

1. NAME OF THE MEDICINAL PRODUCT

OncoTICE[®], powder for instillation fluid for intravesical use containing 2-8 x 10⁸ 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 x 10⁸ colony forming units (CFU). After reconstitution in 50 ml saline the suspension contains 0.4-1.6 x 10⁷ CFU/ml.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Powder for instillation fluid for intravesical use.

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 T_A (grade 2 or 3) or T₁ (grade 1, 2 or 3). OncoTICE is only recommended for stage T_A grade 1 papillary tumors, when there is judged to be a high risk of tumor recurrence.

4.2 Posology and method of administration

For preparation of the OncoTICE suspension see section 6.6.

DOSAGE

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

ADMINISTRATION

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

Connect the 50 ml syringe containing the prepared OncoTICE suspension to the catheter, and instill the suspension into the bladder. After instillation 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

- 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.
- 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 like streptomycin, para-aminosalicylic acid (PAS), isoniazid (INH), rifampicin and ethambutol.
- Impaired immune response irrespective of whether this impairment is congenital or caused by disease, drugs or other therapy.
- Positive HIV serology
- Pregnancy and lactation

4.4 Special warnings and precautions for use

- Before the first 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.
- 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 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 systemic 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.

- The use of OncoTICE may sensitize patients to tuberculin resulting in a positive reaction to PPD.
- Reconstitution, preparation and administration of the OncoTICE suspension should be performed under aseptic conditions.
- 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 OncoTICE could occur through self-inoculation, by dermal exposure through an open wound, or by inhalation or ingestion of OncoTICE suspension. OncoTICE 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.

4.5 Interaction with other medicinal products and other forms of interaction

OncoTICE is sensitive to most antibiotics and in particular to the routinely used anti-tuberculosis drugs like streptomycin, para-amino-salicylic acid (PAS), isoniazid (INH), rifampicin and ethambutol. Therefore the anti-tumor 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 "Contra-indications").

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

4.6 Pregnancy and lactation

OncoTICE instillation for the treatment of carcinoma of the bladder is contra-indicated during pregnancy and lactation (see section 4.3).

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

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-tumor activity of the BCG. In most cases, the symptoms disappear within two days after instillation and the cystitis does not require treatment. During maintenance treatment with BCG, the symptoms of cystitis may be more pronounced and prolonged. In these cases, when severe symptoms are present, isoniazid (300 mg 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). 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.

Table 1 Side effects reported during post-marketing surveillance

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
	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

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

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. 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 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 Tice BCG is contraindicated.

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 anti-tuberculosis drugs.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

OncoTICE is an immunostimulating agent (ATC code L 03AX03). It has anti-tumor activity, but the exact mechanism of action is not known. Study data suggest that an active nonspecific immune response takes place. BCG invokes a local inflammatory response involving a variety of immune cells, such as macrophages, natural killer cells and T cells.

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 in section 6.6. Other incompatibility studies have not been performed.

6.3 Shelf life

OncoTICE has a shelf-life of 12 months, provided it is stored under the prescribed conditions (see Special precautions for storage). 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.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

OncoTICE is packed in Type I glass vials.

OncoTICE is available in packagings of 1 vial or 3 vials each containing 2-8 x 10⁸ CFU Tice BCG.

It is possible that one or more of these presentations are not available in this country.

6.6 Instructions for use and handling and disposal

OncoTICE contains live, attenuated mycobacteria. Because of the potential risk for transmission, it should be prepared, handled and disposed of as a biohazard material (see section 4.4).

Perform the following procedures under aseptic conditions :

Reconstitution

Add 1 ml of a sterile physiological saline solution by means of a sterile syringe to the contents of 1 vial of OncoTICE and 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

Transfer the reconstituted suspension from the vial into a sterile 50 ml syringe. Rinse the empty vial with 1 ml of sterile physiological saline. Add the rinse fluid to the reconstituted suspension in the 50 ml syringe.

Finally dilute the contents of the 50 ml syringe (1 ml OncoTICE + 1 ml rinse fluid) by adding sterile physiological saline solution up to a total volume of 50 ml. Mix the suspension carefully. The suspension is now ready for use; it contains a total of $2-8 \times 10^8$ CFU.

7. **MARKETING AUTHORISATION HOLDER**

8. **MARKETING AUTHORISATION NUMBER(S)**

9. **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

10. **DATE OF REVISION OF THE TEXT**
April 2004