## PACKAGE INSERT SAMPLE TEXT - HEALTH PROFESSIONALS

**Diphtheria Antitoxin (DAT)**
1,000 UI/mL equine-derived immunoglobulin against the diphtheria toxin

**DOSAGE FORM**
Injectable solution

Each mL of DAT neutralizes at least 1,000 IU of diphtheria toxin out of at least a total of a 10,000 IU in a 10 mL vial.

Each carton contains 5 vials with 10 mL of diphtheria antitoxin.

Diphtheria antitoxin is supplied in 10 mL vial containing an injectable solution of the specific and purified $F(ab')_2$ equine-derived immunoglobulin fractions. Each vial neutralizes at least 10,000 IU of toxin produced by *Corynebacterium diphtheriae* (serum neutralization in guinea pigs).

Diphtheria antitoxin is produced from the plasma of horses hyperimmunized with diphtheria anatoxin.

**ROUTE OF ADMINISTRATION: INTRAVENOUS.**

**ADULT AND PEDIATRIC USE**.

**COMPOSITION 1,000 IU/mL**
Each 10 mL vial contains:
- $F(ab')_2$ equine-derived immunoglobulin fractions neutralizing at least 10,000 IU of the diphtheria toxin (serum neutralization in guinea pigs):
- phenol ---------- ---------- 35 mg (maximum);
- saline solution at 0.85%---------- ---------- q.s. 10 mL.

**TECHNICAL INFORMATION FOR HEALTHCARE PROFESSIONALS**

**1. INDICATIONS**
This product is indicated for the treatment of patients with diphtheria. Diphtheria antitoxin is the only effective drug that neutralizes the toxin secreted by the diphtheria bacillus (*Corynebacterium diphtheriae*). The antibodies (specific immunoglobulins) contained in the antitoxin specifically bind to the toxin that is not yet fixed to the tissues and neutralize it. In these conditions, the earlier the administration of the antitoxin, the better its therapeutic response, therefore, treatment should be started as soon as possible.

**2. EFFICACY RESULTS**
There are no controlled clinical trials assessing the efficacy of DAT originating from horse plasma, however, its ability to neutralize the toxic activities of the toxins has been demonstrated in laboratory animal models and in the systematic use in patients.

## 3. PHARMACOLOGICAL CHARACTERISTICS

Diphtheria antitoxin is an isotonic solution of equine-derived specific immunoglobulins (IgG), purified by enzymatic, non-pyrogenic digestion. The immunoglobulins derive from the plasma of healthy horses, hyperimmunized with diphtheria anatoxin. The neutralizing biological activity of the antitoxin against the diphtheria toxin is assessed by the protection obtained in guinea pigs, after subcutaneous inoculation of mixtures of different volumes of antitoxin with a fixed amount of the reference diphtheria toxin. The neutralizing power of DAT should be of at least 1,000 International Units (IU) per mL of product.

Equine plasma enzymatically digested by pepsin reduces IgG molecular weight from 160 kDa to 90 kDa or 100 kDa, eliminating the Fc fraction from the immunoglobulin molecule that is responsible for the activation of the classical complement pathway. Thus, a purer molecule that is less reactive to hypersensitivity events observed in patients is obtained. The neutralizing activity of the antigen-binding site of pepsin-treated immunoglobulin molecules remains unchanged and there is a significant reduction in the probability of spontaneous formation of protein aggregates, which is also responsible for undesirable allergic reactions. Despite the highly purified degree of the antitoxin, there is still a small potential for allergic reactions in hypersensitive individuals. Among the undesirable reactions, anaphylaxis can occur by mast cell degranulation or complement system activation, although lethal anaphylactic shock is very rare.

Once attached to the tissues, the diphtheria toxin is not neutralized by DAT.

Diphtheria antitoxin neutralizes circulating diphtheria toxin but does not eliminate *C. diphtheriae* from the bloodstream.

## 4. CONTRAINDICATIONS

There are practically no contraindications but in patients with an allergic history or sensitivity to equine-derived immunoglobulins, DAT should be administered alongside strict medical observation.

**NOTES:**

- Diphtheria antitoxin is not contraindicated in pregnancy but the physician should be informed about this condition;
- Prior feeding and/or drinking do not contraindicate the use of the DAT, but greater care is required due to the risk of vomiting aspiration.

## 5. WARNINGS AND PRECAUTIONS FOR USE

**Diphtheria antitoxin should be administered intravenously and under medical supervision.**

**Store DAT refrigerated 2-8°C. DO NOT FREEZE.**

**Once open the DAT vial should be used immediately.**

**NOTES:**

- Success of diphtheria treatment with DAT is directly related to the earliest possible administration of the correct doses after the onset of symptoms thus requiring prompt diagnosis;
- The recommended doses are the same for children, adults and the elderly. Patients with a history of allergy or sensitivity to equine-derived immunoglobulins are considered risk groups;
- Treatment discontinuation should only occur if recommended by a physician.

## 6. DRUG INTERACTIONS

No concomitant medication is contraindicated to be administered with DAT but physicians should be informed about any medications used by patients.

## 7. DRUG STORAGE AND HANDLING

Diphtheria antitoxin should be stored and transported at 2-8°C. Do not store in a freezer. Freezing is strictly contraindicated. Once open, the drug should be used immediately.

**SHELF-LIFE:**

Shelf life of DAT is of 36 months from date of manufacture provided it has been stored refrigerated at 2-8°C as indicated on the package. These instructions have to be strictly followed.

**Batch number and date of manufacture and date of expiry: see packaging.**

**Do not take this medicine after the expiry date. Store in original packaging.**

The product is a clear to slightly opalescent liquid, which is colorless to pale yellow. Do not use the DAT if turbidity or precipitates are present.

**Inspect the appearance of the drug before using it.**

**Store medicines out of the reach of children.**

## 8. DOSAGE AND ADMINISTRATION

Diphtheria antitoxin should be administered intravenously, in a single application, under medical supervision and at the doses prescribed according to clinical form or severity:

**MILD FORM (nose, skin, tonsils):** 40,000 IU

**MODERATE FORM (larynx, tonsils or mixed):** 60,000 to 80,000 IU

**SEVERE OR LATE FORM (4 days after disease onset):** 80,000 to 100,000 IU

Administer DAT by slow intravenous infusion. The antitoxin dose should be diluted in 100 mL of normal saline solution or as required. Note, however, for the risk of volume overload in children and patients with heart failure. Doses of DAT should not be fractionated. The frequency of reactions to DAT appears to be lower when the diluted product is administered.

**SPECIAL RECOMMENDATIONS:**

- Diphtheria antitoxin is effective only for the treatment of diphtheria;
- Antibiotic therapy should also be introduced and administered to eliminate *C. diphtheriae* and thereby interrupt the production of diphtheria toxin;
- Treatment discontinuation should only occur if recommended by a physician.
- Administer the same dose of DAT for the treatment of diphtheria in adults and children.

## 9. ADVERSE REACTIONS

**Very common reactions (occur in 10% of patients taking this drug):**

Immediate and early reactions may occur during the infusion and for two hours thereafter, and up to 24 hours after administration of the DAT. They are often mild reactions. In addition to releasing histamine, animal-derived proteins can lead to the formation of protein or immunocomplex aggregates that activate the complement system. This, in turn, can lead to the formation of anaphylatoxins and trigger the release of mast cell and basophil chemical mediators. The most common signs and symptoms are pruritus, urticaria, flushing, angioedema, morbilliform rash, tachycardia, rhinorrhea, sneezing, coughing, nausea, abdominal cramps and diarrhea.

**Common reactions (occur in 1-10% of patients taking this drug):**
Late reaction, also known as Serum Sickness, can occur 5 to 24 days after the use of animal-derived immunoglobulins. The reaction is initially characterized by fever, urticaria, different size and irregularly distributed. Joint involvement can occur, at times severe and usually involving large joints, presenting with swelling with no redness, spontaneous and pressure-related pain and difficulty in motion. Lymph node infarction produces generalized adenopathy of different intensity, resulting in palpable, mobile and painful nodes. They usually heal with no sequelae. Vasculitis and nephritis rarely occur.

**Uncommon reactions (occur in 0.1-1% of the patients taking this drug):**
Pyrogenic reaction, described with decreasing frequency, occurs during the use of the antitoxin and can lead to high temperature (up to 39ºC), accompanied by chills and sweating. In such cases, the infusion should be discontinued and antipyretic medication administered. After symptom remission, DAT infusion should be resumed. If symptoms recur, discard the antitoxin solution and prepare a new antitoxin solution.

**Rare reactions (occur in 0.01-0.1% of the patients taking this drug):**
Immediate reactions can rarely progress to severe conditions in which case pallor, dyspnea, glottis edema, respiratory failure with hypoxemia, severe tachycardia, bradycardia, hypotension, which may progress to shock and syncope, loss of consciousness and persistent circulatory collapse are observed.

**Very rare reactions (occur in less than 0.01% of the patients taking this drug):** Not described in the literature.

**PREVENTION OF REACTIONS:**
- Ask the patient about previous use of animal-derived immunoglobulin (tetanus, diphtheria, rabies or antivenom) and for any allergic history;
- Absence of allergy history does not rule out the possibility of adverse reactions. There is no consensus on pre-medication with histamine receptor blockers to prevent or reduce allergic manifestations. Thus, the administration of antihistamines ($H_1$ and $H_2$) and corticosteroids 15 minutes before the recommended DAT dose is at the discretion of the physician;
- Sensitivity testing should not be performed as it is unable to detect patient sensitivity and may trigger reactions on its own. In addition, the time spent on performing sensitivity testing delays the administration of DAT.

**TREATMENT OF EARLY REACTIONS:**
Once the reaction is diagnosed, temporarily stop DAT administration and start treatment. In case of generalized hives, asthma-like attacks, glottis edema and shock an intramuscular (IM), dose of 0.01 mg/kg (0.01 mL/kg) up to a maximum dose of 0.5 mL of an aqueous solution of adrenaline (1:1,000, millesimal, 1 mg/mL) should be immediately administered on the anterolateral thigh (vastus lateralis). If there is no response, the same dose can be repeated at 5-15 minutes intervals. Corticosteroids and antihistamines play a secondary role in controlling these reactions and may also be used. Patients that continue to present bronchospasms, administer β2 inhaled agonists, such as fenoterol. Resume DAT administration after the remission of hypersensitivity manifestations.
In the event of severe early reactions (rare), which usually progress with hypotension, shock and/or acute respiratory failure, the patient should be placed in the supine position if hypotensive or in shock (if patient tolerates the position and is not in respiratory failure), or left lateral position if the patient is vomiting. Volume replacement with a saline IV solution (20 mL/kg) should be initiated and supplied according to the response. Orotracheal intubation may be eventually needed in cases of severe respiratory failure.

**NOTE:**
- Once an early severe reaction is controlled, DAT administration should be resumed.

**In case of adverse events notify the Adverse Event Reporting System - VIGIMED, available at http://portal.anvisa.gov.br/vigimed or the State or Municipal Health Surveillance.**

**10. OVERDOSE**
There is no information on cases and/or consequences of DAT overdose.

**If you need further information in case of poisoning call 0800 722 6001.**

**DISCLAIMERS:**

MS Registry Number: 1.2234.0011

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Prescription use.

Not for retail.

**This package insert was approved by ANVISA on XX/XX/2019.**

**Diphtheria Antitoxin**