SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT:

DIPHTHERIA ANTITOXIN 10000 I.U. B.P. (10mL liquid vial)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each mL contains:
Enzyme refined, Equine Diphtheria antitoxic immunoglobulin fragments not less than 1000 IU.

3. PHARMACEUTICAL DOSAGE FORM:

Solution for injection.

Description:
Clear to opalescent and colorless to very faintly yellow liquid. They are free from turbidity.

4. CLINICAL PARTICULARS

4.1.THERAPEUTIC INDICATIONS:

Diphtheria antitoxin has been used to provide passive immunity against Diphtheria.

Eligibility: (According to "Use of Diphtheria Antitoxin (DAT) for Suspected Diphtheria Cases. Diphtheria Antitoxin (DAT) Protocol, CDC, September 21, 2016).

Therapeutic Use:
Patients who have probable or confirmed respiratory diphtheria are eligible to receive DAT. The Council of State and Territorial Epidemiologists approved of the following clinical case definition for respiratory diphtheria: an upper respiratory tract illness characterized by sore throat, a low grade fever, and an adherent membrane of the tonsil(s), pharynx, larynx, and/or nose.
Laboratory criteria for diagnosis: Isolation of Corynebacterium diphtheriae from a clinical specimen or histopathologic diagnosis of diphtheria.
Case classification: For reporting purposes, cases are classified as probable or confirmed:
Probable: a clinically compatible case that is not laboratory confirmed and is not epidemiologically linked to a laboratory-confirmed case
Confirmed: a clinically compatible case that is either laboratory confirmed or epidemiologically linked to a laboratory-confirmed case
A patient's eligibility for treatment will be determined by the treating physician. DAT should be administered without delay to:

A. All cases of respiratory diphtheria with laboratory-confirmed toxigenic Corynebacterium diphtheriae or diphtheria-like cases with laboratory-confirmed toxigenic Corynebacterium ulcerans.
B. Probable cases. Diphtheria should be strongly suspected in a probable case-patient who is toxic in appearance and one or more of the following:

- is without another clearly established diagnosis
- has rapidly worsening illness
- has history of recent travel to a country where diphtheria is endemic or epidemic
- was exposed to travelers from countries with endemic or epidemic diphtheria
- has history of recent contact with dairy animals,

- was never vaccinated or is not up-to-date with diphtheria toxoid vaccination

For probable cases which are considered to have a low probability for diphtheria, treating physician can consider other diagnoses. However the final decision to administer DAT to a patient lies with the treating physician.

C. Case-patients who have isolated or localized lesions in the nose, eye, skin, or other anatomical sites from which C. diphtheriae is obtained, and in whom there are signs of systemic toxicity (fever, tachycardia (myocarditis), and weakness (neuropathy)).

Otherwise, DAT treatment is not routinely indicated for treatment of cutaneous diphtheria skin infection; toxigenic sequelae are rare when the infection is limited to the skin and when the case-patient is up-to-date on vaccination with diphtheria toxoid.

Prophylactic Use:

DAT is used prophylactically only under exceptional circumstances. Eligibility for prophylactic use of DAT will be limited to the following situations:

1. An individual who:
   - Has had known exposure to toxigenic *C. diphtheria* (or possibly other toxigenic Cornybacteria) AND
   - Is not up-to-date for vaccination against diphtheria AND
   - Cannot be kept under surveillance for the development of clinical symptoms or is not available for follow-up of results of culturing for the diphtheria organism.
2. An individual who has suspected or known injection of diphtheria toxin (e.g., laboratorians).

Needle sticks do not qualify as injections.

Under the rare circumstances when these conditions are met, the recommended prophylactic dose of DAT is 10,000 units (after appropriate sensitivity testing). Patients in situation #1 above also should be given prophylactic antibiotics and appropriate up-date vaccination with diphtheria toxoid. Patients in situation #2 do not need prophylactic antibiotics because they have not been exposed to the bacteria.

Tests for Sensitivity to DAT

A test for sensitivity to DAT should be carried out each time DAT is administered. Sensitivity to DAT may be assessed by two methods: the scratch, prick, or puncture skin test is followed by an intradermal (ID) test if the skin test is negative. This order is recommended as the skin test is thought to be safe while the ID test has been reported to cause fatal anaphylactic reactions.

A. Scratch, prick, or puncture skin test

After cleaning a skin site on the volar surface of the patient's forearm with alcohol and air drying, make a superficial scratch, prick, or puncture using a sterile needle or other sterile sharp instrument, breaking the skin but not drawing blood.

In persons with a negative history for animal allergy and no prior exposure to animal serum, apply one drop of a 1:100 dilution of the serum in normal saline to the site.

In patients with a positive history for animal allergy or prior exposure to animal serum suggesting increased risk, apply one drop of a 1:1,000 dilution of the serum in normal saline to the site. If the test is negative, repeat it using a 1:100 dilution.

Positive (histamine) and negative (physiologic saline) control tests should also be applied to similar scratch, prick, or puncture sites. A positive scratch test is a wheal with surrounding erythema at least 3 mm larger than the negative control test, read at 15-20 minutes. The

histamine control must be positive for valid interpretation; a positive response consists of a wheal at the scratch site surrounded by an erythematous area. If the scratch test is negative, an ID test is performed. If the scratch test is positive, follow procedures for desensitization.

B. ID test

In persons with a negative history for animal allergy and no prior exposure to animal serum, administer a reduced dose of 0.02 ml of 1:100 saline-diluted serum ID; this quantity should raise a small ID wheal.

In patients with a positive history for animal allergy or prior exposure to animal serum suggesting increased risk, administer a reduced dose of 0.02 ml of 1:1,000 saline-diluted serum ID; this quantity should raise a small ID wheal. If the test is negative, repeat it using a 1:100 dilution.

Positive (histamine) and negative (physiologic saline) ID control tests should be applied. Interpretation of the ID test is done as with the scratch test.

A positive skin test indicates the probability of sensitivity with some correlation between the severity of the reaction on skin testing and the likelihood and severity of reaction to the DAT. However, a negative skin test does not preclude the possibility of an adverse reaction and DAT should still be administered cautiously. In addition, antihistamines (and possibly other drugs such as tricyclic antidepressants) administered previously can interfere with the results of skin testing for periods of one day or longer depending on the antihistamine.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION:

Route:

The IV route is the preferred route of administration of DAT, especially in severe cases. The antitoxin dose should be mixed in 250 –500 mL of normal saline and administered slowly over 2 – 4 hours, closely monitoring for anaphylaxis. The antitoxin may be given IM in mild or moderate cases.

Temperature:

Antitoxin should be warmed to 32° – 34°C (90 – 95°F) before injection. Warming above the recommended temperature should be carefully avoided because the DAT proteins will denature.

Dosage:

A. Perform sensitivity tests, and desensitization if necessary.
B. Give the entire treatment dose of antitoxin IV (or IM) in a single administration (except for series of injections needed for desensitization).
C. The recommended DAT treatment dosage ranges are:

Table 1. Pediatric and Adult DAT Dose

Diphtheria clinical presentation	DAT dose (units)
Pharyngeal or laryngeal disease of 2 days duration	20,000 – 40,000
Nasopharyngeal disease	40,000 – 60,000
Extensive disease of 3 or more days duration, or any patient with diffuse swelling of neck	80,000 – 100,000
Skin lesions only (rare case where treatment is indicated)	20,000 – 40,000

D. Give children the same dose as adults.

E. Repeated doses of DAT after an appropriate initial dose are not recommended and may increase the risk of adverse reactions.

Appropriate antimicrobial agents in full therapeutic dosages should be started immediately upon suspicion of respiratory diphtheria (and ideally after specimen collection). For cutaneous diphtheria, antitoxin is rarely required, attention should focus on wound hygiene and antimicrobial agent treatment. The antibiotic of choice for treatment of cutaneous diphtheria is erythromycin or penicillin.

Any person with clinical symptoms of diphtheria should receive DAT as soon as it can be made available, without waiting for bacteriologic confirmation of the diagnosis. Supportive treatment should be continued until all local and general symptoms are controlled.

Prophylactic regimen

Prophylactic treatment with DAT can be considered for contacts but is recommended only in exceptional circumstances. If it is concluded that a close contact may benefit from receiving DAT, DAT can be administered in addition to antimicrobial prophylaxis and immunization with diphtheria toxoid.

Before administering DAT:

A. Perform appropriate sensitivity tests.

B. If sensitivity testing is negative, give 10,000 units IM.

C. If sensitivity testing is positive, proceed with desensitization schedule outlined in Section 6.4, and then administer 10,000 units of DAT IM.

Pediatric dose:

The recommended dosage for the children is the same dose as for adults.

4.3 CONTRAINDICATIONS:

Injection of the antitoxin to persons with a history of allergic reactions to equine protein and to individuals with asthma, infantile eczema is contraindicated. Adrenaline and other supportive measures should be available in case of an anaphylactic reaction.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

Injection of diphtheria antitoxin in horse-serum-sensitive individuals can produce immediate reaction of acute anaphylaxis which could be treated by injecting 1 mL of 1:1000 adrenaline intramuscularly.

Before injection of diphtheria antitoxin, it is necessary to enquire from the patient (1) whether he/she has had injections of any serum before, (2) whether there is personal or family history of allergy i.e. asthma, eczema or drug allergy.

The sensitivity of the patient to serum is tested by injecting subcutaneously 0.1 mL of diphtheria antitoxin diluted 1:10 in physiological saline and the patient is observed for 30 minutes for local and general reactions. If the test dose shows either local reaction such as wheal and flare or general anaphylactic reaction such as pallor, sweating, nausea, vomiting, urticaria or fall of blood pressure these should be treated with 1 mL of 1:1000 adrenaline (which should always be kept handy) before injecting the main dose of diphtheria antitoxin. Half the dose of adrenaline may be repeated 15 minutes later if necessary.

In allergic individuals Diphtheria antitoxin is to be injected 15 to 30 min. after administration of antihistamines such as injectable Pheniramine maleate and injectable hydrocortisone intramuscularly. One mL of adrenaline (1:1000) may be injected intramuscularly at the same

time as the antiserum. Administration of hydrocortisone or adrenaline may be repeated if necessary.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION:

Immunoglobulins may interfere with the ability of live vaccines to induce an immune response. Suitable interval should be given when using both.

4.6 FERTILITY, PREGNANCY AND LACTATION:
Pregnancy is not a contraindication to the use of diphtheria antitoxin unless clearly indicated.

Lactation
Breastfeeding is not a contraindication to diphtheria antitoxin unless clearly indicated. It is not known if antitoxin antibodies are excreted into breast milk.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:
No effects on ability to drive and use machines have been observed.

4.8 SIDE/ADVERSE/UNDESIRABLE EFFECTS:
Anaphylactic Reaction
Although onset and severity are highly variable, anaphylaxis usually begins in susceptible patients within minutes after exposure to DAT; in general, the more rapid the onset, the more severe the reaction. The major manifestations are

1) cutaneous, including pruritus, flushing, urticaria, and angioedema;
2) respiratory, including hoarse voice and stridor, wheeze, dyspnea, and cyanosis;
3) cardiovascular, including a rapid, weak pulse, hypotension, and arrhythmias. Anaphylaxis is a major medical emergency.

In the event of an anaphylactic reaction, treatment will depend on the nature and severity of the reaction. Parenterally-administered epinephrine is the primary drug for all types of reactions. Antihistamines should also be given. Additional medications, depending on the severity of the reaction may include corticosteroids, alpha-adrenergic blocking agents, aminophylline, and beta-2 agonists.

Febrile Reaction
When fever occurs, it usually develops twenty minutes to one hour after exposure to DAT. It is characterized by a chilly sensation, slight dyspnea and a rapid rise in temperature. Most febrile reactions are mild and can be treated with antipyretics alone; severe reactions may require other measures (tepid water baths, etc.) to reduce the temperature.

Serum Sickness
The symptoms of serum sickness are fever, maculopapular skin rashes, or urticaria in milder forms (90% of instances) with arthritis, arthralgia, and lymphadenopathy also possible in more severe forms. Rarely, angioedema, glomerulonephritis, Guillain-Barré syndrome, peripheral neuritis, or myocarditis can occur. The onset of symptoms is usually 7 to 10 days (range 5 –24 days) after initial exposure to DAT. Onset can be as short as several hours to 3 days after administration of DAT in persons who have received a dose of animal serum in

the past; these individuals are also more likely to develop serum sickness. Mild cases of serum sickness frequently resolve spontaneously over a few days to 2 weeks. Medications that may be helpful include antihistamines, non-steroidal anti-inflammatory drugs, and corticosteroids.
Febrile reactions and serum sickness are not IgE-mediated and therefore are not predicted by skin testing. The frequency of anaphylaxis and serum sickness is partially dependent on the frequency of previous administration of animal serums in the population; this frequency is now low. Recent data on the frequency of adverse reactions to horse serum products is extremely limited due to their infrequent use. In a review of 1,433 diphtheria cases treated with antitoxin between 1940 and 1950, the frequency of adverse reactions was as follows: anaphylaxis, 0.6% (without any fatalities); febrile reactions, 4.0%; and serum sickness, 8.8%. Given the potential risk of serious adverse reactions related to DAT administration, DAT should be administered under close monitoring in a setting with appropriate medical intervention if needed.
The clinical determination regarding DAT treatment should be based on risk-benefit assessment and the clinical status of the patient. Given the life-threatening nature of respiratory diphtheria and the toxin neutralizing effect of DAT, treatment with DAT may potentially reduce morbidity and enhance survival of patients with diphtheria.

4.9 OVERDOSE:
The dose is usually dependent on the severity of the infection, a symptomatic treatment should be given in case of overdose and supportive therapies are recommended

5 PHARMACOLOGICAL PROPERTIES:
Neutralises the toxin produced by *Corynebacterium diphtheriae* locally at the site of infection and in the circulation.

6. PHARMACEUTICAL PARTICULARS
6.1. List of excipients

Preservative	:	Cresol B.P ≤ 0.25% v/v as a preservative
Stabilizer	:	Glycine B.P.
Excipient	:	Sodium Chloride B.P.

6.2.Incompatibilities

6.3 Shelf-life:
24. Months

6.4 Special precautions for storage
The liquid Diphtheria antitoxin should be stored at 2°C to 8°C. It should not be allowed to freeze.

6.5 Nature and contents of Container Pack:
Vial: 10 mL Flint, 20 mm Moulded USP type-1 clear Glass vials.
Closure: 20 mm plain grey, Bromo Butyl floro coated Rubber
Stoppers **Seal:** 20 mm Aluminium Flip off seals.

6.6 Special precaution for disposal and other handling:

Left over product and used vials should be discarded as Biomedical waste.

7. Marketing authorization holder

Vins Bioproducts Limited,
Sy.117, Thimmapur (Village), Kothur (Mandal),
Ranga Reddy (Dist)-509325, Telangana, India.

8. Marketing authorisation number (s)

TAN 21 HM 0427

9. Date pf first authorisation/renewal of the authorisation

2021-08-20

10. Date of revision of the text