FAVIREPT

EQUINE ANTI-VENOM IMMUNOGLOBULIN F(ab')$_2$ FRAGMENTS AGAINST BITIS, ECHIS, NAJA, CERASTES AND MACROVIPERA

In this package insert:

COMPOSITION

The active ingredients are equine anti-venom immunoglobulin F(ab')$_2$ fragments, of a sufficient quantity to neutralize at least:

– *Bitis arietans* venom ..... ≥ 25 LD 50
– *Echis leucogaster* venom ..... ≥ 25 LD 50
– *Naja haje* venom ..... ≥ 25 LD 50
– *Naja nigricollis* venom ..... ≥ 20 LD 50
– *Cerastes cerastes* venom ..... ≥ 20 LD 50
– *Macrovipera deserti* venom ..... ≥ 20 LD 50

for 1 ml

The other ingredients are: sodium chloride, polysorbate 80 and water for injections.

Concentrated hydrochloric acid or sodium hydroxide are used to adjust the pH.

MARKETING AUTHORIZATION HOLDER

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1. What is FAVIREPT and when is it used?

FAVIREPT is a solution for administration by slow intravenous injection, available in a box containing one 10 ml ampoule or a box of ten 10 ml ampoules.

FAVIREPT is indicated for the treatment of envenomation caused by most venomous snakes found in the Middle East or North Africa (Bitis, Echis, Naja, Cerastes and Macrovipera).

The use of FAVIREPT is recommended in at-risk subjects, such as:

– children, due to their unfavourable ratio of the quantity of venom/body weight,
– pregnant women, since certain constituents of the venom can pass through the placental barrier and result in foetal death.

In the complete absence of physical clinical disorders and biological disorders, immunotherapy is not indicated. Clinical monitoring (to detect neurological disorders, oedema or bleeding) and biological monitoring (clotting time on dry tube) should be performed 3 hours and 24 hours after admission.

In the presence of isolated oedema, particularly if it is mild (stage 1 or 2), immunotherapy may be considered. In all cases, the monitoring is the same as that recommended for immunotherapy treatment. For stage 3 oedema, immunotherapy is indicated.

The observation of bleeding of any kind and/or a clotting time (CT) on dry tube greater than 30 minutes represent an absolute indication for immunotherapy.

Finally, the observation of objective neurological disorders indicating envenomation by *Elapidae* (ptosis, drop in tonicity and tendon reflexes, dysarthria, dypsnea) also requires immunotherapy.

The indication for immunotherapy must be evaluated according to the following table:

Clinical	Biology	Guidelines to follow
No oedema No bleeding	CT* < 30 min CT > 30 min	Place under observation Viper envenomation Infusion immunotherapy
Isolated oedema No bleeding	CT < 30 min CT > 30 min	Place under observation Viper envenomation Infusion immunotherapy◊
Bleeding (irrespective of stage) with or without oedema	CT < 30 min CT > 30 min	Viper envenomation Infusion immunotherapy Viper envenomation DIV immunotherapy
Neurological signs: ptosis, trismus, dyspnea, etc.	CT < 30 min	Cobra envenomation DIV immunotherapy

*: clotting time on dry tube.
◊: may be replaced by DIV according to the hospital equipment and/or envenomation treatment management.

2. Information required before using FAVIREPT

Do not use FAVIREPT

If the patient has a known history of allergy to heterologous proteins of equine origin.

This contra-indication should be considered in relation to the vital risk presented by the envenomation, provided that treatment for possible anaphylactic shock can be implemented immediately.

Take special precautions with FAVIREPT

In order to detect if they are pre-sensitized to heterologous proteins, subjects must be questioned in detail on their history of allergies, paying particular attention to previous injections of heterologous sera and possible reactions, and on animal contact allergies (particularly to horses) or food allergy.

Given the heterologous nature of FAVIREPT, the risk of anaphylactic type undesirable reactions should always be assessed in relation to the severity of the envenomation. This risk should be considered as rare given the high purity of FAVIREPT.

The infusion should always be started under strict medical supervision at a slow rate of 15 drops/minute or 50 ml/hour. In the event of signs of intolerance, slow down or stop the infusion, if necessary. A syringe containing adrenaline and suitable intensive care measures should be immediately available.

Pregnancy - Lactation

Pregnant women represent an at-risk population, since the venom can pass through the placental barrier. The administration of FAVIREPT has not been the subject of specific studies on pregnant or lactating women.

Ability to drive and use machinery

No data concerning effects on the ability to drive and use machinery is available.

Use of other medicinal products

No known interaction.

3. How to use FAVIREPT

Clinical grading of envenomation

In the presence of a subject bitten by Bitis, Echis, Naja, Cerastes or Macrovipera, the clinical grading of the envenomation must be performed according to the table below:

Oedema	Grade	Bleeding
NAD	0	NAD
Spreads up leg or forearm without reaching the knee or elbow	1	Persistence of bleeding for over one hour at the bitten point
Reaches the knee or elbow	2	Appearance of bleeding at skin lesions other than the bitten point (scarring, oedema)
Spreads past the knee or elbow without reaching the root of the limb	3	Appearance of bleeding on a mucous membrane (gingival bleeding, epistaxis)
Reaches root of limb	4	Bleeding on non-wounded skin (purpura)
Spreads past root of limb	5	Exteriorization of deep visceral bleeding (haemoptysis, haematomesis, melaena)

Manent P., Mouchon D., Nicolas P. Med. Trop. 1992; 52 : 415-421.

Since the clinical situation may change, it is recommended to repeat the assessment of the grade.

First aid treatment

It is strongly recommended not to perform first aid acts such as cauterization, amputation, tourniquets, etc. The use of aspiration or applying black stone remain up to the decision of the first-aid worker, provided that these measures do not slow down the transfer of the patient to a health center.

It is recommended to limit first aid treatment to the following acts:

– quick but thorough cleansing of the wound (alcohol, antiseptics or soap),
– slight compression of the bitten limb with a bandage (except in the event of oedema),
– immobilization of the bitten limb,
– analgesic and mild sedative treatment (paracetamol and antihistamine),
– transfer to a health center.

Specific severity factors of envenomation

The presence of hypovolaemic shock, pulmonary oedema, kidney failure, diffuse intravascular coagulation, anaphylactic shock or hyperleukocytosis above 20 x 10^9/l are signs of severe envenomation.

Hospital treatment

In all cases of envenomation, the subject must be brought to a health center as soon as possible.

The confirmation of envenomation includes the detection of patent physical symptoms (oedema, bleeding) and performing a clotting test on a dry tube. Finally, the clinical grading of the patient must be performed before treatment is initiated.

The victim must be immobilized, reassured and provided relief by the use of analgesics (except for salicylate analgesics and anti-inflammatory drugs). Local disinfection must be performed or completed. In the event of superinfection, a general antibiotic treatment covering anaerobic germs must be considered. Vaccination and passive immunoprophylaxis against tetanus must be performed systematically for unprotected subjects.

Upon the onset of signs of envenomation, it is essential to install a large peripheral venous catheter, contra-lateral to the bitten limb, to provide a fluid supply adapted to the haemodynamic situation.

In the event of collapse, perform vascular filling and, if necessary, administer vasopressor amines.

If anaphylactic shock to the venom is suspected, inject 0.5 mg of adrenaline by the subcutaneous route, or 1 to 2 µg/kg by the intravenous route, to be repeated according to the development of the situation, with maintenance treatment by means of a syringe pump (0.001 to 0.005 µg/kg/min).

Dosage

Take up the product in a syringe and inject immediately by the direct intravenous route or in a solution for infusion.

You must use FAVIREPT according to the following dosage:

Initial dosage

For adults and children, irrespective of weight, the recommended initial dose by intravenous infusion is 20 ml (2 x 10 ml ampoules) for grades ≥ 2. Grades 0 and 1 should be monitored closely for at least 12 hours to detect any evolution to grade 2.

According to the medical facility's equipment and/or the management of the envenomation, the total administration time is 5 minutes by direct slow intravenous injection and 1 hour by infusion diluted in 250 ml of infusion solution (0.9% sodium chloride solution or 5% glucose solution).

For cases of envenomation treated at a late stage, the therapeutic benefit will, however, be less marked. This emphasises the interest of initiating treatment with FAVIREPT quickly, preferably within six hours.

Total dosage

The total dosage depends on the development of the subject's clinical condition and the clinical response to the first infusion. The changes in the clotting time on dry tube (≥ 30 minutes), the bleeding stage (≥ 2) and/or the persistence of neurological disorders must be taken into account in any decision to repeat administration.

If there is no improvement in the subject's condition within two hours after the end of the infusion, or if improvement is transient, a second administration by intravenous infusion must be performed.

A third intravenous infusion may also be considered using the same criteria, four hours after the end of the second infusion or 6 hours after the end of the first.

The administration schedule is summarized on the figure below:

|////|: administration of 20 ml (2 ampoules) by DIV for 5 minutes or by infusion diluted in 250 ml of infusion solution (0.9% sodium chloride solution or 5% glucose solution) for 1 hour.
↑: clinical and biological examination and decision to administer FAVIREPT.
*: administration in the event of clotting time ≥ 30 min and/or bleeding stage ≥ 2 or appearance and/or persistence of neurological disorders.

Followed by examination every morning and readministration if the bleeding stage is ≥ 2.

4. What are the possible undesirable effects?

Like all medicinal products, FAVIREPT is liable to have undesirable effect : the undesirable reactions liable to occur after the use of equine anti-venom F(ab')$_2$ fragments are essentially immediate or delayed allergic type reactions.

Immediate reactions

The reactions liable to be observed are anaphylactoid reactions with hypotension, dyspnea, urticaria. More serious reactions such as Quincke's oedema or anaphylactic shock may occur. Nevertheless, true anaphylactic shock remains exceptional.

Delayed reactions

Serum sickness like reactions after the administration of heterologous proteins may occur about six days after the beginning of treatment. They consist of an inflammatory reaction due to complement activation and formation of immune complexes (type III hypersensitivity reaction). Clinical symptoms are fever, pruritus, rash or urticaria, adenopathy and arthralgia.

Undesirable effects must be treated as follows:

In the event of a severe anaphylactic type reaction during the administration FAVIREPT, the injection must be stopped immediately.

If the effect persists despite the discontinuation of the infusion, a symptomatic treatment must be initiated.

The treatment of anaphylactic type shock essentially consists of:

– intravenous fluid support,
– administering the patient with oxygen and, if necessary, intubation and placing under artificial respiration,
– injecting 0.5 ml of a 1/1000 adrenaline solution subcutaneously until a satisfactory haemodynamic condition is obtained,
– antihistamines can be administered as a complementary treatment associated with corticosteroids if necessary.

Serum sickness is treated by administering corticosteroids (e.g. 1 mg/kg of methylprednisolone followed by diminishing dosage) and antihistamines.

5. How to store FAVIREPT?

Store FAVIREPT at a temperature between + 2°C and + 8°C (in a refrigerator).
Do not freeze.
Keep out of the reach and sight of children.
Do not use after the expiry date marked on the box.

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