SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ANTIDIPHTHERIA SERUM BUL BIO, Diphtheria antitoxin

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One dose (5000 IU/ampoule) contains:

	Component	Quantity
Active substance	*Corynebacterium diphtheriae* antitoxic immunoglobulins	5 000 IU (≥ 1 000 IU/ml) (protein: ≤ 170 g/l)
Excipients	Phenol	not more than 2,5 g/l
	Sodium chloride	9 g/l
	Water for injections	up to volume

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection for subcutaneous (s.c.) and intramuscular (i.m.) administration
Clear slightly yellowish liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

The serum is indicated for the treatment of diphtheria.

4.2 Posology and method of administration

ANTIDIPHTHERIA SERUM BUL BIO should be administered by a qualified healthcare professional only.
The serum is administered intramuscularly or subcutaneously at doses of 500 to 3000 IU (International Units) per kg body weight, depending on the age and condition of the patient. In severe toxic forms 100 000 IU per day or more may be injected.
Serum is administered immediately after diagnosis. In pronounced clinical symptoms, proceed immediately to the injection of the serum, without waiting for the result of the bacteriological testing.
The therapeutic dose can be introduced one or more times in the following days.

4.3 Contraindications

There are no absolute contraindications for use of ANTIDIPHTHERIA SERUM BUL BIO. A positive test for hypersensitivity to equine protein is not a contraindication to the administration of the serum. In patients with hypersensitivity to horse protein, hypoallergenic therapy is held in parallel with the injection of serum.

4.4 Special warnings and precautions for use

Test for sensitivity to serum should be done before any injection.

The test is carried out as follows: 0.1 ml serum of a 1:100 dilution in sodium chloride solution (9 g/l) is injected intradermally into the inner surface of the forearm. The evaluation of the reaction is carried out after 30 minutes. **If redness occurs, the sample is considered positive.**
If negative sample: 0.1 ml serum of a 1:10 dilution in sodium chloride solution (9 g/l) is injected intradermally. The evaluation of the reaction is performed after 30 minutes.
If negative sample: 0.1 ml non-diluted serum is injected intradermally. The evaluation of the reaction is performed after 30 minutes.
If local or general signs of hypersensitivity do not occur, the required quantity of the serum can be administered.
It is recommended that patient remains under medical supervision for another 1-2 hours and is advised of the possibility of serum sickness to occur 7-14 days after the administration of the serum.
If the sample in one of the above cases is positive, desensitization of the patient according to Bezredka's method should be carried out by serial injections of gradually increasing doses of serum at intervals of 30 minutes, as indicated below:

0.10 ml serum of 1:100 dilution in sodium chloride solution (9 g/l)	intradermally
0.50 ml serum of 1:100 dilution in sodium chloride solution (9 g/l)	subcutaneously
1.00 ml serum of 1:100 dilution in sodium chloride solution (9 g/l)	subcutaneously
3.00 ml serum of 1:100 dilution in sodium chloride solution (9 g/l)	subcutaneously
0.10 ml serum of 1:10 dilution in sodium chloride solution (9 g/l)	intradermally
0.50 ml serum of 1:10 dilution in sodium chloride solution (9 g/l)	subcutaneously
0.10 ml non-diluted serum	intradermally
0.50 ml non-diluted serum	subcutaneously
1.00 ml non-diluted serum	subcutaneously
3.00 ml non-diluted serum	subcutaneously

The remaining quantity of the indicated serum is administered intamuscularly.

In parallel, anti-allergic treatment is carried out for 2-3 days following administration of the serum.

If symptoms of anaphylactic shock develop the following measures should be taken:

- Patient is placed in supine position.
- 0.1% epinephrine (adrenaline) is injected subcutaneously. The dose may vary from 0.3 to 0.5 ml depending on the body weight of the patient. 0.1- 0.2 ml is infiltrated around and below the administration site of ANTIDIPHTHERIA SERUM BUL BIO. The remaining quantity is injected subcutaneously into the other arm.
- In case of severe or rapidly developing shock, 0.3 – 0.5 ml of 0.1% epinephrine (adrenaline) is injected intramuscularly or intravenously. In intravenous administration, the dose is 0.3 ml (pre-diluted to 1:10 000 with sodium chloride solution (9 g/l), administered very slowly (over 15-20 min), if possible via perfusion pump. One ampule (1 ml) of 0.1% adrenaline, diluted in 500 ml sodium chloride solution (9 g/l) may be administered dropwise at a rate of 1 ml/min.
- In children 0.1% epinephrine (adrenaline) is diven a dose of 0.01 ml per kg of body weight, however the single dose should not exceed 0.3 ml. It is administered subcutaneously at minimum two separated injection sites.
- Depending on the general condition and the blood pressure of the patient, subcutaneous administration of 0.3–0.5 ml of 0.1% epinephrine (adrenaline) is continued at intervals of 15-30 minutes. Methylprednisolone 1-2 mg/kg (80-120 mg) is given intravenously in parallel. Immediately thereafter the same amount of methylprednisolone, diluted in 500 ml of glucose solution (5 g/l) and sodium chloride solution (9 g/l) is administered. Infusion is continued until the blood pressure is stabilized and all symptoms of shock disappear.
- Deliver oxygen by mask or nasal catheter.
- Establish and maintain patent airways.
- The patient has to be transported to intensive care unit as soon as possible.

If **serum sickness** develops, antihistamines combined with epinephrine, corticosteroids, etc. are recommended as appropriate.

4.5 Interaction with other medicinal products and other forms of interaction

There are no data available on drug and other interactions.
Pathogenic and symptomatic treatment is held in parallel with the administration of the serum.

4.6 Pregnancy and lactation

The serum is administered to **pregnant or breast-feeding** women only if strictly indicated. There are no data indicating harmful effects with respect to feto/neonatal toxicity when used during pregnancy or breastfeeding.

4.7 Effects on ability to drive and use machines

There are no data indicating that ANTIDIPHTHERIA SERUM BUL BIO impairs the ability to drive and use machines. The patient should be informed by the doctor about the effects of other medicines (especially antihistamines) concomitantly administered with the serum.

4.8 Undesirable effects

The introduction of horse serum in the human body can cause an immediate reaction - *anaphylactic shock* or late response - *serum sickness.* These reactions are result of sensitization of the organism in the primary penetration of the horse protein or are due to specific reactogenicity of the body. Anaphylactic shock can occur immediately following either subcutaneous or intramuscular administration. Symptoms of anaphylactic shock include: difficulty breathing (dyspnea), blue discoloration of the skin (cyanosis), weak rapid pulse, sweating, vomiting, drop in blood pressure, diarrhea, and in severe cases - progressive collapse resulting in death.

In 2 to 6% of the cases, serum sickness may occur 7 to14 days following administration of horse serum. It is characterized by mild transient erythema or urticaria (hives), and in some cases complications may occur, characterized by joint pain and swelling of the lymph nodes.
In case adverse reactions occur, please report them to BB - NCIPD Ltd-1504 Sofia, Bulgaria, 26 Yanko Sakazov Blvd., Phone: +359 2 8468155.

4.9 Overdose

Not applicable

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacotherapeutic group: Immune sera, ATC code: J06AA01

ANTIDIPHTHERIA SERUM BUL BIO is a purified and concentrated immune serum, consisting of $(Fab)_2$ immunoglobulin fragments, which specifically neutralize *Corynebacterium diphtheriae* toxins, and induces passive immunity.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

No preclinical studies of safety pharmacology have been performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Phenol - not more than 2,5 g/ l
Sodium chloride - 9 g/l
Water for injections - up to volume

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.
There are no known data on physicochemical incompatibility of the product with other medicinal products.
In concomitant administration of ANTIDIPHTHERIA SERUM BUL BIO with other injectable medicines, a separate, sterile syringe and needle and different injection sites must be used to withdraw the dose and administer each product.

6.3 Shelf life

3 years (36 months) at the indicated storage conditions.

6.4 Special precautions for storage

ANTIDIPHTHERIA SERUM BUL BIO is stored and transported refrigerated (2°C – 8°C) in the original package in order to protect from light.
Do not freeze!
Keep this medicine out of the sight and reach of children.

6.5 Nature and contents of container

Ampoule 10 ml – self-breaking, transparent, colourless, first hydrolytic class glass (Type I). One ampoule of 10 ml contains not more than 5 ml immune serum.
Available in carton packs containing 1 or 10 ampoules.

6.6 Special precautions for disposal and other handling

ANTIDIPHTHERIA SERUM BUL BIO is a clear slightly yellowish liquid.
Do not use this medicine if you notice visible signs of deterioration.
Do not use frozen serum and/or if the appearance of the solution is changed!
Before use, the ampoule with the serum is warmed to body temperature.
Do not use after the expiry date!
Do not use if the integrity of the ampoule is compromised or the labelling is deleted.
To be administered immediately after opening of the ampoule.

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

7. MARKETING AUTHORISATION HOLDER

BB – NCIPD Ltd
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8. MARKETING AUTHORISATION NUMBER(S)

II 6386/20.11.2002
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9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20/11/2002, № 20020930

10. DATE OF REVISION OF THE TEXT

07/2016