AUSTRALIAN PRODUCT INFORMATION

ONCOTICE®

Mycobacterium bovis (Bacillus Calmette and Guerin (BCG) strain) Powder for injection

1 NAME OF THE MEDICINE

Mycobacterium bovis (Bacillus Calmette and Guerin (BCG) strain)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

OncoTICE® is a freeze-dried preparation of live, attenuated Mycobacterium bovis (Bacillus Calmette and Guerin (BCG) strain) (Tice™ BCG).

The freeze-dried BCG preparation contains 2-8 × 10^8 colony forming units (CFU) of Tice BCG. After reconstitution in 50 mL saline (0.9% sodium chloride solution) the suspension contains 0.4-1.6 × 10^7 CFU/mL.

For the full list of excipients, see **Section 6.1 List of Excipients.**

3 PHARMACEUTICAL FORM

White to off-white cake or powder (for instillation fluid for intravesical use) containing 2-8 × 10^8 CFU Tice BCG.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

OncoTICE is used as a treatment of primary or recurrent carcinoma in situ (CIS) of the urinary bladder. OncoTICE is also used after transurethral resection for the prevention of recurrence of high grade and/or relapsing superficial papillary transitional cell carcinoma of the urinary bladder (viz papillary carcinoma stage T_A [grade 2 or 3] or T_1 [grade 1, 2, or 3]). OncoTICE is only recommended for stage T_A grade 1 tumours, when there is judged to be a high risk of tumour recurrence.

4.2 DOSE AND METHOD OF ADMINISTRATION

Reconstitution, preparation and administration of OncoTICE Suspension for bladder instillation

OncoTICE is incompatible with hypotonic and hypertonic solutions.

OncoTICE contains live, attenuated mycobacteria. Because of the potential risk for transmission, it should be prepared, handled and disposed of as a biohazard material. The use of needleless closed-system transfer device products may be considered when transferring OncoTICE from primary packaging to instillation equipment.

Perform the following procedures under aseptic conditions:

Reconstitution

Add 1 mL of preservative-free sterile physiological saline (0.9% sodium chloride) solution by means of a sterile syringe to the contents of 1 vial of OncoTICE. Ensure that the needle is inserted through the centre of the rubber stopper of the vial. Allow to stand for a few minutes. Then gently swirl the vial until a homogenous suspension is obtained. (Caution: avoid forceful agitation.)

Preparation of the suspension for instillation

Dilute the reconstituted suspension in sterile physiological saline (0.9% sodium chloride) up to a volume of 49 ml.

Rinse the vial with another 1 mL of preservative-free sterile physiological saline (0.9% sodium chloride).

Add the rinse fluid to the reconstituted 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 × 10^8 CFU of BCG.

Note: Do not filter the contents of the OncoTICE vial.

Dosage

Each instillation comprises 2-8 × 10^8 CFU the contents of one reconstituted and diluted vial of OncoTICE suspended in physiological saline (0.9% sodium chloride) up to a total volume of 50 mL as indicated above.

Carcinoma in situ of the bladder (CIS)

After biopsy or traumatic catheterisation, OncoTICE should not be given for 7 to 14 days or until the urinary mucosa has healed (see **Section 4.4 Special Warnings and Precautions for Use**). The treatment schedule for CIS of the bladder comprises a weekly instillation with OncoTICE during the first 6 weeks, the 'induction treatment' followed by a maintenance treatment consisting of monthly OncoTICE instillations over a period of 12 months.

Adjuvant therapy after transurethral resection of superficial papillary carcinoma of the bladder (free of CIS)

After transurethral resection of superficial papillary carcinoma of the bladder, adjuvant therapy with OncoTICE (where indicated) should not be given for 10 to 15 days or until the urinary mucosa has healed (see **Section 4.4 Special Warnings and Precautions for Use**). The treatment schedule comprises the weekly instillation of OncoTICE during the first 6 weeks, followed by an instillation in the 8th week and the 12th week and thereafter monthly instillations for months 4 through 12 after initiation of treatment.

The duration and frequency of the maintenance treatment course should be evaluated on the basis of tumour classification and clinical diagnosis.

Administration

Insert a catheter via the urethra into the bladder and drain the bladder completely.

The reconstituted 50 mL OncoTICE suspension is instilled into the bladder by gravity flow (i.e. natural flow without force or added pressure) via the catheter.

After instillation, remove the catheter.

The instilled OncoTICE suspension must remain in the bladder for a period of 2 hours.

During this period care should be taken that the instilled OncoTICE suspension has sufficient contact with the whole mucosal surface of the bladder. Therefore the patient should not be immobilised or, in the case of a bed-ridden patient, should be turned over from back to abdomen and vice versa every 15 minutes.

When the OncoTICE suspension has been retained in the bladder for two hours, have the patient void the instilled suspension. Urine should be voided in the 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 must not ingest any fluid during a period starting 4 hours prior to instillation, until bladder evacuation is permitted (i.e. 2 hours after instillation).

4.3 CONTRAINDICATIONS

The intravesical instillation of OncoTICE is contra-indicated in the following cases:

- Urinary tract infections, or concurrent febrile illness. Therapy with OncoTICE should be interrupted until the bacterial culture from urine becomes negative and therapy with antibiotics or urinary antiseptics is stopped.
- Gross haematuria. In these cases, OncoTICE therapy should be stopped or postponed until the haematuria has been successfully treated or has resolved.
- Clinical evidence of existing active tuberculosis.
- Active tuberculosis should be ruled out in individuals who are PPD positive before starting treatment with OncoTICE.
- Treatment with anti-tuberculosis drugs such as streptomycin, para-amino salicylic acid (PAS), isoniazid (INH), rifampicin and ethambutol.
- Patients with impaired immune response irrespective whether this impairment is congenital or caused by disease (e.g. AIDS, leukaemia, lymphoma) drugs or other therapy (cytotoxic drugs, radiation).
- Asymptomatic carriers with a positive HIV serology and in patients receiving steroids at immunosuppressive doses or other immunosuppressive therapies.
- Pregnancy and lactation.
- Seven to fourteen days should elapse before BCG is administered following biopsy or traumatic catheterisation.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

- OncoTICE is not a vaccine for the prevention of cancer.
- The use of OncoTICE may cause tuberculin sensitivity.
- The use of OncoTICE has been associated with disseminated BCG infection and in some cases death has resulted. Most cases have involved patients with impaired immune response.
- Intravesical instillations should be postponed in the presence of fever, suspected infection, or during treatment with antibiotics.
- Small bladder capacity has been associated with increased risk of severe local reactions and should be considered in deciding to use OncoTICE therapy.
- OncoTICE contains viable attenuated mycobacteria and should be handled as potentially infectious. All equipment and material used during reconstitution and instillation should be handled and disposed of as biohazardous material.
- Before the first intravesical instillation of OncoTICE, a tuberculin test should be performed. If this test is positive, the intravesical instillation of OncoTICE is contra-indicated only if there is supplementary medical evidence for an active tuberculous infection.
- Instillation of OncoTICE onto a bleeding mucosa may increase the risk of systemic BCG infection. It is recommended to delay OncoTICE administration in such patients until mucosal damage has been healed.
- Traumatic catheterisation or other injuries to the urethra or bladder mucosa can promote systemic BCG infection. It is recommended to delay OncoTICE administration in such patients until mucosal damage has healed.
- It is recommended that patients known to be at risk of HIV infection be adequately screened prior to commencing therapy.
- Patients should be monitored for the presence of symptoms of BCG infection and signs of toxicity after each intravesical treatment.
- OncoTICE should not be administered intravenously, subcutaneously nor intramuscularly.
- 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.
- Reconstitution, preparation and administration of the OncoTICE suspension should be performed under aseptic conditions.
- Spillage of OncoTICE suspension may cause Tice BCG contamination. Any spilled OncoTICE suspension should be cleaned by covering with paper towels soaked with tuberculocidal disinfectant for at least 10 minutes. All waste materials should be disposed of as biohazard material.
- Accidental exposure to Tice BCG could occur through self-inoculation, by dermal exposure through an open wound, or by inhalation or ingestion of OncoTICE suspension. Tice BCG exposure should not produce significant adverse health outcomes in healthy individuals. However, in case of suspected, accidental self-inoculation, PPD skin testing is advised at the time of the accident and six weeks later to detect skin test conversion.
- Care should be taken not to traumatise the urinary tract or to introduce contaminants into the urinary system.

Use in the elderly

No data available.

Paediatric use

Safety and effectiveness for carcinoma of the urinary bladder in children have not been established.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

OncoTICE is sensitive to most antibiotics and in particular the routinely used anti-tuberculous drugs such as streptomycin, para-amino salicylic acid (PAS), isoniazid (INH), rifampicin and ethambutol. It is unknown whether interactions occur during the intravesical instillation of OncoTICE. Therefore the anti-tumour activity of OncoTICE may be influenced by concomitant therapy with antibiotics. If a patient is being treated with an antibiotic, postponement of the intravesical instillation is recommended until the end of the antibiotic treatment (see also **Section 4.3 Contraindications**).

Studies on possible interactions with other drugs have not been performed.

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available.

Use in pregnancy

Pregnancy Category B2

OncoTICE instillation for carcinoma of the bladder is contra-indicated during pregnancy.

Use in lactation

OncoTICE instillation for carcinoma of the bladder is contra-indicated during lactation.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration. However, based on the pharmacodynamic profile of OncoTICE, it is assumed that the product will not affect the ability to drive and to use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trial Data

Intravesical OncoTICE therapy for superficial urothelial cell carcinoma of the bladder was generally well tolerated by most patients during clinical trials. Toxicity and side effects appear to be directly related to the cumulative number of CFU of BCG administered during the total number of instillations.

Common side effects of intravesical OncoTICE instillation are:

- Frequency and urgency of micturition, haematuria and dysuria. In most patients these symptoms develop from the second or third instillation onwards. The cystitis and typically inflammatory reactions (granulomata) which occur in the mucosa of the urinary bladder

after instillation of BCG, and which cause these symptoms, may be an essential part of the anti-tumour activity of the BCG instillation. Often the symptoms disappear within two days after instillation and the cystitis does not require treatment. During the maintenance treatment course with BCG, the symptoms of cystitis may be more pronounced and prolonged. Symptomatic treatment; postpone next OncoTICE treatment until complete resolution. If complete resolution has not occurred within one week, administer isoniazid 300 mg daily until complete resolution.

- Malaise, a low grade fever and/or flu-like syndrome. These symptoms usually appear within 4 hours after instillation and last for 24 - 48 hours.

Complications other than the above-mentioned inflammatory symptoms are far less frequent and among these the most common are:

- Fever higher than 39°C. The fever typically resolves within 1 or 2 days when treated with antipyretics (preferably paracetamol) and fluids. However, frequently, it is not possible to distinguish these uncomplicated febrile reactions from an early systemic BCG infection and treatment with tuberculostatic chemotherapeutics may be indicated.
- Systemic infection due to traumatic catheterisation, bladder perforation or early BCG instillation after extensive TUR of the urothelial cell carcinoma of the bladder. There is a possibility of death if systemic BCG infection occurs. These systemic infections may be manifested initially by pneumonitis, hepatitis and/or cytopenia after a period of fever and malaise during which symptoms progressively increase. Patients with manifest symptoms of therapy-induced systemic tuberculous BCG infection should be adequately treated with tuberculostatic agents according to treatment schedules used for tuberculous infections. In case of systemic infection, initial therapy comprises the triple drug therapy (isoniazid - rifampicin - ethambutol) with or without cycloserine for some weeks and can be continued 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 treatment with the Tice BCG is contra-indicated.
- Granulomatous prostatitis. The majority of these patients are asymptomatic and require no treatment.
- Haemorrhagic cystitis may also occur.

In rare cases, arthritis/arthralgias, major haematuria, hepatic granuloma, coagulopathy, skin rash, transient urethral obstruction, orchitis, epididymitis or bladder contracture may occur. If these rare complications occur, it is almost exclusively during the maintenance treatment regimen with OncoTICE. Cases of arthritis, arthralgia, and skin rash may be hypersensitivity reactions of the patient to BCG.

The percentage of patients with at least one adverse event, with causality to the study drug, are tabulated below for the comparative study of intravesical instillation of Mitomycin-c, RIVM BCG and Tice BCG (Nijmegen study), and the comparative study of intravesical instillation of Tice BCG and Mitomycin-c (SWOG study). It includes all adverse events reported with an incidence of 1% or greater. A dash represents an incidence of less than 1%

Table 1: Nijmegen study

Body system	Study group		
	Tice BCG (n=140) %	RIVM BCG (n=149) %	Mitomycin-C (n=148) %
Bacterial cystitis	27	23	18
Drug-induced cystitis	30	32	17
Other local adverse events	16	15	5
Allergic symptoms	2	2	5
Fever <38.5°C	5	3	-
Fever >38.5°C	1	-	-
Flu-like symptoms	8	3	-
Nausea	1	-	-
General malaise	7	3	1
Other systemic symptoms	3	7	1

Table 2: SWOG study

Body system	Study group	
	Tice BCG (n=163) %	Mitomycin-C (n=170) %
Local effects		
Bladder cramps	4	5
Bladder – other	1	-
Dysuria	45	23
GU – other	2	2
Haematuria	27	14
Hemorrhage cystitis	6	4
Incontinence	2	-
Increased urgency/frequency	36	19
Pain	11	6
Urinary retention	1	1
Urinary tract infection	1	1
Systemic effects		
Anemia	-	2
Chills	7	-
Creatinine increase	-	1
Dizziness/vertigo	1	1
Erythema	-	5
Fever without infection	13	-
Headache	-	1
Infection	1	-
Leukopenia	1	-
Malaise/fatigue/lethargy	19	11
Myalgia/arthralgia	2	-
Nausea	4	3
Other flu-like symptoms	2	-
Skin rash	2	4
Sweats	2	-
Vomiting	1	1
Miscellaneous - others	1	-

Post-marketing experience

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. Micturition frequency and urgency 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.

Table 3: Side effects reported during post-marketing surveillance (MeDRA 6.1)

Occurrence	MedDRA SOClass	Preferred terms
Very common (>1/10)	Renal and urinary disorders	Cystitis, dysuria, pollakiuria, haematuria
	General disorders and administration site conditions	Influenza-like illness, pyrexia, malaise, fatigue
Common (>1/100, <1/10)	Infections and infestations	Urinary tract infection
	Blood and lymphatic system disorders	Anaemia
	Respiratory, thoracic and mediastinal disorders	Pneumonitis
	Gastrointestinal disorders	Abdominal pain, nausea, vomiting, diarrhoea
	Musculoskeletal and connective tissue disorders	Arthralgia, arthritis, myalgia
	Renal and urinary disorders	Urinary incontinence, micturition urgency, urine analysis abnormal
	General disorders and administration site conditions	Rigors
Uncommon (>1/1,000, <1/100)	Infections and infestations	Tuberculous infections[1]
	Blood and lymphatic system disorders	Pancytopenia, thrombocytopenia
	Hepatobiliary disorders	Hepatitis
	Skin and subcutaneous tissue disorders	Rashes, eruptions and exanthems NEC[1]
	Renal and urinary disorders	Bladder constriction, pyuria, urinary retention, ureteric obstruction
	Investigations	Hepatic enzyme increased
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

Occurrence	MedDRA SOClass	Preferred terms
	Blood and lymphatic system disorders	Lymphadenopathy
	Metabolism and nutrition disorders	Anorexia
	Psychiatric disorders	Confusional state
	Nervous system disorders	Dizziness, dysaesthesia[3], hyperaesthesia[3], paraesthesia, somnolence, headache, hypertonia, neuralgia[3]
	Eye disorders	Conjunctivitis
	Ear and labyrinth disorders	Vertigo[3]
	Vascular disorders	Hypotension
	Respiratory, thoracic and mediastinal disorders	Bronchitis, dyspnoea, rhinitis
	Gastrointestinal disorders	Dyspepsia[3], flatulence[3]
	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[3]
	General disorders and administration site conditions	Chest pain, oedema peripheral, granuloma[2]
	Investigations	Prostatic specific antigen increased, weight decreased
Unknown	Infections and infestations	Intervertebral discitis[4], osteomyelitis[4]

NEC = Not elsewhere classified

[1] High Level Term instead of preferred term.
[2] Granuloma NOS has been observed in various organs including the aorta, bladder, epididymis, gastrointestinal tract, kidney, liver, lungs, lymph nodes, peritoneum and prostate.
[3] Only isolated cases reported during post-marketing surveillance.
[4] The frequency cannot be estimated from the available data.

Also commonly observed are 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. However, it is frequently not possible to distinguish these uncomplicated febrile reactions from early systemic BCG infection and antituberculosis treatment may be indicated.

Systemic BCG infections could be due to traumatic catheterisation, bladder perforation or premature BCG instillation after extensive TUR of a superficial carcinoma of the bladder. These systemic infections may be manifested by pneumonitis, hepatitis, cytopenia, vasculitis, infective aneurysm, osteomyelitis, intervertebral discitis and/or sepsis after a period of fever and malaise during which symptoms progressively increase. Disseminated infection may

present many months to years after treatment. Patients with symptoms of therapy-induced systemic BCG infection should be adequately treated with anti-tuberculosis drugs according to treatment schedules used for tuberculosis infections. In these cases, further treatment with OncoTICE BCG is contraindicated.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Administration of more than one vial of OncoTICE per instillation constitutes an overdose. In case of overdosage, the patient should be closely monitored for signs of systemic BCG infection and, if indicated, treated with anti-tuberculous medication.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

OncoTICE is an immunostimulating agent (ATC code L03AX03). It has anti-tumour 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.

Clinical trials

A clinical trial has been carried out to compare the efficacy and safety of intravesically administered Tice BCG, RIVM BCG and Mitomycin-c in 469 patients with primary and recurrent superficial bladder cancer including CIS (Nijmegen study). Patients in the BCG groups received 6 weekly instillations of one ampoule BCG. In patients who received BCG as initial treatment, if recurrence was detected at 3 months then the tumour was resected and a second 6 week course of BCG was given. At the end of the study 79 patients (56%) of the 140 evaluable subjects treated with Tice BCG were free of bladder cancer.

The efficacy and toxicity of intravesical Mitomycin-c and Tice BCG for recurrent superficial stage TA and T1 transitional cell carcinoma of the bladder were studied in a comparative clinical study in which 349 patients were included (SWOG study). Patients in the BCG group received instillations of one ampoule of Tice BCG weekly for 6 weeks, in week 8 and 12, and thereafter monthly for months 4 through 12. At the end of the study 133 of 174 (76%) of evaluable patients treated with Tice BCG were disease free.

In all these studies children were not included.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Tice BCG can bind specifically to fibronectin in the bladder wall.

Distribution

Not applicable.

Metabolism

Not applicable.

Excretion

Most instilled OncoTICE will be excreted with the first urine void two hours after the instillation.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No remarkable results.

Carcinogenicity

No remarkable results.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The culture medium from which the freeze-dried cake is prepared has the following relative composition: lactose monohydrate 150 g, Sauton medium 250 mL and water 750 mL. The following excipients are also included: asparagine, citric acid monohydrate, dibasic potassium phosphate, magnesium sulfate heptahydrate, ferric ammonium citrate, glycerol, zinc formate dihydrate and strong ammonia solution. No preservatives have been added.

6.2 INCOMPATIBILITIES

OncoTICE is incompatible with hypotonic and hypertonic solutions.

6.3 SHELF LIFE

The expiry date indicated on the label only applies if the vials are stored under the conditions indicated.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Freeze-dried OncoTICE must be stored at a temperature between 2 and 8°C and protected from light.

In-use stability of the reconstituted product has been demonstrated for 2 hours at 2-8°C protected from light. To reduce microbial hazard, the product should be used immediately. If storage is necessary, hold at 2-8°C for not more than 2 hours.

6.5 NATURE AND CONTENTS OF CONTAINER

Pack of one, three or six* glass vials. Each 2 mL capacity vial contains 2-8 × 10^8 CFU of *Mycobacterium bovis* (Bacillus Calmette and Guerin (BCG) strain) in freeze-dried form.

*Not available in Australia

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

No data available.

CAS number

The CAS Registry Number is 76-60-8

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (Schedule 4)

8 SPONSOR

Merck Sharp & Dohme (Australia) Pty Limited
Level 1, Building A, 26 Talavera Road
Macquarie Park NSW 2113
www.msd-australia.com.au

9 DATE OF FIRST APPROVAL

27th May 1997

10 DATE OF REVISION

28 February 2025

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.2	Removal of reference to M.E.R.C.I. device

RCN000027266-AU