OncoTICE®
Powder for solution for instillation

1. NAME OF THE MEDICINAL PRODUCT

OncoTICE®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

OncoTICE BCG containing 2-8 x 10^8 CFU Tice BCG per vial.

After reconstitution in 50 ml saline the suspension contains 0.4-1.6 x 10^7 CFU/ml.
OncoTICE is a freeze-dried preparation containing attenuated bacilli of Mycobacterium bovis, prepared from a culture of Bacillus Calmette-Guérin (BCG).
For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for instillation

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 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.
Posology
The contents of one vial of **OncoTICE**, reconstituted and diluted as indicated, 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 “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. Treatment should also be delayed in cases of gross haematuria. Delay in treatment should be considered in cases of major bladder irritability.

Maintenance treatment
Maintenance 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.

Method of administration
Intravesical instillation
Insert a catheter via the urethra into the bladder and drain the bladder completely.
Connect the 50ml syringe containing the prepared **OncoTICE** suspension to the catheter, and instill the suspension into the bladder. If a closed-system transfer device is not available, the 50 ml **OncoTICE** suspension is instilled into the bladder by gravity flow. 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 case of a

bed-ridden patient, should be turned over from back to abdomen and vice versa every 15 minutes. 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 must not ingest any fluid for a period starting 4 hours prior to instillation, until bladder evacuation is permitted (i.e. 2 hours after instillation).

4.3 Contra-indications

Hypersensitivity to the active substance (Tice BCG) or to any of the excipients listed in section 6.1.

Urinary tract infections. Therapy with **OncoTICE** should be interrupted until the bacterial culture from urine becomes negative and 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.

In patients with a positive Tuberculin test, **OncoTICE** instillations are contra-indicated only if there is supplementary medical evidence for an active tuberculous infection.

Treatment with anti-tuberculosis drugs like streptomycin, para-amino-salicylic 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 special precautions for use

Before the first intravesical instillation of **OncoTICE**, a Tuberculin test (PPD) should be performed. If the test is positive, **OncoTICE** instillations are contraindicated only if there is supplementary medical evidence for an active tuberculous infection.

Traumatic catheterisation or other injuries to the urethra or bladder mucosa can promote systemic BCG infection. Administration of **OncoTICE** should be delayed 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 or 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 sensitise patients to tuberculin resulting in a positive reaction to PPD.

Reconstitution and 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 with paper towels soaked with tuberculocidal disinfectant, such as household bleach, 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.

4.5 Interaction with other medicinal products and other forms of interaction

Tice BCG 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-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 "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-tumour efficacy and should therefore not be used in combination with **OncoTICE**.

4.6 Pregnancy and lactation

OncoTICE instillation for carcinoma of the bladder is contraindicated during pregnancy and lactation (see section 4.3).

4.7 Effects on ability to drive and use machines

Not relevant

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-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 (300 mg daily) and analgesics can be given until disappearance of symptoms.

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

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 localised irritative toxicicities that often reflect hypersensitivity reactions and be treated symptomatically. These symptoms usually appear within 4 hours after instillation and last for 24 to 48 hours. Fever higher than 39ºC 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^{O}C that does not resolve

within 12 hours despite antipyretic therapy must be considered as systemic BCG-infection, necessitating clinical confirmatory diagnostics and treatment.

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 drugs 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 medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il

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 03-AX03).
It has anti-tumor 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

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.

5.3 Preclinical safety data

As a result of the wide clinical application of BCG vaccination in the preceding decades the risks of BCG in human subjects are well-characterised. Intra-vesical administration to dogs has been found to be safe and without significant toxicity. No evidence of birth defects, genetic damage or carcinogenecity in humans are available from the extensive adverse reaction literature of BCG used as a vaccine.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
L-Asparagine monohydrate
Citric acid monohydrate
Potassium phosphate dibasic
Magnesium sulfate heptahydrate
Iron ammonium citrate
Glycerin
Zinc formate

Ammonium hydroxide

6.2 Incompatibilities

OncoTICE is incompatible with hypo 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

The expiry date of the product is indicated on the packaging materials. 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

Store at 2-8ºC, protect from light.

6.5 Nature and contents of containers

2 ml Type 1 glass vials in packs of 1 and 3.
Not all pack sizes may be marketed.

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 (see section 4.4).

Perform the following procedures under aseptic conditions using sterile physiological saline solution as the diluent and suitable techniques to ensure protection of the health care worker. The use of closed-system transfer device products may be considered when transferring **OncoTICE** from primary packaging to instillation equipment.

Reconstitution
Transfer 50ml of the diluent into a sterile container and add 1ml from the sterile container to the vial. Ensure that the needle is inserted through the center of the rubber stopper Allow to stand for a few minutes then gently swirl until a homogenous suspension is obtained. Forceful agitation should be avoided.

Preparation of the solution for instillation
Transfer the reconstituted contents of the vial back into the container. Rinse the vial by transferring 1ml from the container back into the vial, then add back to the container. If a closed-system transfer device is not available, dilute the reconstituted 1ml suspension in sterile physiological saline up to a volume of 49ml. Then 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, with a total volume of 50ml is now ready for instillation; it contains a total of 2-8 x 10^8 CFU of Tice BCG.

7 MANUFACTURER
Organon N.V., Oss, The Netherlands.

8 MARKETING AUTHORIZATION HOLDER
Merck Sharp & Dohme (Israel-1996) Company Ltd, P.O.Box 7121, Petah-Tikva 49170

9 REGISTRATION NUMBER
103-18-28561

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