SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

CALGEVAX, powder for suspension
(BCG for immunotherapy)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

After reconstitution, each ampoule contains:
Live bacteria of Calmette and Guérin (Mycobacterium bovis BCG) – 11.25 mg
(37.5 mg semi-dry bacterial mass)
1.0 - 3.0 x 10^8 viable units
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for suspension
White lyophilized compact mass.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

INTRAVESICALLY:
- for prophylaxis of recurrences of the superficial tumors of the bladder after transurethral resection;
- for treatment of carcinoma *"in situ"* of the bladder.

PERCUTANEOUSLY:
- in the treatment of malignant melanoma,
- for non-specific adjuvant immunostimulating therapy of other newly emerged malignant growths (lung, breast cancer, acute leukemia, lymphosarcoma or osteosarcoma).

4.2. Posology and method of administration

4.2.1 Intravesical administration

CALGEVAX is administered at least 14 days after the performance of a biopsy, transurethral resection or traumatic catheterization of the bladder. The application of CALGEVAX should be done using aseptic equipment and under the control of an urologist, having experience in the application of the product. Three or four ampoules of the product are used in each intravesical instillation at the discretion of the urologist performing the treatment.
For instructions regarding the preparation of the suspension, please, refer to section 6.6
Applied intravesically using catheter.
The product remains in the bladder in the course of two hours. While the CALGEVAX is being retained in the bladder, every 15 minutes the patient alternates the following positions: semi-left turning, semi-right turning, left side, right side.

The standard scheme of administration includes one intravesical instillation once a week in the course of six weeks (inducing therapy). The maintenance therapy is determined on a case-by-case basis. The following schemes can be used: monthly administration in the course of minimum 6-12 months or three weekly instillations at the 3rd, 6th, 12th, 18th, 24th, 30th and 36th month of the date of the first instillation.

4.2.2 Percutaneous administration after scarification of the skin

Ten horizontal and ten vertical lines are made by the syringe needle on an area of 5/5 cm. The scarification should tear only the epidermal layer without causing extensive bleeding.
A multipuncture apparatus can also be used to regulate the depth of the scarification.
For instructions regarding the preparation of the suspension, please, refer to section 6.6.
The scarification spot is treated by 0.5 ml of the prepared suspension. One ampoule is used for one scarification. Prior to the procedure, the area should be treated with acetone after which its full evaporation should be awaited. A new area is chosen for every following scarification. The frequency and duration of administration are determined by the doctor, performing the treatment.

CALGEVAX is not recommended for children due to the absence of sufficient data about the safety and efficiency of the product regarding children.

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients, listed in item 6.1
CALGEVAX is not administered:

- in case of patients with immunosuppression;
- in case of patients with inherent or acquired immune insufficiency caused by a disease or an antitumor therapy;
- in case of HIV-positive persons and patients on immunosuppression doses of steroids or other immunosuppressants;
- in febrile conditions;
- in case of infection of the urinary tracts or massive haematuria, as well as in a parallel anti-microbe therapy;
- in active tuberculosis; a positive tuberculin Mantoux test is a contraindication only in case of certified active tuberculosis infection;
- in case of ongoing or previous systemic BCG reaction (i.e. a systemic granulomatous disease, which can be revealed after the administration of BCG; it is determined on the basis of the following symptoms: fever ≥39.5°C for ≥12 hours; fever ≥38.5°C for ≥48 hours, pneumonitis, hepatitis or another organ disfunction outside the urinary-genital tract involving a granulomatous inflammation, which is established through biopsy, or the classical symptoms of sepsis).

4.4. Special warnings and precautions for use

- Patients, who have had the medicine administered intravesically, should maintain adequate hydration.
- The intravesical administration of CALGEVAX may result in local inflammation of the urinary bladder, accompanied by haematuria, dysuria, pollakiuria and flu-like symptoms. Patients with a small capacity of the bladder are exposed to a higher risk of a heavier local inflammation.

- In case of a doubt about a systemic BCG infection after the administration of CALGEVAX, which may proceed with a fever of over 39^0C, persisting temperature of over 38 ^{0}C or fatigue, a prompt antituberculosis treatment is carried out after consulting a specialist.
- CALGEVAX contains live bacteria and should be treated as infectious material. Persons with immunosuppression should not handle CALGEVAX.
- The catheterization of the bladder should be performed carefully avoiding traumatization of the mucous membrane. If the doctor, performing the treatment, decides that the catheterization is traumatic (for example, involves bleeding), the administration of the product should be postponed by at least 14 days.
- In case of serious overall adverse reactions, the intervals between the separate administrations are extended. The treatment with CALGEVAX may be terminated at the discretion of the doctor, performing the treatment. Antituberculosis treatment is recommended in case of disseminated BCG infection.

4.5. Interaction with other medicinal products and other forms of interaction.

- Taking of CALGEVAX may result in an increased sensitivity towards tuberculin, which would complicate the interpretation of the skin reaction to tuberculin in a future testing for suspected mycobacterial infections. In this context, it is recommended to determine the patient's reaction to tuberculin prior to the immunotherapy with CALGEVAX.

4.6. Fertility, pregnancy and lactation

The risk/benefit balance is assessed carefully, when the medicinal product should be administered during pregnancy and lactation due to the absence of clinical data about its administration in these cases. It is known that a lactating woman with a systemic BCG infection may infect her child.

4.7. Effects on ability to drive and use machines

The effect of CALGEVAX on the ability to drive and operate machinery has not been studied.

4.8. Undesirable effects

4.8.1 Intravesical administration

- **Local reactions:** transitory dysuria, pollakiuria, haematuria, bacterial infection of the urinary tract, granulomatous prostatitis, epididymitis, orchitis.
- **General reactions:** malaise, increased temperature, fever, sweating, sickness, vomiting, headache, muscle pain, abdominal colic, diffuse rash, liver toxicity, disseminated BCG infection, generalized hypersensitivity, erythema nodosium, conjunctivitis, uveitis, vitiligo, arthritis, leucopenia or pancytopenia, splenomegaly.

In case of intravesical administration, adverse reactions (dysuria, pollakiuria, fever) emerge 3-4 hours after the instillation and are transitory – they last 24-72 hours. A localized (epididymistis, orchitis, prostatitis) or a systemic BCG infection occurs more rarely.

4.8.2 Percutaneous administration

- **Local reactions:** localized itching or rash, painful ulcer at the place of administration, regional adenopathy.
- **General reactions:** fatigue, increased temperature, fever, sweating, sickness, vomiting, headache, muscle pain, abdominal colic, diffuse rash, liver toxicity, disseminated BCG infection, generalized hypersensitivity, erythema nodosium, conjunctivitis, uveitis, vitiligo, arthritis, leucopenia or pancytopenia, splenomegaly.

Reporting of suspected adverse reactions

Reporting of suspected adverse reactions after authorization of the use of the medicinal product is important. This allows to continue montoring the benefit/risk balance. It is required from the medicial experts to report any suspected adverse reaction through the national reporting system, pointed out below:

Bulgarian Drug Agency
8, Damyan Grouev St., 1303 Sofia,
tel.: + 359 28903417, website: www.bda.bg

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other cytokines and immunomodulators
ATC code: **L03AX 03**

Mechanism of action

CALGEVAX is a freeze-dried and vacuum stored preparation containing live bacteria derived from a culture of the Bacillus of Calmette and Guérin (BCG) and sodium glutamate as stabilizer.

The most important thing for the action of BCG is the interaction between the BCG bacteria and the cells of the immune system. The following factors also influence the ultimate effect: the BCG sub-strain used, the doze, the frequency and duration of treatment.

BCG predetermines proliferation, activation and changes in the behaviour and the distribution of the T-cells, exerts an impact on the B-cell immune response, activates specifically or non-specifically the macrophages and increases the activity of the “natural killer-cells” and the “killer-cells”. It has been proved that BCG stimulates the expression of different cytokines. Experimental and clinical studies of the immune reaction of patients with superficial tumors of the bladder to the BCG antigens show a relationship between the T-cell immune response and the response to the BCG therapy. Evidence is being accumulated that a specific antitumor immunity is predetermined. The clinical efficiency of BCG during its initial contact with the epithelium has been studied. The local inflammatory reaction of the mucosa is characterized by a high number of T-cells, while the number of NK-cells is lower. High levels of cytokines in patient’s urine are established after recurrent administration of BCG. The phenomenon of inducing BAK-cells or BCG-activated “killer-cells” has been discovered. BCG considerably reduces the proliferative capacity of the tumor cell lines. The role of the locally present leukocytes and cytokines for the antitumor activity of BCG, the prognostic significance of the cytokines in the urine, the role of the attachment and the viability of BCG in predetermining immune response and antitumor activity is being clarified. The biological activity of BCG substrain plays a central role.

While developing the BCG vaccine CALGEVAX, specially designed for immunotherapy of new malignant formations, special attention has been paid to the phenotypic characteristics of the BCG bacteria, because it is known that they have an antitumor effect. The experimental evaluation has been made based on the following criteria: L-asparaginase activity, virulence for hamsters, ability to activate macrophages (listeria clearance test), inducing of lymphoproliferation (remote index for mice), establishing the potential for antibody-dependent cytotoxicity, inducing the formation of a tumor-necrosis factor and immunomorphological studies. Their study, as well as the laboratory tests of the indicators - viability, dispersity, oxygen consumption of the bacteria and skin reaction, as tested in a guinea pig – show that the product possesses high immunopotenting activity.

Clinical efficacy and safety

The administration of CALGEVAX to patients with malignant melanoma in a randomized clinical trial shows a favourable result as a means of adjuvant immunotherapy. The intravesical immunotherapy with CALGEVAX is a method for treatment of carcinoma *in situ* and a method for prophylaxis of recurrent growth and the progression of the aggressive superficial transitional-cell carcinoma of the bladder after their surgical removal.

5.2. Pharmacokinetic properties

Not applicable

5.3. Preclinical safety data

Preclinical studies of the safety of the medicinal product have not been performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium glutamate.

6.2. Incompatibilities

Incompatibilities with other medicinal products are not known.

6.3. Shelf life

The shelf life of CALGEVAX is two years. After reconstitution, avoid exposure to light and administer promptly.

6.4. Special precautions for storage

Store at a temperature of +2 °C to +8 °C.
Store in a cardboard package in order to avoid exposure to light.
Keep out of the reach of children.

6.5. Nature and contents of container

5 ml dark ampoules (glass, type I).
Pack: 4 or 10 ampoules in a cardboard box.

6.6. Special precautions for disposal and other handling

Instructions for preparation and handling the product

- **Intravesical administration**

Three or four ampoules of the product are used in each intravesical instillation at the discretion of the urologist performing the treatment. The content of each ampoule is reconstituted into 1 ml of sterile saline (a solution of sodium chloride with concentration of 9 g/l), carefully shaken until obtaining a homogeneous suspension. The mixture is drawn by syringe and then returned to the ampoule three times in order to ensure thorough mixing, which minimizes the clumping of mycobacteria. The content of the ampoules is transferred in a syringe of 50 ml. A supplementary volume of sterile saline is added bringing the total volume to 50 ml.

- **Percutaneous administration**

The content of one ampoule is mixed with 0.5 ml of sterile saline to obtain concentration of 75 mg/ml.

Unused amounts of the suspension, ampoules, needles, syringes and catheters are destroyed in accordance with the rules for disposal of infectious materials. In case of a spill, the area is cleaned by a 70% solution of ethyl alcohol.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER

20020683/02.08.2002

9. DATE OF FIRST AUTHORISATION FOR USE

2 August 2002

10. DATE OF REVISION OF THE TEXT: 03/2015