1 PRODUCT NAME
OncoTICE® powder for instillation fluid for intravesical use containing 2-8 × 10^8 colony forming units (CFU), Tice™ BCG.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
OncoTICE is a freeze-dried preparation containing attenuated bacilli of Mycobacterium bovis, prepared from a culture of Bacillus Calmette-Guérin (BCG).
The freeze-dried OncoTICE is delivered in sealed glass vials, each containing 2-8 × 10^8 CFU. After reconstitution in 50 ml saline the suspension contains 0.4-1.6 × 10^7 CFU/mL.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Vial: a 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 flat urothelial cell carcinoma in situ (CIS) of the bladder, and as an adjuvant therapy after transurethral resection (TUR) of a primary or relapsing superficial papillary urothelial cell carcinoma of the bladder stage TA (grade 2 or 3) or T1 (grade 1, 2 or 3). OncoTICE is only recommended for stage TA grade 1 papillary tumours when there is judged to be a high risk of tumour recurrence.

4.2 Dose and method of administration

Dose
Per instillation, the contents of one reconstituted and diluted vial of OncoTICE, are instilled into the urinary bladder.

Induction Treatment
Weekly instillation with OncoTICE during the first 6 weeks.
When used as an adjuvant therapy after TUR of a superficial urothelial cell carcinoma of the bladder (see Section 4.1 Therapeutic 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.

Maintenance Treatment
Maintenance treatment is indicated for all patients and consists of weekly instillation with OncoTICE during 3 consecutive weeks at months 3, 6, and 12 after initiation of the treatment. The need for maintenance treatment every 6 months beyond the first year of treatment should be evaluated on the basis of tumour classification and clinical response.
**Paediatric population**
No data available.

**Method of administration**
Precautions to be taken before handling or administering the medicine. For instructions on reconstitution and dilution, see Section 6.6 Special precautions for disposal and other handling.

**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 by gravity flow via the catheter. After instillation of the OncoTICE suspension, 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 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 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 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
• Impaired immune response irrespective of whether this impairment is congenital or caused by disease, medicines or other therapy
• Positive HIV serology
• Pregnancy and lactation
• Urinary tract infections. In these cases, therapy with OncoTICE should be interrupted until the bacterial culture from urine becomes negative and the therapy with antibiotics and/or urinary antiseptics is stopped
• Treatment with antituberculosis agents like streptomycin, para-amino-salicylic acid (PAS), isoniazide (INH), rifampicin and ethambutol
• 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
4.4 Special warnings and precautions for use

- **OncoTICE** should not be administered intravenously, subcutaneously nor intramuscularly.
- Reconstitution, preparation and administration of the OncoTICE suspension should be performed under aseptic conditions or else with the use of a closed reconstitution device such as M.E.R.C.I.
- Before the first instillation of OncoTICE, a tuberculin test should be performed. If this test is positive, the intravesical instillation of OncoTICE is contraindicated only if there is supplementary medical evidence for an active tuberculous infection.
- Traumatic catheterization 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 been healed.
- 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.
- The use of OncoTICE may sensitise patients to tuberculin, resulting in a positive reaction to PPD.
- 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 systemic BCG infection and signs of toxicity after each intravesical treatment.
- Spillings 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.

**Paediatric population**

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

4.5 Interaction with other medicines and other forms of interaction

OncoTICE is sensitive to most antibiotics and in particular to the routinely used anti-tuberculosis agents like streptomycin, para-aminosalicylic acid (PAS), isoniazide (IHN), rifampicin and ethambutol. Therefore the anti-tumour activity of OncoTICE may be influenced by concomitant therapy with antibiotics. If a patient is being treated with an antibiotic it is recommended to postpone the intravesical instillation until the end of the antibiotic-treatment (see also Section 4.3 Contraindications). 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.
Paediatric population
No data available.

4.6 Fertility, pregnancy and lactation

Pregnancy
OncoTICE instillation for the treatment of carcinoma of the bladder is contraindicated during pregnancy.

Breast-feeding
OncoTICE instillation for the treatment of carcinoma of the bladder is contraindicated during lactation.

Fertility
No data available.

4.7 Effects on ability to drive and use machines
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 Undesirable effects

Summary of the safety profile
The side effects of intravesical OncoTICE therapy are generally mild and transient. 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. In these cases, when severe symptoms are present, isoniazid (300mg daily) and analgesics can be given until disappearance of symptoms.

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. 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 infection and antituberculosis treatment may be indicated. 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 diagnostics and treatment.
Tabulated list of adverse reactions

Table 1: Side effects reported during post-marketing surveillance

<table>
<thead>
<tr>
<th>Occurrence</th>
<th>MedDRA SOCClass</th>
<th>Preferred terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common (&gt;1/10)</td>
<td>Renal and urinary disorders</td>
<td>Cystitis, dysuria, pollakiuria, haematuria</td>
</tr>
<tr>
<td></td>
<td>General disorders and administration site conditions</td>
<td>Influenza-like illness, pyrexia, malaise, fatigue</td>
</tr>
<tr>
<td>Common (&gt;1/100, &lt;1/10)</td>
<td>Infections and infestations</td>
<td>Urinary tract infection</td>
</tr>
<tr>
<td></td>
<td>Blood and lymphatic system disorders</td>
<td>Anaemia</td>
</tr>
<tr>
<td></td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Pneumonitis</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal disorders</td>
<td>Abdominal pain, nausea, vomiting, diarrhoea</td>
</tr>
<tr>
<td></td>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Arthralgia, arthritis, myalgia</td>
</tr>
<tr>
<td></td>
<td>Renal and urinary disorders</td>
<td>Urinary incontinence, micturition urgency, urine analysis abnormal</td>
</tr>
<tr>
<td></td>
<td>General disorders and administration site conditions</td>
<td>Rigors</td>
</tr>
<tr>
<td>Uncommon (&gt;1/1000, &lt;1/100)</td>
<td>Infections and infestations</td>
<td>Tuberculous infections¹</td>
</tr>
<tr>
<td></td>
<td>Blood and lymphatic system disorders</td>
<td>Pancytopenia, thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td>Hepatobiliary disorders</td>
<td>Hepatitis</td>
</tr>
<tr>
<td></td>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rashes, eruptions and exanthems NEC¹</td>
</tr>
<tr>
<td></td>
<td>Renal and urinary disorders</td>
<td>Bladder constriction, pyuria, urinary retention, ureteric obstruction</td>
</tr>
<tr>
<td></td>
<td>Investigations</td>
<td>Hepatic enzyme increased</td>
</tr>
<tr>
<td>Rare (&gt;1/10,000, &lt;1/1,000)</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Cough</td>
</tr>
<tr>
<td></td>
<td>Reproductive system and breast disorders</td>
<td>Epididymitis</td>
</tr>
<tr>
<td>Occurrence</td>
<td>MedDRA SOCClass</td>
<td>Preferred terms</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>-------------------------------------------------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Very rare (&lt;1/10,000)</td>
<td>Infections and infestations</td>
<td>Pharyngitis, orchitis, Reiter’s syndrome, Lupus vulgaris</td>
</tr>
<tr>
<td></td>
<td>Blood and lymphatic system disorders</td>
<td>Lymphadenopathy</td>
</tr>
<tr>
<td></td>
<td>Metabolismand nutrition disorders</td>
<td>Anorexia</td>
</tr>
<tr>
<td></td>
<td>Psychiatric disorders</td>
<td>Confusional state</td>
</tr>
<tr>
<td></td>
<td>Nervous system disorders</td>
<td>Dizziness, dyseaesthesia(^3), hyperaesthesia(^3), paraesthesia, somnolence, headache, hypertonia, neuralgia(^3)</td>
</tr>
<tr>
<td></td>
<td>Eye disorders</td>
<td>Conjunctivitis</td>
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<tr>
<td></td>
<td>Ear and labyrinth disorders</td>
<td>Vertigo(^3)</td>
</tr>
<tr>
<td></td>
<td>Vascular disorders</td>
<td>Hypotension</td>
</tr>
<tr>
<td></td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Bronchitis, dyspnoea, rhinitis</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal disorders</td>
<td>Dyspepsia(^3), flatulence(^3)</td>
</tr>
<tr>
<td></td>
<td>Skin and subcutaneous tissue disorders</td>
<td>Alopecia, hyperhidrosis</td>
</tr>
<tr>
<td></td>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Back pain</td>
</tr>
<tr>
<td></td>
<td>Renal and urinary disorders</td>
<td>Renal failure acute</td>
</tr>
<tr>
<td></td>
<td>Reproductive system and breast disorders</td>
<td>Balanoposthitis, prostates, vulvovaginal discomfort(^3)</td>
</tr>
<tr>
<td></td>
<td>General disorders and administration site conditions</td>
<td>Chest pain, oedema peripheral, granuloma(^2)</td>
</tr>
<tr>
<td></td>
<td>Investigations</td>
<td>Prostatic specific antigen increased, weight decreased</td>
</tr>
</tbody>
</table>

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, lymphnodes, peritoneum, prostate

3 Only isolated cases reported during post-marketing surveillance.
Description of selected adverse reactions

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 and/or sepsis after a period of fever and malaise during which symptoms progressively increase. Patients with symptoms of therapy-induced systemic BCG infection should be adequately treated with anti-tuberculosis agents according to treatment schedules used for tuberculosis infections. In these cases, further treatment with Tice BCG is contraindicated.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Overdosage occurs when more than one vial of OncoTICE is administered per instillation. In case of overdosage, the patient should be closely monitored for signs of systemic BCG infection and if necessary treated with tuberculostatic agents.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS, IMMUNOSTIMULANTS, ATC code: L 03AX03

Mechanism of action

OncoTICE is an immunostimulating agent. It 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.

5.2 Pharmacokinetic properties

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.

5.3 Preclinical safety data

No remarkable results.
6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
- lactose
- asparagine
- citric acid (E330)
- potassium phosphate (dibasic)
- magnesium sulphate
- iron ammonium citrate
- glycerin (E422)
- ammonium hydroxide (E527)
- zinc formate

6.2 Incompatibilities
OncoTICE is incompatible with hypotonic and hypertonic solutions. OncoTICE should only be mixed with physiological saline as described under Section 4.2 Dose and method of administration. Other incompatibility studies have not been performed.

6.3 Shelf life
12 months.

6.4 Special precautions for storage
Vials with freeze-dried OncoTICE must be stored at a temperature between 2-8°C and protected from light.

OncoTICE has a shelf-life of 12 months, provided it is stored under the prescribed conditions (see above). The date printed on the carton and the label of the vial is the expiry date; this is the date up to which OncoTICE can be used.

No preservatives have been added.
In-use stability of the reconstituted product has been demonstrated for 2 hours at 2-8°C protected from light. From a microbiological point-of-view, unless the method of opening/reconstitution/dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.5 Nature and contents of container

Package Quantities
Type 1 glass vials.
Packaging with 1 vial of 2ml containing approximately 2-8 × 10^8 CFU of Tice BCG in freeze-dried form. Packaging with 3 vials of 2ml each containing approximately 2-8 × 10^8 CFU of Tice BCG in freeze-dried form.
Packaging with 6 vials of 2ml each containing approximately 2-8 × 10^8 CFU of Tice BCG in freeze-dried form.
Composition

OncoTICE is a freeze-dried preparation containing attenuated bacilli of Mycobacterium bovis, prepared from a culture of Bacillus of Calmette-Guerin (BCG, strain Tice). The culture medium from which the freeze-dried cake is prepared has the following relative composition: lactose 150 gram, Sauton medium 250ml and water 750ml. The freeze-dried BCG preparation is delivered in sealed glass vials, each containing approximately 2-8 × 10⁸ colony forming units (CFU) of Tice BCG. After reconstitution in 50ml saline the suspension contains 0.4-1.6 × 10⁷ CFU/ml. No preservatives have been added.

6.6 Special precautions for disposal and other handling

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.

This is an infectious agent. Take appropriate care during preparation and instillation. Wear mask and gloves. Do not expose to open cuts or sores. Discard all equipment used, including gloves, syringes and catheters, into a suitable infectious waste container.

Perform the following procedures under aseptic conditions:

Reconstitution

Option A:
Add 1ml of a sterile physiological saline 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 homogeneous suspension is obtained. (Caution: avoid forceful agitation).

Preparation of the solution for instillation

Dilute the reconstituted suspension in sterile physiological saline up to a volume of 49 ml. Rinse the empty vial with 1ml of sterile physiological saline.
Add the rinse fluid to the reconstituted suspension for a final volume of 50ml. Mix the suspension carefully.
The suspension is now ready for use; it contains a total of 2-8 × 10⁸ CFU of Tice BCG.

Option B:
Aseptic conditions are not necessary if OncoTICE is reconstituted and administered using a closed reconstitution system such as M.E.R.C.I.
7 MEDICINE SCHEDULE
Prescription Medicine.

8 SPONSOR
Merck Sharp & Dohme (New Zealand) Ltd
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Auckland 1149
NEW ZEALAND
Tel: 0800 500 673

9 DATE OF FIRST APPROVAL
05 September 1991

10 DATE OF REVISION OF THE TEXT
24 August 2023

SUMMARY TABLE OF CHANGES

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<thead>
<tr>
<th>Section changed</th>
<th>Summary of new information</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Addition of Company Copyright Statement</td>
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</table>

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