PROFESSIONAL INFORMATION

SCHEDULING STATUS

S2

1 NAME OF THE MEDICINE

VesiCulture freeze-dried powder for reconstitution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of live VesiCulture contains a semi-dry mass of 30 mg *Mycobacterium bovis* BCG, Danish strain 1331 with approximately 2,5 x 10^8 CFU. It also contains 40 mg sodium glutamate.

There is no bactericidal or bacteriostatic agent present.

Sugar free.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Freeze-dried powder for reconstitution.

Brown glass vials containing a white to off-white freeze-dried powder.

Reconstituted product: slightly opaque and colourless suspension.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

VesiCulture is intended for instillation in the urinary tract after transurethral resection, as immunoprophylaxis in primary or recurrent grade Ta or T1 superficial bladder cancer, or for immunotherapy treatment of non-invasive carcinoma *in-situ* of the bladder.

4.2 Posology and method of administration

Posology

The recommended dose for immunotherapy or immunoprophylaxis is 120 mg, or

approximately 1 x 10^9 CFU. This dose should not be exceeded.

Seven to fourteen days should elapse after a transurethral section, bladder biopsy, or traumatic catheterisation before initiating treatment with VesiCulture.

The standard schedule of treatment consists of 6 installations, with an interval of one week between each instillation. This treatment schedule may be repeated once if insufficient or no response is achieved after the first immunotherapy treatment. Maintenance treatment may be recommended for certain high risk patients.

Intravesical dosage: The required dosage of VesiCulture, (normal dose = 120 mg = 4 reconstituted vials) is resuspended in 50 ml sterile saline (preservative free 0,9 % sodium chloride).

Method of administration

FOR INTRALUMINAL URINARY TRACT USE ONLY

Must not be administered intravenously, subcutaneously or intramuscularly.

The VesiCulture should not be prepared in the same sterile area as chemotherapeutic agents due to the possible iatrogenic transmission of BCG to these agents.

Aseptic conditions are necessary and care must be taken in order to properly resuspend clusters of freeze-dried bacteria. Using a disposable syringe add approximately 2-3 ml sterile saline to the first vial.

GENTLY release/push back the plunger to thoroughly resuspend the living BCG CULTURE. Each vial must be carefully inverted a few times, then gently swirled (AVOID VIGOROUS SHAKING) before being transferred to a syringe. Transfer the contents of the vial to a 50 ml syringe. Repeat for vials 2, 3 and 4. Add a further volume of the sterile saline, until the total volume is 50 ml. The suspension should be homogenous, and slightly cloudy. The suspension must be prepared shortly before use (less than 4 hours) and should not be exposed to light.

Aseptic insertion of a urethral catheter must be performed atraumatically to avoid damage to the surface of the urethra and bladder. Treatment with VesiCulture must be postponed if the

urothelium becomes traumatised during catheterisation, as a lesion in the urothelium increases the risk of systemic BCG infection. Only small quantities of lubricants should be used during catheterisation as large quantities may inhibit BCG viability.

The 50 ml BCG CULTURE is slowly instilled into the empty bladder, taking care never to force the flow. At the end of instillation, the catheter is removed, and the patient is instructed to retain the suspension in the bladder for 2 hours, if possible. (Restrictions of fluid intake 3 – 6 hours prior to and during the instillation may be recommended for patients with a limited bladder capacity). As BCG CULTURE is not a biohazardous material, the suspension may be voided in a normal manner, and no special precautions are necessary.

Paediatric population

There is no experience in treatment of children.

4.3 Contraindications

- Hypersensitivity to *Mycobacterium bovis* BCG or any of the excipients of VesiCulture (see section 6.1)
- Clinically verified or suspected active tuberculosis. Active tuberculosis should be excluded in patients with a positive Mantoux test before they begin treatment with VesiCulture.
- Treatment with anti-tuberculosis medicines such as isoniazid, rifampicin and ethambutol.
- Reduced immune response, including active HIV disease, regardless of whether congenital or triggered by illness, medication or other treatment, e.g. high dose systemic corticosteroid therapy.
- Pregnancy and breastfeeding.
- Medical history including radiation therapy of the bladder.

4.4 Special warnings and precautions for use

Treatment with VesiCulture should only be carried out by doctors with special expertise in

malignant illnesses and their treatment.

VesiCulture may only be used for instillation in the bladder. VesiCulture must not be used for BCG vaccination. A Mantoux test should be performed prior to intravesicular instillation. If the test is positive, VesiCulture is contraindicated if there is any further medical evidence of active tuberculosis infection.

Urinary tract infection should be ruled out prior to every bladder instillation of VesiCulture (inflammation of the mucous membranes of the bladder can increase the risk of haematological spread of BCG). If a urinary tract infection is diagnosed during VesiCulture treatment, treatment should be discontinued until a negative urine culture is achieved and treatment with antibiotics and/or antiseptics has been discontinued.

Immunotherapy with VesiCulture should be postponed in patients with a urinary tract infection, or unexplained fever, until a negative urine culture is obtained, and treatment with antibiotics and/or antiseptics has ceased.

Macroscopic haematuria: Such cases are considered signs of mucous membrane lesions in the urinary tract; treatment should therefore be stopped or deferred until haematuria has been completely treated or has been spontaneously resolved.

Damage to the urethra or mucous membranes of the bladder, e.g. when triggered by traumatic catheterisation, may result in systemic BCG infection in conjunction with treatment with VesiCulture. Treatment should be deferred until the mucous membranes have healed. Traumatic instillation can result in BCG septicaemia reactions, potentially accompanied by septic shock and fatality.

Infection of implants and transplants has been reported after treatment with BCG bladder irrigation in patients with, for example, aneurysm or prosthesis. Patients should be monitored for presence of symptoms of systemic BCG infection and toxic symptoms after each bladder irrigation.

It is recommended to screen patients who may be HIV-positive prior to initiating treatment. In order to protect the patient's partner, it is recommended that the patient either abstain from intercourse for one week after bladder irrigation or use a condom.

Use of VesiCulture may sensitise patients to tuberculin, which will result in a positive Mantoux test.

The risk of bladder contraction may increase in patients with low bladder capacity.
In patients with tissue type HLA-B27, presence of reactive arthritis or Reiter’s syndrome may increase.

Spillage of VesiCulture can cause BCG contamination. Any spilt VesiCulture must therefore be covered with paper wetted with hospital disinfectant or 10 % chloramine solution for at least 10 minutes. All waste materials must be disposed of as potentially hazardous waste.

Personnel may be exposed to BCG through self-inoculation, such as on the skin through an open wound, through inhalation or through ingestion of VesiCulture. Exposure to BCG has no health consequences for healthy individuals. If there is any suspicion of self-inoculation, it is recommended to carry out a Mantoux test on the skin immediately and then again 6 weeks later.

Patients with reduced immune response should avoid contact with patients being treated with BCG.

4.5 Interaction with other medicines and other forms of interaction

VesiCulture is sensitive to most antibiotics (see BCG strain's sensitivity to antibiotics in section 4.8). The effect of VesiCulture may be affected by simultaneous treatment with antibiotics. If the patient is being treated with antibiotics, it is recommended to defer bladder irrigation until the antibiotic treatment is completed (see also section 4.3).

Immunosuppressants, bone marrow suppressants and/or radiation therapy may ffect immune response and thereby also the therapeutic effect of VesiCulture. These types of medications should therefore not be used in combination with VesiCulture.

Medicines with known anti-mycobacterial action should not be co-administered with VesiCulture. These include common anti-tuberculosis medicines as well as amino glycosides and fluoroquinolones.

4.6 Fertility, pregnancy and lactation

Pregnancy

VesiCulture is contraindicated during pregnancy (see section 4.3).

Breastfeeding

VesiCulture is contraindicated during breastfeeding (see section 4.3).

4.7 Effects on ability to drive and use machines

VesiCulture has minor or moderate influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

Toxicity and undesirable effects appear to be directly related to the cumulative quantity of CFU of BCG given in a treatment course. Treatment results in cystitis and inflammatory reactions (granulomas), resulting in pollakiuria and dysuria in approx. 90 % of patients. These reactions are probably an essential part of BCG's anti-tumour activity. These symptoms usually subside

within 2 days after instillation and do not require treatment. During the course of treatment, cystitis symptoms may become more pronounced and persistent. Episodes of severe symptoms may be treated with isoniazid 300 mg daily and analgesics until symptoms have subsided.

Common (≥ 1/100 to < 1/10) undesirable effects include general malaise, low to moderate fever and/or influenza-like symptoms (fever, stiffness, malaise and muscle pain). Symptoms usually appear within 4 hours after instillation and last 24 - 48 hours. Fever above 39 °C usually disappears within 24 - 48 hours when the patient is treated with antipyretics (preferably paracetamol) and fluids. It is often difficult to differentiate uncomplicated fever reactions from early symptoms of a systemic BCG infection, where anti-tuberculosis treatment is indicated. Fever over 39 °C that does not subside within 12 hours despite antipyretic treatment should be considered a systemic BCG infection, which necessitates clinical diagnosis and treatment.

b. Tabulated summary of adverse reactions

Very common (≥ 1/10), Common (≥ 1/100 to < 1/10), Rare (≥ 1/10,000 to < 1/1,000), Very rare (< 1/10,000)

MedDRA system organ class	**Frequency**	**Adverse reactions**
Infections and infestations	Common	Cystitis[1].
	Rare	Orchitis.
	Very rare	Systemic BCG infections[2].
Skin and subcutaneous tissue disorders	Rare	Cutaneous rash.

MedDRA system organ class	**Frequency**	**Adverse reactions**
Musculoskeletal and connective tissue disorders	Rare	Arthritis/arthralgia.
Renal and urinary disorders	Very common	Pollakiuria.
	Common	Inflammation of the mucous membranes of the bladder.
	Rare	Macroscopic haematuria, temporary urethral obstruction.
	Very rare	Bladder contraction.
Reproductive system and breast disorders	Rare	Granulomatous prostatitis.
General disorders and administration site conditions	Common	Malaise, subfebrile, influenza-like symptoms.
	Uncommon	Fever > 39 °C.

[1] During maintenance treatment, cystitis symptoms can become pronounced and long-term. In the event of pronounced symptoms, treatment with anti-tuberculosis medicines may be indicated.

[2] Systemic BCG infections are very rare, but may be seen after traumatic catheterisation, bladder perforation, overdose or premature BCG instillation after extensive transurethral resection of urothelial cell carcinoma. Systemic BCG infection may manifest as pneumonia, hepatitis and/or cytopenia after a period of fever and malaise during which symptoms worsen. Patients with symptoms of systemic BCG infection should be treated with anti-tuberculosis medicines in accordance with applicable treatment schedules for tuberculosis infections. In such cases, further treatment with VesiCulture is contraindicated.

Guidance from a specialist should always be sought concerning correct treatment of systemic infections or persistent local infections as a result of treatment with VesiCulture.

BCG strain sensitivity to antibiotics

There is no official definition concerning the sensitivity of BCG Danish strain 1331 to anti-tuberculosis medicines. Accordingly, the definition for Mycobacterium tuberculosis is used. Isoniazid's MIC for BCG Danish strain 1331 is 0,4 mg/L, per Bactec 460. It has not been established whether *M. bovis* BCG can be classified as sensitive, intermediately sensitive or resistant to isoniazid, when MIC is 0,4 mg/L, but on the basis of the criteria for *Mycobacterium tuberculosis* the strain can be considered to be intermediately sensitive to isoniazid and completely sensitive to streptomycin, rifampicin and ethambutol. BCG Danish strain 1331 is resistant to pyrazinamide.

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

The risk of BCG infection is expected to increase in the event of an overdose. If an overdose takes place, the patient should be observed for symptoms of systemic BCG infection and, if necessary, treated with anti-tuberculosis medicines (see section 4.8).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A.30.1 Biologicals – Antigen

Pharmacotherapeutic group: L 03 AX 03 – BCG vaccine, other immune stimulants

The effect of BCG immune therapy is attributed to various immunological and inflammatory reactions that have not all been fully described.

Intravesical BCG suspension produces a granulomatous response locally and in regional lymph nodes; the inflammatory response stimulates production of macrophages that have tumoricidal effects. However, the relationship of these effects to the antineoplastic effect of BCG is unknown.

It has been clinically demonstrated that immune therapy with VesiCulture reduces recurrence – and presumably also progression – of superficial bladder cancer.

5.2 Pharmacokinetic properties

No relevant data available.

5.3 Preclinical safety data

No relevant data available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Monosodium glutamate (E621).

6.2 Incompatibilities

VesiCulture must not be mixed with other medicines except those mentioned in section 6.6.

6.3 Shelf life

36 months.

The resuspended solution may be kept for 4 hours at room temperature, protected from light.

VesiCulture will deteriorate when exposed even for short periods to direct sunlight and diffuse daylight (also indoors).

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).

Store in the original package in order to protect from light.

For storage condition of the resuspended solution, see section 6.3.

6.5 Nature and contents of container

Packs of four 4 ml brown glass vials closed with grey rubber stoppers capped with an aluminium overseal, each containing 30 mg of VesiCulture.

6.6 Special precautions for disposal and other handling

Must not be mixed with other medicines except isotonic saline.

Any unused VesiCulture or waste material should be disposed of in accordance with local requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Kahma Biotech (Pty) Ltd.

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South Africa

8 REGISTRATION NUMBER

32/30.1/0745

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 13 May 2006

10 DATE OF REVISION OF THE TEXT

25 April 2018