FULL PRESCRIBING INFORMATION (FPI)

Antivipmyn®Tri

Fabotherapic polyvalent snake antivenom

DOSAGE FORM AND COMPOSITION:

Antivipmyn® Tri lyophilizate for injectable solution is presented in a box containing 1 vial with lyophilizate

Formula:

The vial with lyophilizate contains:
Fabotherapic polyvalent snake antivenom modified by enzymatic digestion and free of albumin, with the capacity to neutralize 780 DL_{50} of dehydrated *Bothrops sp.* venom.....30 mg
Fabotherapic polyvalent snake antivenom modified by enzymatic digestion and free of albumin, with the capacity to neutralize 220 DL_{50} of dehydrated *Crotalus sp.* venom.....15 mg
Fabotherapic polyvalent snake antivenom modified by enzymatic digestion and free of albumin, with the capacity to neutralize 200 DL_{50} of dehydrated *Lachesis sp.* venom.....15 mg
Cresol (Additive).....No more than 0.4 %

THERAPEUTIC INDICATIONS:

Antivipmyn® Tri Fabotherapic polyvalent snake antivenom is indicated for the treatment of intoxication by the bite of vipers, such as:

- ***Crotalus durissus terrificus*****,** Crotalus durissus durissus (*Cascabel*, *hocico de puerco* (pig's snout), *tziripa*, *saye*, *cascabel tropical*, *shunu*, *tzab-can*, etc.).
- ***Bothrops asper, Bothrops atrox*** (*Nauyaca*, *cuatro narices* (four noses), *barba amarilla* (yellow beard), *terciopelo*, *equis* ("x"), *mapana*, *jararaca*, *toboba*, *cola de hueso*, *víbora de árbol*, *víbora verde*, *nauyaca real*, *nauyaca del río*, *nauyaca chatilla*, *palanca*, *palanca lora*, *vívora sorda*, *tepoch*, *cornezuelo*, *nescascuatl*, *torito*, *chac-can*, etc.).
- ***Bothrops neuwiedii, Bothrops alternatus*** *(urutu),* ***Bothrops jararacussu, Bothrops venezuelensis, Bothrps pictus, Bothrops brazili*****.**
- ***Lachessis muta stenophrys, Lachesis muta muta*** (*Lora machaco*, *cascabel muda*, *rieca*, *verrugoso*, *sururucucu*, *lorita*, *patoco*, *patuquillo*.
- ***Sistrurus spp.*** **(***cascabel de nueve placas*).

- ***Agkistrodon spp.*** (Cantil, *zolcuate*, moccasin snake, *cantil de agua*, *castellana*, *cumcoatl*, *metapil*, *puchucuate*, *volpoch*, etc.

PHARMACOKINETICS AND PHARMACODYNAMICS:

The active ingredients of **Antivipmyn® Tri** Fabotherapic are the $F(ab)_2$ and Fab fragments of immunoglobulin G (IgG), and it does not contain albumin.

IgG is a glycoprotein, whose main function is to recognize the antigen, and, from a therapeutic point of view, it is able to neutralize toxins.

IgG is formed by two regions: The Fc fragment (crystallizable fragment) responsible for type I hypersensitivity reactions, that is, anaphylaxis, and type III reactions or serum sickness and the Fab fragment (antigen binding fragment)

Fab fragments (2 per each IgG) are able to recognize antigenic determinants and, in this case, toxins in order to neutralize their activity.

The antigen binding fragments without the Fc fragment are known as Fab fragments. These bivalent fragments that bind to the antigen (of an antibody) are obtained when separating the Fc fragment from the Fab fragments by enzymatic activity at acidic pH conditions, producing, as a result, $F(ab)_2$ fragments.

In Fabotherapics, such as **Antivipmyn® Tri**, when removing the Fc fraction, the possibility that type I and III hypersensitivity reactions occur is eliminated.

The molecular weight of the $F(ab)_2$ fragment is lower than that of the whole IgG; therefore, it distributes better in the vascular space and, mainly, in the extravascular space. This allows the $F(ab)_2$ fragment to effectively neutralize the several components of venoms that act outside the vascular space. Besides, since it has a better clearance, it neutralizes venom faster.

The maximum concentration is reached in 1 h for superficial tissues and in 6 hours for deep tissues; the circulation half-life of $F(ab)_2$ fragments is of 124 h, approximately.

The $F(ab)_2$ fragment maintains the specificity of native IgG; it does not activate the complement; it does not cross the placenta, bind to the receptors of mononuclear cells, neutrophils, T and B lymphocytes, and it practically does not induce the generation of anti-IgG and anti-IgE.

The action of an antivenom is based on the coupling of the antigen with the appropriate antibody. The neutralization of the antigen is a mechanism different to precipitation. The neutralization process implies a structural change that modifies the normal functioning of the native antigen: in this case, the venom or whole toxin. If the structural change affects the active site of the antigen, its activity is modified.

Because the immunological properties of the antibody are in the $F(ab)_2$ fragment, its neutralization mechanism is similar to that of the whole IgG molecule.
The elimination route of venom-antibody complexes has not yet been identified clearly, but the reticuloendothelial tissue seems to be involved in the catabolism of $F(ab)_2$-venom complexes.

CONTRAINDICATIONS

Known hypersensitivity to heterologous proteins.

GENERAL PRECAUTIONS

A patient who has recently been bitten and shows fang marks but not symptoms must be under observation for at least 15 h. Reassure the patient. The canalization of a venous access must be performed in order to administer isotonic saline solution. To reduce the venom distribution, the affected limb must be splinted or immobilized, as muscle contractions in a free-moving, affected limb allow the venom to spread through normal circulation.

At the slightest manifestation of intoxication, begin the administration of **Antivipmyn® Tri**, since envenoming by viper bite is an emergency.

Even if the patient receives belated attention, it is useful to administer **Antivipmyn® Tri** in order to neutralize the active fractions of the venom.

Remove any ring, bracelet or tight clothing that may interrupt blood circulation since edemas occur frequently. Such circumstances may aggravate the profile and cause or aggravate tissue hypoxia and necrosis.

If the patient has a tourniquet, it must be removed slowly, by gradually loosening it, while **Antivipmyn® Tri** is being administered.

Antivipmyn® Tri is the specific treatment; however, supporting treatments, such as parenteral hydration, broad-spectrum antimicrobial agents, tetanus toxoid, central analgesics, such as metamizole, tramadol, dextropropoxyphene, must also be administered. Never use NSAIDs, as they increase bleeding caused by venom.

Surgical management must take place after a sufficient administration of **Antivipmyn® Tri**.

Do not administer any food or liquids orally since there is a risk of suffocation by bronchoaspiration, mainly for the moderate to very severe grades of intoxication.

Steroids do not have a pharmacological action against viper venom.

USE RESTRICTIONS DURING PREGNANCY AND BREAST-FEEDING

Due to the characteristics and therapeutic indications of **Antivipmyn® Tri**, it is not contraindicated for pregnant women who have suffered a viper bite; on the contrary, if it is not administered, the mother is at risk of death, and the risk of preterm labor and even of intrauterine death is very high.

Due to the severity of a viper bite accident, breastfeeding must be discontinued, not because of **Antivipmyn® Tri** Fabotherapic, but because envenoming is very serious. Once discharged, lactation may resume.

SIDE EFFECTS AND ADVERSE REACTIONS

Type I and III hypersensitivity reactions may occur; however, they are extremely rare when using **Antivipmyn® Tri** Fabotherapic, though it is possible they do occur in hyperreactive individuals. Likewise, a reaction of the immune complexes, characterized by hives and arthralgias, very rarely occurs 5-10 days after the administration of the product.

Since asthmatic patients are hyperreactive, they must be carefully supervised to prevent the intoxication profile, which is severe in itself, from aggravating due to an asthma attack.

DRUG INTERACTIONS AND OTHER FORMS OF INTERACTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) must not be employed, as they increase bleeding caused by venom.

So far, there have been no reports of interactions with other medicinal products, such as: antihistamines, antibiotics, hydroelectrolytic solutions, antihypertensive drugs, insulins, oral hypoglycemic drugs, central analgesics, tetanus toxoid, and hyperimmune human anti-tetanus immunoglobulin

If the patient suffers from an additional pathology, such as high blood pressure, diabetes or any other condition, they must be carefully supervised and their profile, controlled, depending on how intense and serious their condition is.

LABORATORY TESTS ABNORMALITIES

So far, there are no reports that **Antivipmyn® Tri** alters laboratory tests. Alterations in the results of the tests of CPK (creatine phosphokinase), serum creatinine, platelet count, arterial blood gases, fibrinogens, and an increase in clotting times, prothrombin, and thromboplastin, are due to the intoxication.

PRECAUTIONS RELATED TO CARCINOGENESIS, MUTAGENESIS, TERATOGENESIS EFFECTS AND TO INFERTILITY

There are no reports so far.

DOSE AND ROUTE OF ADMINISTRATION

The ideal route of administration is intravenous, by diluting the dose to be administered in isotonic saline solution 0.9 %.

When it is not possible to administer it to the vein by diluting it in isotonic saline solution 0.9 %, it may be administered directly but slowly to the vein, by preparing the lyophilizate with isotonic saline solution 0.9 %.

The number of vials marked as initial or supporting dose (depending on the grade of envenoming) must be diluted and transferred to 500 ml of isotonic saline solution 0.9 % for adults and to 250 ml for children, which shall be administered by dripping over a period of 4 hours. Proceed in the same way with the supporting dose. The treatment shall last for as long as necessary.

If it is administered directly to the vein, the initial dose must be applied slowly and every 4 h. Continue with the supporting dose later, which must be administered even 4 h for as long as necessary.

A maximum dose limit is not specified; the necessary doses for neutralizing the venom must be applied.

In addition, it is recommended to mark the bitten limb with three or four different dots and measure their diameter. Measure such diameter frequently in order to assess if the edema increases or decreases; a decrease indicates a good prognosis.

The patient's improvement is characterized by the decrease in clotting disorders, the stopping of edema production, and the normalization of CPK because myonecrosis has finally ceased.

If there is not a laboratory and creatine phosphokinase (CPK) cannot be determined, the supporting dose to be administered is the one that managed to stop the edema and said dose must be administered every 4 h.

DOSE

The following dosage scheme is suggested, depending on the grade of intoxication:

GRADE OF ENVENOMING	SYMPTOMS (CLINICAL PROFILE)	ADULTS		CHILDREN	
		INITIAL DOSE	SUPPORTING DOSE	INITIAL DOSE	SUPPORTING DOSE
SUSPICION	History of recent snake bite, fang marks, and local pain.	**REMARK**			
GRADE I OR MILD	History of recent snake bite, fang marks, bleeding through fang marks, pain around the bite site, affected limb swelling with an increase in diameter of 10 cm or less.	3 to 5 Vials IV	5 Vials IV	6 to 10 Vials IV	5 Vials IV
GRADE II OR MODERATE	Same as the profile of Grade I, but more marked, plus: inflammation of 10 cm or more of the affected limb, nausea, vomit, blisters with liquid of whitish or bloody color, decrease in the amount of urine. If there is a laboratory, the results of the tests of clotting and of other tests are altered.	6 to 10 Vials IV	5 Vials IV	15 Vials IV	5 Vials IV
GRADE III OR SEVERE	Same as the profile of Grade 2, but more marked, plus: bitten limb or area has a foul-smelling, dark tissue (death tissue), abdominal pain, hemorrhage of the nose, mouth, or anus or of all of them, blood in urine, and very altered laboratory tests.	11 to 15 Vials IV	6 to 8 Vials IV	20 to 30 Vials IV	10 to 15 Vials IV
GRADE IV OR VERY SEVERE	Same as the profile of Grade 3, but more marked and accompanied multiple organ alterations and loss of consciousness.	16 or more Vials IV	8 or more Vials IV	31 or more Vials IV	16 or more Vials IV

<u>At the end of the initial dose, continue with the supporting dose and repeat it every 4 h.</u>

MANIFESTATIONS AND MANAGEMENT OF OVERDOSE OR ACCIDENTAL INGESTION

There is no risk of overdose.

In individuals with hyperreactivity to heterologous proteins, anaphylactic reactions may occur; in such cases, administer adrenaline 1 x 1000.

PACKAGES

Box with 1 vial containing lyophilizate.

STORAGE RECOMMENDATIONS
Refrigeration is not required.
Store in a dry place at 25 ºC or below.

WARNING LABELS
Literature exclusively for physicians.
Keep out of the reach of children.
This medicinal product is to be used with caution.
Read the attached instructions.
Once mixed, administer the product immediately.
If all the product is not administered, discard the remaining portion.
Do not administer if the seal has been tampered with.
Do not administer if the solution is not transparent, if it contains suspended particles or sediments.
If adverse reactions are suspected, report them to the email: farmacovigilancia@silanes.com.mx

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