skin rash
- Eye complaints (such as pain, irritation or redness)
- Jaundice
- Nausea or vomiting
- allergic reactions
- BCG infection in the blood (sepsis)
- Abnormal arterial dilation for bacterial infection (infective aneurysm)

This is not the complete list of side effects. If you notice any side effects not mentioned in this patient information, please notify your treating physician.

HOW TO STORE IT

Keep OncoTICE® out of the reach and site of children.

OncoTICE® will be stored in the hospital according to the instruction given by the manufacturer on the packaging.

Store at 2°C – 8°C (in a refrigerator).

Do not use OncoTICE® after the expiry date which is stated on the carton and label.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

You should be attentive to side effects, such as fever, chills, malaise, flu-like symptoms, or increased fatigue.

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

If you experience any of the following side effects, your physician should be notified:

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

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- Report online at www.healthcanada.gc.ca/medeffect
 - Call toll-free at 1-866-234-2345
 - Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-678-6789, or
 - Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701D
Ottawa, Ontario
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found or by contacting the sponsor Merck Canada Inc.

This leaflet was prepared by Merck Canada Inc.

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