OncoTice® BCG

1. Trade name of the medicinal product
OncoTICE

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 glass sealed ampoules or vials, each containing approximately 5 x 10^8 colony forming units (CFU). No preservatives have been added.

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 of the bladder (CIS) 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 1, 2 or 3) or T1, (grade 1, 2 or 3).

4.2 Dosage and method of administration

Reconstitution, preparation and administration of the OncoTICE-suspension
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 ampoule/vial of OncoTICE and allow to stand for a few minutes.

Then gently swirl the ampoule/vial until a homogeneous suspension is obtained. (Caution: avoid forceful agitation).

Preparation of the solution for instillation
Transfer the reconstituted suspension from the ampoule/vial into a sterile 50 ml syringe. Rinse the empty ampoule/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 approximately 5 x 10^8 CFU.

4.3 Contra-indications
• impaired immune response irrespective of whether this impairment is congenital or caused by disease, drugs or other therapy.
• positive HIV serology.
• pregnancy and lactation.
• positive tuberculin reaction in conjunction with clinical evidence of existing active tuberculosis.
• 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 tuberculostatic chemotherapeutics like streptomycin, para- amino-salicylic acid (PAS), isoniazide (INH), rifampicin and ethambutol.

4.4 Special warnings and special 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.
• Contamination with Tice BCG by spilling of the OncoTICE suspension should be avoided.
• Before the first instillation of OncoTICE, a tuberculin test should be performed. In case this test is positive, the intravesical instillation of OncoTICE is contra-indicated only if there is supplementary medical evidence for an active tuberculous infection.
Common side effects of intravesical BCG instillation are:

• Frequency and urgency of micturation and dysuria. In most patients these symptoms develop from the second or third instillation onwards.

The cystitis and typical 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-tumor activity of the BCG instillation. In most cases, the symptoms disappear within two days after instillation and the cystitis does not require treatment.

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

Complications other than the abovementioned inflammatory symptoms are far less frequent and among these the three most common are:

• Fever higher than 39°C. The fever typically resolves within 24 to 48 hours 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.

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

• Systemic BCG infections due to traumatic catheterisation, bladder perforation or early 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.

4.5 Interactions with other medicaments and other forms of interaction

OncoTICE is sensitive to the most antibiotics and in particular to the routinely used tuberculostatic chemotherapeutics like streptomycin, para-amino-salicylic acid (PAS), isoniazide (IHN), rifampicin and ethambutol. It is unknown whether interactions occur during the intravesical instillation of OncoTICE, or whether these interactions result in a clinically relevant reduction of the multiplication activity of Tice BCG. Therefore it is unclear whether the anti-tumour activity of OncoTICE is influenced by concomitant therapy with antibiotics. If a patient is being treated with an antibiotic it should be considered to postpone the intravesical instillation until the end of the antibiotic-treatment (see also ‘Contra-indications’).

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

4.6 Use during pregnancy and lactation

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

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 Side 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.

• Traumatic catheterisation can promote systemic BCG infection. It is recommended to delay OncoTICE administration in such patients until mucosal damage has been healed.

• In patients with known risk factors for HIV infection, it is recommended to perform adequate HIV assays prior to therapy.

• In order to protect the partner, it is recommended to refrain from intercourse within one week after OncoTICE instillation, or to use a condom.

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Patients with 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 Tice BCG is contraindicated.

- Granulomatous prostatitis.

In rare cases, arthritis/arthralgia, major haematoria, 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. In most cases of arthritis, arthralgia and skin rash, these can be attributed to hypersensitivity reactions of the patient to BCG.

4.9 Overdosage

Overdosage occurs when more than one ampoule/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.

5. Pharmacological properties

5.1 Pharmacodynamic properties

In patients with flat urothelial cell carcinoma in situ of the bladder it has been demonstrated that the intravesical instillation of OncoTICE can accomplish a macroscopically observable and histologically establishable remission of the carcinoma.

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
potassium phosphate (dibasic)
magnesium sulphate
iron ammonium citrate
glycerin
ammonium hydroxide
zinc formate

6.2 Incompatibilities

OncoTICE is incompatible with hypotonic and hypertonic solutions.

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 mentioned on the carton and on the label of the ampoule or vial is the expiry date; this is the date up to which OncoTICE may be used.

After reconstitution and dilution, the solution can be stored for a maximum of 2 hours when refrigerated at 2–8°C and protected from light.

6.4 Special precautions for storage

Ampoules/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

Packaging with 1 ampoule/vial of OncoTICE containing approximately 5 x 10^8 CFU Tice BCG.

Packaging with 3 ampoules/vials of OncoTICE each containing approximately 5 x 10^8 CFU Tice BCG.

Packaging with 6 ampoules/vials of OncoTICE each containing approximately 5 x 10^8 CFU Tice BCG.

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

6.6 Instructions for use/handling

For instructions for use, see ‘Dosage and method of administration’.
7. Date of revision
December 1999