LÆGEMIDDELSTYRELSEN
DANISH MEDICINES AGENCY

**16 August 2019**

# SUMMARY OF PRODUCT CHARACTERISTICS

**for**

# BCG Culture 'SSI', powder for bladder irrigation

## 0. DANISH SPECIALITY NUMBER
8740

## 1. NAME OF THE MEDICINAL PRODUCT
BCG Culture 'SSI'

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION
*Mycobacterium bovis* BCG (Bacillus Calmette-Guérin), Danish strain 1331, live attenuated, 30 mg/vial.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM
Powder for bladder irrigation.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications
Treatment of primary/recurrent flat urothelial cell carcinoma *in situ* of the bladder.
Adjuvant treatment after transurethral resection of primary or recurrent superficial urothelial cell carcinoma of the bladder in stage $T_A$ or $T_1$, grade 1, 2 or 3.

### 4.2 Posology and method of administration
Dispensed in the form of freeze-dried instillation substance in vials. The content of 4 vials (= total of 120 mg) is usually instilled dissolved in 50 ml sterile isotonic unpreserved sodium chloride (saline) intravesically once every week for 6 weeks. Irrigation may be repeated where relevant.

Treatment is started 7 to 14 days after transurethral manipulation.

**Paediatric population:**
There is no experience in treatment of children.

## 4.3 Contraindications

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

- Active tuberculosis. Active tuberculosis should be excluded in patients with a positive Mantoux test before they begin treatment with BCG Culture 'SSI'.
- Treatment with anti-tuberculosis medicines such as isoniazid, rifampicin and ethambutol.
- Reduced immune response, regardless of whether congenital or triggered by illness, medications or other treatment.
- HIV infection.
- Pregnancy and breast-feeding.
- Medical history including radiation therapy of the bladder.
- Hypersensitivity to BCG or to any of the excipients.

## 4.4 Special warnings and precautions for use

Treatment with BCG Culture 'SSI' should only be carried out by doctors with special expertise in malignant illnesses and their treatment.

- BCG Culture 'SSI' may only be used for instillation in the bladder.
- BCG Culture 'SSI' must not be used for BCG vaccination.
- A Mantoux test should be performed prior to intravesicular instillation. If the test is positive, BCG Culture 'SSI' 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 BCG Culture 'SSI' (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 BCG treatment, treatment should be discontinued until a negative urine culture is achieved and treatment with antibiotics and/or antiseptics has been discontinued.
- 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 BCG Culture 'SSI'. 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 BCG Culture 'SSI' 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.

- Preparation and administration of bladder irrigation fluid must take place under antiseptic conditions.
- BCG Culture 'SSI' should not be handled in the same room or by the same personnel preparing cytostatics for intravenous administration.
- Spillage of BCG Culture 'SSI' can cause BCG contamination. Any spilt BCG Culture 'SSI' 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 BCG Culture 'SSI'. 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 medicinal products and other forms of interaction**

BCG Culture 'SSI' is sensitive to most antibiotics (see BCG strain's sensitivity to antibiotics in section 4.8). The effect of BCG Culture 'SSI' 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 affect immune response and thereby also the therapeutic effect of BCG Culture 'SSI'. These types of medications should therefore not be used in combination with BCG Culture 'SSI'.

**4.6 Fertility, pregnancy and lactation**

Pregnancy:
BCG Culture 'SSI' is contraindicated during pregnancy (see section 4.3).

Breastfeeding:
BCG Culture 'SSI' is contraindicated during breast-feeding (see section 4.3).

**4.7 Effects on ability to drive and use machines**

Not marked.
BCG Culture 'SSI' can, because of undesirable effects, have minor or moderate influence on the ability to drive and use machines.

**4.8 Undesirable effects**

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.

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| **Renal and urinary disorders**<br>Very common (≥1/10) | Pollakiuria. |
| Common (≥1/100 to <1/10) | Inflammation of the mucous membranes of the bladder. |
| Rare (≥1/10,000 to <1/1,000) | Macroscopic haematuria, temporary urethral obstruction. |
| Very rare (<1/10,000) | Bladder contraction. |
| **Skin and subcutaneous tissue disorders**<br>Rare (≥1/10,000 to <1/1,000) | Cutaneous rash. |
| **Musculoskeletal and connective tissue disorders**<br>Rare (≥1/10,000 to <1/1,000) | Arthritis/arthralgia. |
| **Infections and infestations**<br>Common (≥1/100 to <1/10) | Cystitis[1]. |
| Rare (≥1/10,000 to <1/1,000) | Orchitis. |
| Very rare (<1/10,000) | Systemic BCG infections[2]. |
| **General disorders and administration site conditions**<br>Common (≥1/100 to <1/10) | Malaise, subfebrile, influenza-like symptoms. |
| Rare (≥1/10,000 to <1/1,000) | Fever > 39°C. |
| **Reproductive system and breast disorders**<br>Rare (≥1/10,000 to <1/1,000) | Granulomatous prostatitis. |

[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 cytopoenia 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 BCG Culture 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 BCG Culture.

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 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:

Lægemiddelstyrelsen
Axel Heides Gade 1
DK-2300 København S
Websted: www.meldenbivirkning.dk
E-mail: dkma@dkma.dk

## 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).

## 4.10 Dispensing group

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# 5. PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacotherapeutic group

L 03 AX 03 – BCG vaccine, other immune stimulants

## 5.2 Pharmacodynamic properties

The effect of BCG immune therapy is attributed to various immunological reactions that have not all been fully described.
It has been clinically demonstrated that immune therapy with BCG Culture 'SSI' 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

Sodium glutamate monohydrate

## 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.
Ready-mixed solution for intravesicular use: 4 hours.

## 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.

## 6.5 Nature and contents of container

Vial (Ph. Eur. type I glass), 30 mg.
Pack size: 4 x 30 mg.

Not all pack sizes may be marketed.

## 6.6 Special precautions for disposal and other handling

Must not be mixed with other medicinal products except isotonic saline.

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

# 7. MARKETING AUTHORISATION HOLDER

AJ Vaccines A/S
5, Artillerivej
DK-2300 Copenhagen
Denmark

# 8. MARKETING AUTHORISATION NUMBER

14785

## 9. DATE OF FIRST AUTHORISATION

21 August 1995

## 10. DATE OF REVISION OF THE TEXT

16 August 2019