Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Vesiculture, 30 mg/vial, powder for intravesical suspension.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Mycobacterium bovis BCG (Bacillus Calmette-Guérin), Danish strain 1331, live attenuated, 30 mg/vial.
After reconstitution, 1 dose (4 vials) contains 120 mg corresponding to 1-14 x 10^8 CFU.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for intravesical suspension.
White, clumped powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Treatment of primary/recurrent flat urothelial cell carcinoma in situ of the bladder in adults.
- Adjuvant treatment after transurethral resection of primary or recurrent superficial urothelial cell carcinoma of the bladder in adults with intermediate or higher risk disease.

4.2 Posology and method of administration

Treatment with Vesiculture shall be managed by healthcare professionals experienced in intravesical instillation with BCG.

Vesiculture is intended for intravesical instillation following reconstitution.

The recommended dose is 4 vials (120 mg in total), corresponding to 1-14 x 10^8 CFU, for all indications. The content of 4 vials is reconstituted in 50 mL sterile sodium chloride 9 mg/mL (0.9%) solution for injection, preservative-free.

Posology

Induction therapy
The BCG treatment is normally initiated at least 2 weeks after transurethral resection of the bladder (TURB) or biopsy and should be repeated at weekly intervals for 6 weeks. Treatment should not be started until mucosal lesions after TURB have healed.

Maintenance therapy
Maintenance therapy following induction therapy is recommended. Patients with intermediate to high-risk NMIBC should receive maintenance BCG therapy for 1 to 3 years after completing the initial BCG induction cycles.
The specific duration depends on the patient's risk profile, tolerability to the treatment and recorded therapeutic response. National recommendations should be followed.

Paediatric population
The safety and efficacy of Vesiculture in children has not been established. No data are available.

Method of administration
Vesiculture shall be administered by intravesical instillation.

A urethral catheter is inserted into the bladder under aseptic conditions. A sufficient quantity of lubricant should be used to avoid traumatising the urinary mucosa and to reduce the discomfort for the patient associated with the procedure. The bladder must be emptied before BCG instillation and the patient should not drink from 4 hours before the instillation and until 2 hours after the instillation. Complete draining of the bladder after catheterisation reduces residual lubricant which may have reached the bladder before Vesiculture is instilled.

The suspension is slowly instilledinto the empty bladder by means of the catheter, taking care not to force the flow. The catheter is removed once instillation is complete and the patient is instructed to retain the suspension in the bladder for 2 hours, if possible. During this period the suspension should have sufficient contact with the entire mucosal surface of the bladder. Therefore, the patient should not be immobilised. If bed-ridden, the patient should be turned over from back to abdomen and vice versa every 15 minutes. After 2 hours, the patient should void the instilled suspension in a sitting position.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

- Vesiculture should not be used in immunosuppressed patients or persons with congenital or acquired immune deficiencies, whether caused by:
    - concurrent disease e.g. HIV infection, leukaemia, lymphoma.
    - cancer therapy with e.g. systemic cytostatic medicinal products or radiation.
    - other immunosuppressive therapy, e.g. with systemic corticosteroids.
- Vesiculture should not be administered to persons with active tuberculosis. The risk of active tuberculosis must be ruled out by appropriate anamnesis and diagnostic tests according to local guidelines.
- Treatment with anti-tuberculosis medicines such as isoniazid, rifampicin, streptomycin and ethambutol.
- Pregnancy and breast-feeding.
- History of radiotherapy of the bladder.
- Acute urinary tract infection (see section 4.4).
- Damage to the urethra or mucous membrane of the bladder which might result in an increased risk of severe systemic infections (see section 4.4).

4.4 Special warnings and precautions for use

Treatment with Vesiculture should be carried out by doctors with special expertise in malignant illnesses in the bladder and their treatment.

Vesiculture shall only be used for instillation in the bladder and must not be used for subcutaneous, intradermal, intramuscular or intravenous administration, or for BCG vaccination.

<u>Severe systemic BCG-infections/reactions</u>

- Damage to the urethra or mucous membrane of the bladder (e.g. triggered by traumatic catheterization) may result in macroscopic haematuria. Treatment with Vesiculture is contraindicated in such cases as BCG infection and sepsis can develop. The treatment should be postponed until the mucous membranes have healed and haematuria has resolved.
- Urinary tract infection should be ruled out before each instillation since inflammation of the mucous membranes of the bladder can increase the risk of haematological spread of BCG. If a urinary tract infection appears during the course of treatment, treatment should be discontinued until a negative urine culture is achieved, and an eventual treatment with antibiotics has been discontinued.
- Patients should be monitored for presence of symptoms of systemic BCG infection after each treatment. The risk of systemic infection is higher in elderly patients and patients with hepatic and renal impairment. This should be considered before treatment with Vesiculture.

- Infection of implants and transplants has been reported after treatment with BCG in patients with e.g. aneurysm or prosthesis.

In case of a suspicion of a systemic infection a physician specialised in infectious diseases should be consulted. BCG-infection can potentially be fatal. For further information please refer to section 4.8.

Flare-up of latent BCG-infection (including delayed diagnosis)
Isolated cases of BCG persisting in the body for several years have been reported. These latent BCG infections can reappear years after the initial infection and can lead to granulomatous pneumonia, abscesses, infected aneurysms, and infection of an implant, graft, or surrounding tissue.
Patients should be warned of the possibility of late reactivation of latent BCG infection and advised on what to do if symptoms such as fever and unexplained weight loss occur.
If reactivation of latent BCG infection is suspected, a physician specializing in infectious diseases should be consulted.

BCG strain sensitivity to antibiotics.
Please see section 4.8.

Handling precautions

- Vesiculture should not be handled in the same room or by the same healthcare professionals preparing cytostatics.
- Vesiculture should not be handled by individuals affected by known immunodeficiencies.
- If a Closed System Transfer Device (CSTD) is not applied, see section 6.6, the reconstitution of the suspension should be performed under aseptic conditions.
- Self-inoculation of BCG can occur through open wounds, inhalation or ingestion of Vesiculture. Exposure to BCG is not expected to have health consequences for healthy individuals. However, in case of suspected self-inoculation, it is recommended to perform a Mantoux test immediately after exposure and after 6 weeks.
- Contact to skin or mucosa with Vesiculture should be avoided. Contamination can lead to a hypersensitivity reaction. Use appropriate skin disinfectant in case of contamination of skin lesions.

Spillage of BCG
Spillage of Vesiculture can cause BCG contamination. Therefore, spilled product must 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 contagious waste.

General hygiene for the patient
It is recommended to wash hands and genital area after micturition, especially after the first micturition following BCG instillation.

Tuberculin tests
Instillation of Vesiculture may sensitise patients to tuberculin after 6-8 weeks, resulting in a positive Mantoux test. Therefore, reactivity to tuberculin should be measured before administration of Vesiculture.

Low bladder capacity
The risk of bladder contraction may increase in patients with low bladder capacity.

HLA-B27
In patients with tissue type HLA-B27 the occurrence of reactive arthritis or Reiter's syndrome may be increased.

Patients with contact to immunosuppressed persons
Patients treated with Vesiculture should avoid contact with immunocompromised individuals.

Sexual transmission
To protect against possible BCG transmission, the patient should be recommended to avoid intercourse or use a condom during intercourse in the first week after treatment.

Traceability
To improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

4.5 Interaction with other medicinal products and other forms of interaction

Vesiculture is sensitive to most antibiotics, in particular to the routinely used anti-tuberculosis drugs like streptomycin, para-amino salicylic acid, isoniazid, rifampicin and ethambutol. Therefore, the anti-tumour activity of Vesiculture may be influenced by concomitant therapy with antibiotics. If the patient is in antibiotic treatment, intravesical instillation with Vesiculture should be deferred until the antibiotic treatment is completed (see also section 4.3).

Immunosuppressants, bone marrow suppressants and/or radiation therapy may affect the immune response and thereby also the therapeutic effect of Vesiculture. These types of medication and therapy should therefore not be applied during treatment with Vesiculture.

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

Not marked.
Undesirable effects of Vesiculture can have minor or moderate influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
The undesirable effects of intravesical treatment with Vesiculture, which can be local and systemic, are in general common but often mild and transient. Toxicity and side effects appear to be directly related to the cumulative number of colony forming units administered over the course of treatment. Approximately 90% of patients develop cystitis and inflammatory reactions, resulting in pollakiuria and dysuria. These reactions are probably related to anti-tumour activity of BCG. In most cases, these symptoms disappear within two days after instillation and do not require treatment. During maintenance treatment with BCG, the symptoms of cystitis may be more pronounced and prolonged. Episodes of severe symptoms may be treated with isoniazid 300 mg daily and analgesics until symptoms have subsided.

Very common (≥1/10) undesirable effects include general malaise, low to moderate fever and/or influenza-like symptoms (fever, stiffness, malaise and muscle pain). Such symptoms usually appear within 4 hours after instillation and lasting for 24-48 hours. Fever above 39°C usually disappears within 24-48 hours when the patient is treated with antipyretics and fluids. It is often difficult to differentiate uncomplicated fever reactions from early symptoms of a systemic BCG infection, in which anti-tuberculosis treatment is indicated. Fever above 39°C that does not subside within 12 hours despite antipyretic treatment could indicate a systemic BCG infection, which necessitates clinical diagnosis and treatment.

Tabulated list of adverse reactions
The adverse reactions listed below are based on data from clinical trials in adults and spontaneous reporting and are classified according to MedDRA System Organ Class.
The following adverse reactions classified by system and organ, according to the MedDRA classification, have been observed. Frequencies below are defined as: Very common (≥1/10), Common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (< 1/10,000) or not known (cannot be estimated from the available data).

System Organ Class	Frequency	Adverse reaction
Renal and urinary disorders	Very common (≥1/10)	Pollakiuria, macroscopic haematuria, dysuria, micturition urgency
	Common (≥1/100 to <1/10)	Inflammation of the mucous membranes of the bladder

	Rare (≥1/10,000 to <1/1,000)	Temporary urethral obstruction
	Very rare (<1/10,000)	Bladder contraction
Skin and subcutaneous tissue disorders	Common (≥1/100 to <1/10)	Cutaneous rash
Musculoskeletal and connective tissue disorders	Common (≥1/100 to <1/10)	Arthritis/arthralgia
Infections and infestations	Very common (≥1/10)	Cystitis
	Rare (≥1/10,000 to <1/1,000)	Orchitis
	Very rare (<1/10,000)	Systemic BCG infections
Gastrointestinal disorders	Very common (≥1/10)	Nausea
General disorders and administration site conditions	Very common (≥1/10)	Influenza-like symptoms (subfebrile, malaise and muscle pain)
	Common (≥1/100 to <1/10)	Fever > 39°C
Reproductive system and breast disorders	Rare (≥1/10,000 to <1/1,000)	Granulomatous prostatitis
	Common (≥1/100 to <1/10)	Epididymitis

Description of selected adverse reactions:
Systemic BCG infections may be caused by traumatic catheterisation, bladder perforation, overdose or premature BCG instillation after extensive transurethral resection of urothelial cell carcinoma. Systemic BCG infection may manifest as pneumonitis, hepatitis, cytopenia, vasculitis, infectious aneurysm and/or sepsis after a period of fever and malaise. BCG infection has also been observed in implants and surrounding tissue. Patients with symptoms of systemic BCG infection should be treated with anti-tuberculosis medicines in accordance with applicable guidance for treatment of tuberculosis infections (see *BCG strain sensitivity to antibiotics*). In such cases, further treatment with Vesiculture is contraindicated.
Systemic infections may occur months to years after the last dose, and patients should be advised to consult a physician if symptoms such as unexplained fever or weight loss appear.
Specialist guidance should always be sought concerning the appropriate 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.
The *minimum inhibitory concentration* (MIC) of isoniazid towards BCG Danish strain 1331 is 0.4 mg/L, as determined by Bactec 460 and Bactec MGIT. It has not been established whether *M. bovis* BCG can be classified as sensitive, intermediately sensitive or resistant to isoniazid, with a MIC of 0.4 mg/L, based on the criteria for *Mycobacterium tuberculosis,* however, the strain can be considered to have intermediate sensitivity to isoniazid. The strain is 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 medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via

HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

The risk of BCG infection may increase in the event of an overdose. In that case 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

Pharmacotherapeutic group: Other immunostimulants, BCG vaccine, ATC-code: L03AX03

Mechanism of action
A non-specific immunological pathway with various immunologic mechanisms is generally believed to be associated with BCG immunotherapy. Treatment with BCG as immunotherapy results in increased number of lymphocytes, macrophages, and

cytokines in the bladder epithelium, which have been demonstrated to play an important role in the anti-tumour effect of BCG immunotherapy. An inflammatory response in the bladder wall is believed to be a prerequisite for successful BCG treatment.

Clinical efficacy and safety
It has been clinically demonstrated that immune therapy with Vesiculture reduces recurrence of superficial bladder cancer.

Vesiculture has been used for the treatment of NMIBC since the 1980s. The data supporting the efficacy of Vesiculture are derived from systematic reviews and meta-analyses of the literature describing the efficacy and safety of BCG immunotherapy for various strains, including Danish strain 1331. These analyses have demonstrated the clinical efficacy of different BCG strains versus placebo or no treatment after transurethral resection of bladder tumour and have shown that intravesical instillation of BCG prevents tumour recurrence in NMIBC. They have also shown that patients treated with intravesical BCG, particularly when a maintenance schedule is added to the initial induction treatment, have higher recurrence-free survival and progression-free survival rates compared to patients treated with chemotherapy. The efficacy of the Danish strain 1331 has been investigated and demonstrated in seven clinical trials, including one randomized, controlled, phase 3 trial comparing Vesiculture with mitomycin-C. This open-label study randomized 261 patients with NMIBC in a 1:1 ratio to receive either Vesiculture 120 mg or intravesical mitomycin-C 40 mg. Both treatments were administered weekly for six weeks, then monthly for one year, and every three months for an additional year (two years in total).

Eligibility criteria included Ta/T1 tumours (WHO grade II) with ≥ 3 recurrences, T1 tumours (WHO grade III), primary or secondary dysplasia (WHO grade II), or primary or secondary carcinoma in situ (WHO grade III). See efficacy table 1 and 2 for results.

Table 1: Recurrence-free period for patients treated with Vesiculture or Mitomycin C 40 mg

	Vesiculture	Mitomycin C 40 mg
	N = 125	N = 125
Recurrence-free survival (median follow-up 39 months)	62 (49%) patients	43 (34%) patients
Recurrence-free survival (median follow-up 63 months)	58 (46%) patients	43 (34%) patients

Table 2: Recurrences for patients treated with Vesiculture or Mitomycin C 40 mg after a median follow-up of 63 months

	Vesiculture		Mitomycin C 40 mg	
	N = 125		N = 125	
Recurrence	67 (54%) patients		82 (66%) patients	
Papillary vs non-papillary cancer	Ta/T1	Cis+Dys	Ta/T1	Cis+Dys
	N = 84	N = 41	N = 83	N = 42
Recurrence	49 (58%) patients	18 (44%) patients	55 (66%) patients	27 (64%) patients

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.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

3 years.
Reconstituted product for intravesicular use: 4 hours.
In-use stability has been demonstrated for 4 hours at room temperature (20ºC ± 5ºC), protected from direct/diffused sunlight.
From a microbiological point of view, unless the method of reconstitution precludes the risk of microbial contamination, the product should be used immediately upon reconstitution.

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 conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Amber 4 mL vial (Ph. Eur. type I glass) with a bromobutyl rubber stopper treated with silicone oil and aluminium covered with a plastic cap. Each vial contains 30 mg powder.
Pack size: 4 x 30 mg.

6.6 Special precautions for disposal and other handling

Vesiculture is to be dissolved in sterile sodium chloride 9 mg/mL (0.9%) solution for injection, preservative-free, before use, and must not be mixed with other medicinal products.

Vesiculture contains live, attenuated mycobacteria and proper attention to avoid bacterial transmission should be exercised.
Reconstitution should be carried out under aseptic conditions.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Instructions for preparation of reconstituted product
For intravesical instillation, 4 vials of Vesiculture are resuspended in 50 mL sterile sodium chloride 9 mg/mL (0.9%) solution for injection, preservative-free, as follows:

1. Using a sterile syringe, transfer approximately 2-3 mL sterile sodium chloride 9 mg/mL (0.9%) solution for injection, preservative-free, to each of the 4 vials. If alcohol swabs are used for disinfection of the rubber stopper, the surface of the stopper must be completely dry before penetrating with the syringe.
2. Resuspend the content of each vial by carefully inverting it a few times, then swirl gently.
Do NOT shake.
3. Transfer the contents of the 4 vials to one single 50 mL syringe.
4. Draw additional sterile sodium chloride 9 mg/mL (0.9%) solution for injection, preservative-free, into the syringe until the total volume is 50 mL.

The suspension in the 50 mL syringe should be homogeneous, and slightly cloudy. The product should be used as soon as possible after reconstitution and within 4 hours. Avoid unnecessary exposure to light.
At the time of administration, the suspension should be swirled gently to homogenise.

A Closed System Transfer Device (CSTD) may be considered when reconstituting and transferring Vesiculture to the instillation equipment. Please refer to the instructions for use provided with the CSTD for a full description of the product reconstitution using CSTD.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA2160/005/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 30th January 2026

10 DATE OF REVISION OF THE TEXT