PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

OncoTICE®

Bacillus Calmette-Guérin (BCG), Strain TICE®

Powder for Solution and after dilution and reconstitution contains 1-8 x 10^8 Colony Forming Units (CFU) of TICE® BCG/vial, equivalent to approximately 50 mg wet weight, for Intravesicular Therapy

Antineoplastic Agent for Bladder Instillation

ATC : L03AX03

Merck Canada Inc.
16750 route Transcanadienne
Kirkland QC Canada H9H 4M7
www.merck.ca

Date of Initial Authorization:
May 6, 1995

Date of Revision:
October 2, 2024

Submission Control Number: 286692

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

TABLE OF CONTENTS 2
1 INDICATIONS 4
1.1 Pediatrics 4
1.2 Geriatrics 4
2 CONTRAINDICATIONS 4
4 DOSAGE AND ADMINISTRATION 5
4.1 Dosing Considerations 5
4.2 Recommended Dose and Dosage Adjustment 5
4.3 Reconstitution 5
4.4 Administration 6
5 OVERDOSAGE 6
6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING 6
7 WARNINGS AND PRECAUTIONS 7
7.1 Special Populations 8
7.1.1 Pregnant Women 8
7.1.2 Breast-feeding 8
7.1.3 Pediatrics (< 18 years of age) 8
7.1.4 Geriatrics 8
8 ADVERSE REACTIONS 8
8.1 Adverse Reaction Overview 8
8.2 Clinical Trial Adverse Reactions 9
8.3 Less Common Clinical Trial Adverse Reactions 12
8.5 Post-Market Adverse Reactions 12
9 DRUG INTERACTIONS 14
9.2 Drug Interactions Overview 14
9.4 Drug-Drug Interactions 14
10 CLINICAL PHARMACOLOGY 14
10.1 Mechanism of Action 14
10.2 Pharmacodynamics 15

10.3 Pharmacokinetics 15
11 STORAGE, STABILITY AND DISPOSAL 15
12 SPECIAL HANDLING INSTRUCTIONS 15
PART II: SCIENTIFIC INFORMATION 16
13 PHARMACEUTICAL INFORMATION 16
14 CLINICAL TRIALS 16
14.1 Efficacy and safety studies 16
14.2 Study results 17
15 MICROBIOLOGY 19
16 NON-CLINICAL TOXICOLOGY 19
PATIENT MEDICATION INFORMATION 20

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

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
- adjuvant therapy after transurethral resection (TUR) of a primary or relapsing superficial papillary urothelial cell carcinoma of the bladder stage T_A (grade 2 or 3) or T_1 (grade 1, 2, or 3). It is only recommended for stage T_A grade 1 papillary tumours when there is judged to be a high risk of tumour recurrence.

OncoTICE® is not indicated for the treatment of invasive bladder cancer. It is not recommended for papillary tumours of stages higher than T_1.

1.1 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics: Evidence from clinical studies and experience suggests that use in the geriatric population is not associated with differences in safety or effectiveness (see 4 DOSAGE AND ADMINISTRATION, 7.1.4. Geriatrics, and 14 CLINICAL TRIALS).

2 CONTRAINDICATIONS

- OncoTICE® is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- 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 (see 9 DRUG INTERACTIONS).
- OncoTICE® should be avoided in patients with a positive HIV serology.
- 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 antitumour activity of BCG may result (see 7 WARNINGS AND PRECAUTIONS and 9 DRUG INTERACTIONS).
- 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.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- OncoTICE® must not be administered intravenously, subcutaneously or intramuscularly (see 7 WARNINGS AND PRECAUTIONS).

4.2 Recommended Dose and Dosage Adjustment

- Prior to instillation into the urinary bladder, the contents of one vial of OncoTICE® (Bacillus Calmette-Guérin [BCG], Strain TICE®) are reconstituted and diluted as indicated (see 4.3 Reconstitution).
- *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.
- Health Canada has not authorized an indication for pediatric use.

4.3 Reconstitution

Perform the following procedures under aseptic conditions:
See 12 SPECIAL HANDLING INSTRUCTIONS regarding optional transfer device products.

Reconstitution-Suspension for Bladder Instillation

- Add 1 mL of a sterile, pyrogen-free and preservative-free physiological saline solution to the vial of OncoTICE® by means of a sterile syringe. Ensure that the needle is inserted through the center of the rubber stopper of the vial. Allow to stand for a few minutes. Then gently swirl the vial until a homogeneous suspension is obtained. Caution: avoid forceful agitation. See 11 STORAGE, STABILITY and DISPOSAL.

Preparation of the solution for instillation:

- Dilute the reconstituted suspension in sterile physiological saline up to a volume of 49 mL. Rinse the vial with another 1 mL of sterile, pyrogen-free and preservative-free physiological saline. Add the rinse fluid to the suspension for a final volume of 50 mL. Mix the suspension carefully. The suspension is now ready for use; it contains a total of 2-8 x 10^8 CFU.
- If a needleless closed-system transfer device product is used, dilute the reconstituted suspension in sterile physiological saline up to a volume of 50 mL, and do not rinse the vial.
- Note: The suspension must not be filtered.
- This suspension is now ready for instillation; it contains a total of 1 to 8 x 10^8 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.

4.4 Administration

Insert a catheter via the urethra into the bladder and drain the bladder completely. The 50 ml OncoTICE® suspension is instilled into the bladder via the catheter by gravity flow (or gentle pressure if a syringe is used).

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. Urine should be voided in a sitting position for 6 hours after treatment, and two cups of household bleach should be added to the toilet before flushing. The bleach and urine should be left to stand in the toilet for 15 minutes before flushing.

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 12 SPECIAL HANDLING INSTRUCTIONS).

5 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 8 ADVERSE REACTIONS).

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal 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

OncoTICE® (Bacillus Calmette-Guérin [BCG], Strain TICE®), is supplied as a freeze-dried preparation in 2 mL vials; each vial contains 1 to 8 x 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.

7 WARNINGS AND PRECAUTIONS

General

- OncoTICE® contains live, potentially pathogenic bacteria. 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 biohazardous (see 12 SPECIAL HANDLING INSTRUCTIONS).
- 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 (see 12 SPECIAL HANDLING INSTRUCTIONS).
- 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.
- 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.
- 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.

Driving and Operating Machinery

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

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.

Transurethral resection (TUR): When used as an adjuvant therapy after TUR of a superficial urothelial cell carcinoma of the bladder (see 1 INDICATIONS), 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.

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®, purified protein derivative (PPD) screening 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 (see 2 CONTRAINDICATIONS).

Reproductive Health: Female and Male Potential

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

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®.

7.1 Special Populations

7.1.1 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 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 (see 16 NON-CLINICAL TOXICOLOGY).

7.1.2 Breast-feeding

It is unknown if OncoTICE® is excreted in human milk. Precaution should be exercised because many drugs can be excreted in human milk (see 7.1.1 Pregnant Women).

7.1.3 Pediatrics (< 18 years of age)

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Evidence from clinical studies and experience suggests that use in the geriatric population is not associated with differences in safety or effectiveness (see 4 DOSAGE AND ADMINISTRATION, 7 WARNINGS AND PRECAUTIONS and 14 CLINICAL TRIALS).

8 ADVERSE REACTIONS

8.1 Adverse 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-tumour 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 oxybutin 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 acetaminophen) 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 7 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 days 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 7 WARNINGS AND PRECAUTIONS – Genitourinary. These systemic infections may be manifested by pneumonitis, hepatitis cytopenia, vasculitis, infective aneurysm and/or sepsis after a period of fever and malaise during which symptoms progressively increase. The presentation of systemic infections may also be delayed by months to years.

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 contraindicated.

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.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use. See 14 CLINICAL TRIALS.

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 2 below. The adverse events reported in other studies have been similar.

Table 2 - Local Adverse Effects

Adverse Reaction	OncoTICE® n = 674 (%)	
	Incidence (%)	**Severe (%)**
Blood and lymphatic system disorders		
Anemia	1.3	0.4
Coagulopathy	0.3	0.3
Leukopenia	0.3	-
Thrombocytopenia	0.3	-
Cardiac disorders		
Cardiac	1.9	1.3
Gastrointestinal disorders		
Nausea/vomiting	3.0	0.3
Abdominal Pain	1.5	0.6
Diarrhea	1.2	0.1
Gastrointestinal (Unclassified)	1.0	-
General disorders and administration site conditions		
Fever	19.9	7.6
Malaise/Fatigue	7.4	-
Shaking Chills	3.3	1.0
Hepatobiliary disorders		
Hepatic Granuloma	0.2	0.2
Hepatitis	0.2	0.2
Immune system disorders		
Allergic	2.1	0.4
Infections and infestations		
Cystitis	5.9	1.9
Urinary Tract Infection	1.5	0.9
Urethritis	1.2	-
Pyuria	0.7	0.1

Epididymitis/Prostatitis	0.3	-
Orchitis	0.2	-
BCG Sepsis	0.4	0.4
Musculoskeletal and connective tissue disorders		
Cramps/Pain	4.0	0.9
Arthritis/Myalgia	2.7	0,4
Renal and urinary disorders		
Dysuria	59.5	10.7
Urinary Frequency	40.4	7.4
Hematuria	26.0	7.4
Urgency	5.8	1.3
Nocturia	4.5	0.6
Urinary Incontinence	2.4	---
Urinary Debris	2.2	0.4
Urinary Obstruction	0.3	-
Contracted Bladder	0.2	-
Reproductive system and breast disorders		
Genital Inflammation/Abscess	1.8	0.4
Metabolism and nutrition disorders		
Anorexia/Weight Loss	2.2	0.1
Nervous system disorders		
Headache/Dizziness	2.4	-
Neurologic	0.9	0.3
Respiratory, thoracic and mediastinal disorders		
Respiratory (Unclassified)	1.6	0.2
Pneumonitis	1.2	0.6
Skin and subcutaneous tissue disorders		
Rash	0.6	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.

8.3 Less Common Clinical Trial Adverse Reactions

Blood and lymphatic system disorders: Anemia, coagulopathy, leukopenia, thrombocytopenia

Cardiac disorders: Cardiac

Gastrointestinal disorders: Diarrhea, gastrointestinal (Unclassified)

Hepatobiliary disorders: Hepatic granuloma, hepatitis

Immune system disorders: Allergy

Infections and infestations: BCG Sepsis, epididymitis/prostatitis, orchitis, pyuria, urethritis, urinary tract infection

Metabolism and nutrition disorders: Anorexia/weight loss

Musculoskeletal and connective tissue disorders: Arthritis/myalgia

Renal and urinary disorders: Urinary Incontinence, Urinary Debris, urinary obstruction, contracted bladder

Nervous system disorders: Headache/dizziness, neurologic

Reproductive system and breast disorders: Genital Inflammation/abscess

Respiratory, thoracic and mediastinal disorders: Respiratory (Unclassified); pneumonitis

Skin and subcutaneous tissue disorders: Rash

8.5 Post-Market Adverse Reactions

The following adverse reactions (Table 3) are reported from the post-market surveillance as serious and unexpected. This information is based on clinical experience and/or published clinical data.

Table 3 – Post-Market Adverse Reactions

Occurrence	MedDRA System Organ Class	Preferred terms
Uncommon (>1/1,000, <1/100)	Infections and infestations	Tuberculous infections[1]
Rare (>1/10,000, <1/1,000)	Respiratory, thoracic and mediastinal disorders	Cough
	Reproductive system and breast disorders	Epididymitis

Occurrence	MedDRA System Organ Class	Preferred terms
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]

Occurrence	MedDRA System Organ Class	Preferred terms
	General disorders and administration site conditions	Chest pain, edema peripheral, granuloma[2]
	Investigations	Prostatic specific antigen increased, weight decreased
Not known (cannot be estimated from the available data)	Eye disorders	endophthalmitis

[1] High Level Term instead of Preferred Term
[2] Only isolated cases reported during post-marketing surveillance
[3] Granuloma NOS has been observed in various organs including the aorta, bladder, epididymis, gastrointestinal tract, kidney, liver, lungs, lymph nodes, peritoneum, prostate

9 DRUG INTERACTIONS

9.2 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®.

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 4 - Established or Potential Drug-Drug Interactions

[Proper/Common name]	Source of Evidence	Effect	Clinical comment
Most antibiotics (In particular: anti-tuberculous agents like streptomycin, para-aminosalicylic acid (PAS), isoniazid (INH), rifampicin and ethambutol except for pyrazinamide.)	Not available	Concomitant therapy with antibiotics may decrease anti-tumour activity of OncoTICE®	If a patient is being treated with antibiotic it is recommended to postpone the intravesical instillation until the end of the antibiotic treatment

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

OncoTICE® has anti-tumour activity but the exact mechanism of action is not known. Study data

suggest that an active non-specific 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.

10.2 Pharmacodynamics

OncoTICE® is an immunostimulating agent (ATC code L03AX03).

10.3 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.

11 STORAGE, STABILITY AND DISPOSAL

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.

Please refer to more detailed safe disposal instructions under 12 SPECIAL HANDLING INSTRUCTIONS.

12 SPECIAL HANDLING INSTRUCTIONS

OncoTICE® contains live attenuated mycobacteria. Reconstitution, preparation of the OncoTICE® suspension for instillation and administration should be performed under aseptic conditions. The use of needleless closed-system transfer device products may be considered when transferring OncoTICE® from primary packaging to instillation equipment.

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 biohazardous.

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 (see 7 WARNINGS AND PRECAUTIONS).

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: OncoTICE®

Chemical name: Bacillus Calmette-Guérin (BCG), Strain TICE®

Physicochemical properties: OncoTICE® - freeze-dried preparation in a glass vial, each containing 1 to 8 x 10^8 CFU, which is equivalent to approximately 50 mg wet weight.

Pharmaceutical standard: [for biologics] Professed

Product Characteristics:

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 10^8 colony forming units (CFU) of TICE® BCG which is equivalent to approximately 50 mg wet weight. No preservatives have been added.

14 CLINICAL TRIALS

14.1 Efficacy and safety studies

Trial Design and Study Demographics

Table 5 - Summary of patient demographics for clinical trials in carcinoma in situ

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
6-study pool: Study No. 1883 Study No. 1111 Study No. 1571 Study No. 1414 Study No. 2951 Study No. 2427	Retrospective, multicentre, non-randomized	Intravesical	153 patients	69 years (38-97 years)	M: 132 F: 19 Unidentified: 2

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 x 108 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 tumour upon cystoscopy. The results of an analysis of the evaluable patients conducted in 1987 are shown in Table 6.

14.2 Study results

Table 6 – 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%)

An updated analysis of these data conducted in 1989 is presented in Table 7. The median duration of follow-up was 47 months.

Table 7 – 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_AT_1 bladder cancer after complete transurethral resection of all papillary tumours 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 tumour within 56 weeks, any stage T1 tumour, or 3 or more tumours 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 were 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 8. 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% ± 10%. No statistically significant differences between the groups were noted in time to tumour progression, tumour invasion, or overall survival.

Table 8 – 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 were 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 tumours. 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 9. The differences in disease-free survival among the 3 arms were not statistically significant by the log-rank test (*P*=0.08).

Table 9 – 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.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

Carcinogenicity: OncoTICE® has not been evaluated for the potential to cause carcinogenicity.

Genotoxicity: OncoTICE® has not been evaluated for the potential to cause genotoxicity.

Reproductive and Developmental Toxicology: OncoTICE® has not been evaluated for the potential to affect fertility in males or females.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

OncoTICE®

Bacillus Calmette-Guérin (BCG), Strain TICE®

Read this carefully before you start taking **OncoTICE®** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **OncoTICE®.**

What is OncoTICE® 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.

How does OncoTICE® work?

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

What are the ingredients in OncoTICE®?

Medicinal ingredients: Bacillus Calmette-Guérin (BCG), Strain TICE®

Non-medicinal ingredients: Lactose 150 grams, Sauton medium (lactose, asparagine, citric acid (E330), potassium phosphate, magnesium sulfate, iron ammonium citrate, glycerol (E422), ammonium hydroxide (E527), zinc formate).

OncoTICE® comes in the following dosage forms:

OncoTICE® is supplied as a freeze-dried preparation in 2 mL vials; each vial contains 1 to 8 x 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.

Do not use OncoTICE® if:

- You are hypersensitive (allergic) to Bacillus Calmette-Guérin (BCG) Strain TICE® or any of the other ingredients of OncoTICE®.
- You suffer from active tuberculosis.
- You are being treated with anti-tuberculosis drugs.
- You are HIV-positive.
- You suffer from an impaired immune system (reduced immunity against infectious diseases), irrespective of the cause.
- You have blood in your urine.
- 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.

To help avoid side effects and ensure proper use, talk to your healthcare professional before starting treatment with OncoTICE®. Talk about any health conditions or problems you may have, including if you have :

- active tuberculosis infection

Other warnings you should know about:

BEFORE you use OncoTICE® talk to your healthcare professional:
Before the first intravesical instillation of OncoTICE®, your healthcare professional 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 healthcare professional 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, talk to your healthcare professional.
- If you are breastfeeding, talk to your healthcare professional.

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

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with OncoTICE®:

- 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 healthcare professional will probably postpone treatment with OncoTICE® until you have stopped these other treatments.

How to take OncoTICE®:

- OncoTICE® will be given to you by a healthcare professional in a healthcare setting.

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 healthcare professional will talk to you about this.

Before it is given

- Do not drink any liquid 4 hours before OncoTICE® is given to you.

- You will be asked to pass water immediately before OncoTICE® is given to you.

When 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 healthcare professional, pharmacist or nurse. It is unlikely that you will receive too much OncoTICE®. If you do have too much, your healthcare professional will check carefully to see whether you have BCG infection. If necessary you will need to have treatment for tuberculosis.

If you think you, or a person you are caring for, have taken too much OncoTICE®, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using OncoTICE®?

These are not all the possible side effects you may have when taking OncoTICE®. If you experience any side effects not listed here, tell your healthcare professional. You should be attentive to side effects, such as fever, chills, malaise, flu-like symptoms, or increased fatigue.

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

- An increase in urinary symptoms (such as burning, or pain upon urination, urgency, frequency of urination, blood in urine)
- Decreased urination or failure to urinate
- Joint or muscle pain
- Cough and/or shortness of breath
- Skin rash
- Eye complaints (such as pain, visual impairment, irritation or redness)
- Jaundice (yellow colouration of the skin or eyes)
- Nausea or vomiting
- Allergic reactions

- BCG infection in the blood (sepsis)
- Abnormal arterial dilation for bacterial infection (infective aneurysm)
- Inflammation of the blood vessels

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

Symptom / effect	Talk to your healthcare professional	
	Only if severe	In all cases
UNCOMMON		
Tuberculous infections		X
RARE		
Cough		X
Epididymitis		X
VERY RARE		
Pharyngitis, orchitis, Reiter's syndrome, Lupus vulgaris		X
Lymphadenopathy		X
Anorexia		X
Confusional state		X
Dizziness, dysaesthesia[1], hyperaesthesia[1], paresthesia, somnolence, headache, hypertonia, neuralgia[1]		X
Conjunctivitis		X
Vertigo		X
Hypotension		X
Bronchitis, dyspnea, rhinitis		X
Dyspepsia[1], flatulence[1]		X
Alopecia, hyperhidrosis		X
NOT KNOWN (cannot be estimated from the available data)		
Back pain		X
Renal failure acute		X
Balanoposthitis, prostatitis, vulvovaginal discomfort[1]		X
Chest pain, edema peripheral, granuloma[2]		X
Prostatic specific antigen increased, weight decreased		X
endophthalmitis		
UNKNOWN		
Increase in urinary symptoms (examples: burning, pain upon urination, urgency, frequency of urination, blood in urine)		X
Decreased urination or failure to urinate		X
Joint or muscle pain		X

Symptom / effect	Talk to your healthcare professional	
	Only if severe	In all cases
Cough and/or shortness of breath		X
Skin rash		X
Eye complaints (examples: pain, visual impairment, irritation or redness)		X
Jaundice (yellow colouration of the skin or eyes)		X
Nausea or vomiting		X
Allergic reactions		X
BCG infection in the blood (sepsis)		X
Abnormal arterial dilation for bacterial infection (infective aneurysm)		X
Inflammation of the blood vessel		X

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
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.

If you want more information about OncoTICE®:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website:

(https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.merck.ca, or by calling 1-800-567-2594.

This leaflet was prepared by Merck Canada Inc.

Last Revised October 2, 2024