

Patient Information Leaflet

CALGEVAX, powder for suspension

(BCG for immunotherapy)

Please read this leaflet carefully before you start taking your medicine because it contains information, which is important for you.

- Keep this leaflet; you may need to read it again.
- If you have further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If you notice any adverse reactions, please, tell your doctor or pharmacist. This includes all possible adverse reactions, which are not pointed out in this leaflet. Please, refer to item 4.

In this leaflet:

1. What CALGEVAX is and what it is used for
2. What you should know before you take CALGEVAX
3. How to take CALGEVAX
4. Possible adverse reactions
5. Storing CALGEVAX
6. Content of the pack and additional information

1. What CALGEVAX is and what it is used for

CALGEVAX is BCG specially designed for cancer immunotherapy.

- Intravesically:
 - for prophylaxis of the 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 nonspecific adjuvant immunostimulating therapy of other newly emerged malignant growths (lung, breast cancer, acute leukemia, lymphosarcoma or osteosarcoma).

2. What should be known before CALGEVAX is given

Do not administer CALGEVAX if:

- there is allergy to the active substance or any of the other ingredients of this medicine (listed in item 6).

Warnings and preventive measures

You should consult your doctor or pharmacist before using CALGEVAX.

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 $\geq 39.5^{\circ}\text{C}$ for ≥ 12 hours; fever $\geq 38.5^{\circ}\text{C}$ 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).

NECESSARY 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 severe local reactions.
- In case of a doubt about a systemic BCG infection after the administration of CALGEVAX, which may proceed with a fever above 39°C , persisting temperature of over 38°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.

Children and adolescents

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

Other medicines and CALGEVAX:

You should inform your doctor or pharmacist if you have taken or can possibly take other medicines. 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.

Pregnancy, lactation and fertility

Do not take this medicine without first consulting your doctor, if you are pregnant or breast-feeding, think that you might be pregnant or plan to become pregnant.

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.

Driving and using machines

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

3. How to administer CALGEVAX

You should take this medicine as described in this leaflet or as your doctor or pharmacist has told you. If you are uncertain about something, ask your doctor or pharmacist.

INTRAVESICAL ADMINISTRATION:

CALGEVAX is administered at least 14 days after the performance of a biopsy, transurethral resection or traumatic catheterization. The application of CALGEVAX should be done using aseptic equipment and under the control of a urologist, having experience in the administration of the product. Three or four ampoules of the product are used for 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 the 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. Light reduces considerably the efficiency of CALGEVAX. Therefore, exposure to direct daylight should be avoided both before and after preparing the suspension. The suspension should be used immediately.

After emptying the bladder, the reconstituted CALGEVAX is instilled slowly into the bladder through urethral catheter. The product remains in the urinary 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.

PERCUTANEOUS ADMINISTRATION:

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.

The scarification spot is treated by the following 0.5-ml suspension: the content of one ampoule is mixed with 0.5 ml of sterile saline to obtain concentration of 75 mg/ml. 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.

4. Possible undesirable reactions:

This medicine, like most other medicines, may cause adverse reaction, although this does not apply to all people.

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 nodosum, 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 (epididymitis, orchitis, prostatitis) or a systemic BCG infection occurs more rarely.

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 nodosum, conjunctivitis, uveitis, vitiligo, arthritis, leucopenia or pancytopenia, splenomegaly.

In case of serious 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.

The patient must inform his doctor of any side effects, not pointed out in the leaflet.

Reporting adverse reactions

If you notice any adverse reactions, please, tell your doctor or pharmacist. This includes all possible adverse reactions, which are not pointed out in this leaflet. You can also report adverse reactions directly through the National Reporting System, pointed out below:

Bulgarian Drug Agency

8, Damyan Grouev St., 1303 Sofia,

tel.: + 359 28903417, website: www.bda.bg

By reporting adverse reactions you may contribute to ensuring more information about the safety of this medicine.

5. Storage of CALGEVAX

Store at a temperature of +2 °C to +8 °C.

Store in a cardboard pack in order to avoid exposure to light.

Keep out of the reach of children.

After resuspending, avoid exposure to light and administer promptly.

The product should not be used beyond its expiry date, pointed out on the pack.
The product is fit for use until the last day of the month indicated.

Special measures at disposal

Unused amounts of the suspension, 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.

6. Content of the package and additional information

Content of CALGEVAX

Active substance - *Mycobacterium bovis BCG* (Bacillus Calmette-Guérin) 11.25 mg (37.5 mg semi-dry bacterial mass) $1,0 - 3,0 \times 10^8$ viable units

Excipients: Sodium glutamate 40 mg

What CALGEVAX looks like and what the package contains

Powder for suspension

White lyophilized compact mass

The cardboard box contains four or ten ampoules and a patient leaflet.

Marketing authorization holder and manufacturer

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