

# ANAVIP- crotalidae immune f(ab)2(equine) injection, powder, lyophilized, for solution

Rare Disease Therapeutics, Inc

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ANAVIP safely and effectively. See full prescribing information for ANAVIP.

**ANAVIP<sup>(R)</sup>**  
**crotalidae immune F(ab')<sub>2</sub> (equine)**  
**Lyophilized Powder for Solution for Injection**  
**For Intravenous Use Only**

**Initial U.S. Approval: 2015**

### RECENT MAJOR CHANGES

Indication and Use (1) April 2021  
Dosage and Administration (2) April 2021  
Animal Toxicology and/or Pharmacology (13.2) April 2021

### INDICATIONS AND USAGE

ANAVIP [crotalidae immune F(ab')<sub>2</sub> (equine)] is an equine-derived antivenin indicated for the management of adult and pediatric patients with North American Pit Viper envenomation. (1)

### DOSAGE AND ADMINISTRATION

**Intravenous use only.**

Dose	No. of Vials	Infusion Rate
Initial Dose	10 vials	Infuse intravenously over 60 minutes.
Additional dose(s) to achieve initial control	10 vials (as needed)	Infuse intravenously over 60 minutes.
Observation and late dosing	4 vials	Infuse intravenously over 60 minutes.

- Initiate administration as soon as possible after North American Pit Viper bite in patients who develop signs of envenomation (e.g., local injury, coagulation abnormality, or systemic signs of envenomation). (2)
- Monitor patients in a health care setting at least 18 hours following initial control of signs and symptoms. Re-emerging symptoms including coagulopathies may be suppressed with an additional 4 vial doses of ANAVIP as needed. (2)
- Reconstitute each vial with 10 milliliters (mL) of sterile normal saline (0.9% NaCl). (2)
- Combine and further dilute to a total of 250 mL with sterile normal saline (0.9% NaCl). (2)

### DOSAGE FORMS AND STRENGTHS

Each vial contains a sterile, lyophilized preparation containing not more than 120 milligrams total protein and not less than the indicated number of mouse LD<sub>50</sub> neutralizing units (3):

Snake Species Used for Standardization	Minimum Mouse LD <sub>50</sub> Units per Vial
<i>Bothrops asper</i> (Terciopelo or fer-de-lance) <sup>1</sup>	780
<i>Crotalus simus</i> (formerly <i>Crotalus durissus</i> ) (Central American Rattlesnake) <sup>1</sup>	790
<i>Crotalus adamanteus</i> (Eastern Diamondback Rattlesnake)	244
<i>Crotalus atrox</i> (Western Diamondback Rattlesnake)	147
<i>Crotalus scutulatus</i> (Mohave Rattlesnake) <sup>2</sup>	185
<i>Agkistrodon contortrix</i>	20

(Copperhead)	40
<i>Agkistrodon piscivorus</i> (Cottonmouth or Water Moccasin)	61

<sup>1</sup>The venom of these species is used in the manufacture of ANAVIP.

<sup>2</sup>The Mohave phenotype A is used for standardization.

----- **CONTRAINDICATIONS** -----

None. (4)

----- **WARNINGS AND PRECAUTIONS** -----

- ANAVIP may cause allergic reactions.
- Patients with known allergies to horse protein are particularly at risk for an anaphylactic reaction. If signs or symptoms of anaphylaxis or hypersensitivity reactions (including urticaria, rash, tightness of the chest, wheezing, hypotension) occur, discontinue immediately and institute appropriate treatment.
- Monitor patients with follow-up visits for signs and symptoms of delayed allergic reactions or serum sickness (rash, fever, myalgia, arthralgia, pruritus, urticarial rash) and treat appropriately if necessary. (5.1)
- ANAVIP is made from equine plasma and may contain infectious agents, e.g., viruses. (5.2)
- Localized reactions and generalized myalgias have been reported with the use of cresol as an injectable excipient. (5.3)

----- **ADVERSE REACTIONS** -----

The most common adverse reactions (>2%) in the clinical trials were: pruritus, nausea, rash, arthralgia, peripheral edema, myalgia, headache, pain in extremity, vomiting and erythema. (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact Rare Disease Therapeutics, Inc., at 1-844-472-7389, or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

**See 17 for PATIENT COUNSELING INFORMATION.**

**Revised: 6/2021**

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## **FULL PRESCRIBING INFORMATION**

### **1 INDICATIONS AND USAGE**

ANAVIP [crotalidae immune F(ab')<sub>2</sub> (equine)] is an equine-derived antivenin indicated for the management of adult and pediatric patients with North American Pit Viper envenomation.

### **2 DOSAGE AND ADMINISTRATION**

#### **For Intravenous use only.**

Administer ANAVIP as soon as possible after North American Pit Viper bite in patients who develop any signs of envenomation (e.g., local injury, coagulation abnormality, or systemic signs of envenomation).

The amount of antivenin required to treat a snake bitten patient is highly variable owing in part to the venom burden, the potency of the venom and the time to health care presentation. Use supportive measures to treat certain manifestations of North American Pit Viper envenomation, such as pain, swelling, hypotension, and wound infection. Contact the local poison control centers for additional individual treatment advice.

Prior to initiating treatment, perform laboratory analyses, including complete blood count, platelet count, PT, PTT, serum fibrinogen level, and routine serum chemistries. Repeat testing at regular intervals to gauge response to therapy and anticipate additional dosing.

#### ***Initial Dose: 10 vials***

- The initial dose of ANAVIP is 10 vials.
- Reconstitute the contents of each vial with 10 milliliters (mL) of sterile normal saline (0.9% NaCl). Average reconstitution time is 11.8 seconds (range 8-26 seconds) per vial when using continuous gentle swirling.
- Inspect the solution visually for particulate matter and discoloration prior to administration. The solution is expected to be clear to yellow/green and opalescent. Do not use if otherwise discolored or turbid.

- Combine the contents of the reconstituted vials promptly and further dilute to a total volume of 250 mL with sterile normal saline (0.9% NaCl). Fluid volumes may need to be adjusted for very small children or infants. Use reconstituted and diluted product within 6 hours. Discard partially or unused reconstituted and diluted product.
- Infuse intravenously over 60 minutes.
  - For the first 10 minutes infuse at a 25-50 mL/hour rate, carefully monitoring for any allergic reactions, including any anaphylactic reactions. Discontinue the infusion if any allergic reaction occurs and institute appropriate emergency treatment. Reassess the risk to benefit before continuing the infusion.
  - If no reactions occur, the infusion rate may be incrementally increased to the full 250 mL/hour rate until completion. If there is any allergic reaction at any time, stop the infusion, treat accordingly, and reassess the need to continue ANAVIP.
- Following the completion of infusion, monitor the patient for at least 60 minutes for any allergic reaction and to determine that local signs of envenomation are not progressing (leading edge of local injury not progressing), systemic symptoms are resolved and coagulation parameters have normalized or are trending toward normal.

#### Additional Dosing to Achieve Initial Control

- Administer additional 10 vial doses if needed to arrest the progressive symptoms and repeat every hour until local signs of envenomation are not progressing, systemic symptoms are resolved and coagulation parameters have normalized or are trending toward normal. There is no known maximum dose.
- Prepare additional loading doses as described above for initial dose.
- Once initial control has been achieved, observe the patient to determine any need for further dosing, as described below.

#### Observation and late Dosing

- Monitor patients in a health care setting at least 18 hours following initial control of signs and symptoms. Re-emerging symptoms including coagulopathies may be suppressed with additional 4 vial doses of ANAVIP as needed. Reconstitute each vial with 10 mL of sterile normal saline (0.9% NaCl). Combine and further dilute to a total of 250 mL. Infuse intravenously over 60 minutes.

### **3 DOSAGE FORMS AND STRENGTHS**

ANAVIP is supplied as a sterile, lyophilized powder. Each vial contains not more than 120 milligrams (mg) total protein and not less than the indicated number of mouse LD<sub>50</sub> neutralizing units:

**Table 1. Minimum Potency Units per Vial in Mouse LD<sub>50</sub> Units**

<b>Snake Species Used for Standardization</b>	<b>Minimum Mouse LD<sub>50</sub> Units per Vial</b>
<i>Bothrops asper</i> (Terciopelo or fer-de-lance) <sup>1</sup>	780
<i>Crotalus simus</i> (formerly <i>Crotalus durissus</i> ) (Central American Rattlesnake) <sup>1</sup>	790

<i>Crotalus adamanteus</i> (Eastern Diamondback Rattlesnake)	244
<i>Crotalus atrox</i> (Western Diamondback Rattlesnake)	147
<i>Crotalus scutulatus</i> (Mohave Rattlesnake) <sup>2</sup>	185
<i>Agkistrodon contortrix</i> (Copperhead)	28
<i>Agkistrodon piscivorus</i> (Cottonmouth or Water Moccasin)	61

<sup>1</sup>The venom of these species is used in the manufacture of ANAVIP.

<sup>2</sup>The Mohave phenotype A is used for standardization.

## 4 CONTRAINDICATIONS

None.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Hypersensitivity

ANAVIP may cause allergic reactions.

- Patients with known allergies to horse protein are particularly at risk for an anaphylactic reaction. If signs or symptoms of anaphylaxis or hypersensitivity reactions (including urticaria, rash, tightness of the chest, wheezing, hypotension) occur, discontinue immediately and institute appropriate treatment.
- Monitor patients with follow-up visits for signs and symptoms of delayed allergic reactions or serum sickness (rash, fever, myalgia, arthralgia, pruritus, urticarial rash) and treat appropriately if necessary.<sup>4</sup>

### 5.2 Transmissible Infectious Agents

ANAVIP is made from equine (horse) plasma and may therefore carry a risk of transmitting infectious agents, e.g., viruses.

### 5.3 Reactions to Cresol

Trace amounts of cresol from the manufacturing process are contained in ANAVIP. Localized reactions and generalized myalgias have been reported with the use of cresol as an injectable excipient.

## 6 ADVERSE REACTIONS

The most common adverse reactions observed in more than 2 percent (2%) of patients in the clinical trials for ANAVIP were: pruritus, nausea, rash, arthralgia, peripheral edema, erythema, headache, myalgia, pain in extremity, and vomiting.

### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction

rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

A total of 86 patients were treated with ANAVIP, ranging from 2 to 80 years old. The patient population was comprised of 60 males and 26 females. Patients were monitored for signs and symptoms of adverse reactions including acute hypersensitivity reactions and serum sickness. Follow-up interviews were conducted at 5, 8, 15 and 22 days after treatment to assess symptoms of ongoing venom effect, serum sickness, and any other adverse reactions.

Table 2 shows the adverse reactions occurring in patients across all clinical trials for ANAVIP. Seventy-six percent (65/86) of patients receiving ANAVIP reported at least one adverse reaction.

**Table 2: Incidence of Adverse Reactions in Clinical Trials of ANAVIP by Body System**

<b>Adverse Reaction</b>	<b>ANAVIP [n=86] (%)</b>
<i>Patients Reporting at Least One Adverse Reactions</i>	65 (76%)
<i>Skin and subcutaneous tissue disorders</i>	47 (55%)
Pruritus	37 (43%)
Rash	10 (12%)
Blister	4 (5%)
Erythema	3 (4%)
<i>Gastrointestinal disorders</i>	28 (33%)
Nausea	20 (23%)
Vomiting	5 (6%)
<i>Musculoskeletal and connective tissue disorders</i>	19 (22%)
Arthralgia	9 (11%)
Myalgia	6 (7%)
Pain in extremity	5 (6%)
<i>General disorders and administration site conditions</i>	21 (24%)
Edema peripheral	7 (8%)
Chills	3 (4%)
Pyrexia	4 (5%)
<i>Nervous system disorders</i>	12 (14%)
Headache	5 (6%)
<i>Psychiatric disorders</i>	4 (5%)
Anxiety	2 (2%)
Insomnia	2 (2%)
<i>Metabolism and nutrition disorders</i>	4 (5%)
Dehydration	2 (2%)
<i>Respiratory, thoracic and mediastinal disorders</i>	5 (6%)

Dyspnea	1 (1%)
<i>Blood and lymphatic system disorders</i>	2 (2%)
Thrombocytopenia	1 (1%)

## 6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of ANAVIP. Because these reactions are reported as monotherapy or in combination with other drugs and voluntarily from a global population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Chest Pain/Discomfort
- Flushing
- Hypersensitivity
- Late Thrombocytopenia
- Necrosis
- Prolonged Prothrombin Time
- Tachycardia
- Treatment failure resulting in death
- Urticaria

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

Animal reproduction studies have not been conducted with ANAVIP. It is also not known whether ANAVIP can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20% respectively.

### 8.2 Lactation

#### Risk Summary

There is no information regarding the presence of ANAVIP in human milk, its effects on the breastfed infant, or its effect on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ANAVIP and any potential adverse effects on the breastfed infant from ANAVIP or from the underlying material condition.

### 8.4 Pediatric Use

Twenty-four percent (21/86) of patients studied in clinical trials were 16 years of age or younger (6 patients were 2 years of age to 5 years of age, 15 patients ranged from at least 5 years of age to 16 years of age). None of the pediatric patients in the phase 3 study experienced a recurrent coagulopathic effect. All adverse reactions in the pediatric patients were non-serious. The most frequent adverse reactions among pediatric patients were nausea and vomiting, itching, and fever. Thus, the safety and efficacy in the pediatric population was not different from adults.

## 8.5 Geriatric Use

Over nine percent (9%; 8/86) of patients studied in clinical trials were over 65 years of age. The efficacy of ANAVIP in the geriatric population appears comparable to the overall population.

## 11 DESCRIPTION

ANAVIP [crotalidae immune F(ab')<sub>2</sub> (equine)] is a sterile, lyophilized, polyvalent preparation of equine immunoglobulin F(ab')<sub>2</sub> fragments, manufactured from the plasma of horses immunized with venom of *Bothrops asper* and *Crotalus simus* (formerly *Crotalus durissus*). The product is obtained by pepsin digestion of horse plasma to remove the F<sub>c</sub> portion of immunoglobulin, followed by fractionation and purification steps. The F(ab')<sub>2</sub> content is not less than 85%, F(ab') content is not more than 7%, and the product contains less than 5% intact immunoglobulin. Each vial of ANAVIP contains 25.2-56.8 mg of sodium chloride, 47.30 - 91.35 mg of sucrose, and 95.03-183.15 mg of glycine as stabilizers. Trace amounts of pepsin ( $\leq 50$  ng/vial), cresol ( $\leq 0.058$  mg/vial), borates ( $\leq 1$  mg/vial), and sulfates ( $\leq 1.7$  mg/vial) may be present from the manufacturing process. Each vial contains no more than 120 mg of protein and will be neutralize not less than 780 times the LD<sub>50</sub> of *Bothrops asper* (Terciopelo or fer-de-lance) venom, 790 times the LD<sub>50</sub> of *Crotalus simus* (formerly *Crotalus durissus*) (Central American Rattlesnake) venom, 244 times the LD<sub>50</sub> of *Crotalus adamanteus* (Eastern Diamondback Rattlesnake) venom, 147 times the LD<sub>50</sub> of *Crotalus atrox* (Western Diamondback Rattlesnake) venom, 185 times the LD<sub>50</sub> of *Crotalus scutulatus* (Mohave Rattlesnake) venom, 28 times the LD<sub>50</sub> of *Agkistrodon contortrix* (Copperhead) venom and 61 times the LD<sub>50</sub> of *Agkistrodon piscivorus* (Cottonmouth or Water Moccasin) venom in a mouse neutralization assay.

The manufacturing procedures that contribute to the reduction of risk of viral transmission include pepsin digestion, ammonium sulfate precipitation/heat treatment and nanofiltration.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

ANAVIP contains venom-specific F(ab')<sub>2</sub> fragments of immunoglobulin G (IgG) that bind and neutralize venom toxins, facilitating redistribution away from target tissues and elimination from the body.<sup>1,2</sup>

### 12.2 Pharmacodynamics

No pharmacodynamic studies were conducted on ANAVIP.

### 12.3 Pharmacokinetics

Thirteen healthy volunteers each received an intravenous (IV) dose of one vial (one vial = 81.86 mg) of an antivenin comparable to ANAVIP both in composition and manufacturing. On the first day of antivenin administration, blood samples were collected from all subjects at 16 specific time points: 0 (prior to drug infusion), 5, 10, 20, 30, 45, 60, 120, and 480 minutes after drug infusion. Additional samples were drawn



just prior to discharge (Day 1), and on days 3, 5, 7, 9, 11, and 21. A two-compartment model best described the concentration-time data. The pharmacokinetic parameters of the antivenin are summarized in Table 3.

**Table 3. Pharmacokinetic Parameters of the ANAVIP Antivenin Following a Single IV Dose to Healthy Volunteers (n=13)**

<b>Parameters</b>	<b>Units</b>	<b>Mean</b>	<b>SD</b>
<b>Area under plasma concentration vs time curve</b>	AUC <sub>0-∞</sub> (µg•h/mL)	4144	670
<b>Steady-state volume of distribution</b>	V <sub>ss</sub> (L)	3.3	0.9
<b>Mean residence time</b>	MRT (h)	157	40
<b>Elimination half-life</b>	Beta-HL (h)	133	53
<b>Total clearance</b>	CL (mL/h)	22	7

### **13 NONCLINICAL TOXICOLOGY**

In a published non-Good Laboratory Practice study<sup>3</sup>, ANAVIP and another licensed North American Pit Viper antivenin were tested and cross-reactivity to the venoms of multiple different North American Pit Vipers was demonstrated in rabbits and mice. Animal studies to determine a no observed adverse effect level were unsuccessful due to technical limitations that prevented determination of a systematically toxic dose.

#### **13.2 Animal Toxicology and/or Pharmacology**

ANAVIP is standardized by its ability to neutralize the lethal action of each of the 7 venom immunogens following intravenous injection in mice. The potency of the product will vary from batch to batch; however, a minimum number of mouse LD<sub>50</sub> neutralizing units against each of the 7 venoms is included in every vial of final product, as shown in Table 1 [see *Dosage Forms and Strengths (3)*].

ANAVIP was effective in neutralizing the venoms of 7 clinically important North American Pit Vipers in a murine lethality model see Table 1 [see *Dosage Forms and Strengths(3)*]. The ED<sub>50</sub> data demonstrate the number of milligrams of antivenom necessary to neutralize a milligram of venom.

The amount of Anavip necessary to neutralize one milligram of venom was determined in a murine model. The dynamic between the venom and antivenom in a murine model provides a controlled environment to test the cross reactivity of antivenom against a variety of different snake venoms. Unlike the potency assays performed, as shown in Table 1 [see *Dosage Forms and Strengths (3)*], the effective dose study provides a mg per mg comparison for venoms from 7 species commonly associated with North American Pit Viper envenomations. The results for each species are shown in Table 4.

**Table 4. Average ED<sub>50</sub> Values for ANAVIP in a Mouse Model When Administered Three LD<sub>50</sub> of Venom**

<b>Challenge Venom</b>	<b>ED<sub>50</sub> (mg antivenin/mg venom)</b>
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<i>B. asper</i> (Terciopelo or fer-de-lance)	1.7
<i>C. simus</i> (formerly <i>C. durissus</i> ) (Central American Rattlesnake)	3.4
<i>C. adamanteus</i> (Eastern Diamondback Rattlesnake)	2.4
<i>C. atrox</i> (Western Diamondback Rattlesnake)	2.9
<i>C. scutulatus</i> A <sup>1</sup> (Mohave Rattlesnake)	14.6
<i>A. contortrix</i> (Copperhead)	8.0
<i>A. piscivorus</i> (Cottonmouth or Water Moccasin)	5.0

<sup>1</sup>*C. scutulatus* A is the Mohave phenotype containing neurotoxic venom

## 14 CLINICAL STUDIES

Study 1 was a randomized, prospective, open-label, controlled, comparative, multicenter study was conducted in 12 patients aged 18 to 70 years of age with signs of North American Pit Viper envenomation.<sup>6</sup> The subjects received either a licensed North American Pit Viper antivenin as an active control, or ANAVIP. The subjects were dosed until initial control was achieved, followed by maintenance doses. All patients in both treatment groups achieved initial control of local injury and coagulopathy following early antivenin treatment.

In the active control group, at the end of maintenance dosing, 5 of 6 subjects had platelet counts above 150,000/mm<sup>3</sup>, and all 6 had fibrinogen levels above 150 mg/dL. During the follow-up phase two patients exhibited platelets below 150,000/mm<sup>3</sup> and fibrinogen below 150 mg/dL, leading to inpatient management with administration of additional doses (one subject received an additional 6 doses (12 vials) and one subject received an additional 4 doses (8 vials)).

In the ANAVIP arm, at the end of maintenance dosing, 5 of 6 subjects had platelet counts above 150,000/mm<sup>3</sup>. One subject's platelets were 114,000/mm<sup>3</sup> and were trending upward, and all 6 had fibrinogen levels above 150 mg/dL. During the follow-up phase, 5 of 6 subjects had platelet counts above 150,000/mm<sup>3</sup>, with no downward trend; 1 subject's platelet count was 127,000/mm<sup>3</sup> on follow-up Day 1, reached 160,000/mm<sup>3</sup> on Day 4, and continued trending upward. All 6 subjects in the ANAVIP group had fibrinogen levels above 150 mg/dL during the follow-up phase. None in the ANAVIP group required rehospitalization or retreatment with ANAVIP.

Study 2 was a randomized, prospective, blinded, controlled, comparative, multicenter study, comparing two ANAVIP regimens with a licensed North American Pit Viper antivenin (comparator) conducted in patients with North American Pit Viper envenomation at 16 sites in the United States. The study had an in-hospital Acute Treatment Phase that included screening and baseline assessments, initial and maintenance dosing, and an outpatient Follow-up Phase that included 4 follow-up visits on Days 5, 8, 15 and 22.

Patients were randomized in a 1:1:1 ratio to one of three groups: ANAVIP with ANAVIP maintenance therapy (Group 1), ANAVIP with placebo maintenance therapy (Group 2), or Comparator product with Comparator product maintenance therapy (Group 3).

Initial dosing consisted of sequential intravenous (IV) doses infused to achieve initial control. If initial control of envenomation was not achieved, treatment was repeated until initial control was attained. Maintenance dosing (4 vials of ANAVIP or placebo [normal saline (0.9% NaCl)], or 2 vials of comparator product) was initiated 6 hours after the start of the last dose required to achieve initial control, and continued every 6 hours for 3 doses.

The Follow-up Phase began immediately after the third maintenance dose. Patients returned to the clinical site on Days 5, 8, and 15 for scheduled follow-up visits. Patients with ongoing signs of envenomation received 4 vials of ANAVIP or 2 vials of Comparator product. Dosing was provided as needed until the patient was stabilized. One hundred twenty-one (121) patients received blinded study drug and were analyzed for safety and efficacy.

The efficacy endpoint was the proportion of patients experiencing a coagulopathic effect as measured on Study Day 5 or 8. Patients were assessed as experiencing a coagulopathic effect if they had any one of the following: absolute platelet levels < 150,000/mm<sup>3</sup> as measured on either Study Day 5 ( $\pm 1$  day) or 8 ( $\pm 1$  day); absolute fibrinogen levels <150 mg/dL as measured on either Study Day 5 ( $\pm 1$  day) or 8 ( $\pm 1$  day); or clinical coagulopathy between end of maintenance dosing and Study Day 5 requiring additional antivenin. The comparison of coagulopathic effect proportions between treatment groups was tested using an exact logistic regression model with terms for treatment and region. Comparisons of the proportion of coagulopathic effect for two levels of ANAVIP versus Comparator product were performed in the following order: ANAVIP with ANAVIP maintenance dose versus Comparator product; then ANAVIP with Placebo maintenance dose versus Comparator product. The number and percentage of patients who experienced a coagulopathic effect is summarized by treatment group in Table 5. The efficacy analysis did not meet the pre-specified statistically defined superiority criterion. However, the percentages of subjects showing prespecified criteria for coagulopathic effect on either Day 5 and/or Day 8 were 10.3% and 5.3% in the Groups 1 and 2 when compared to 29.7% in Group 3 indicating efficacy of ANAVIP in management of coagulopathic effect in patients with North American Pit Viper envenomation.

**Table 5. Comparison of Coagulopathic Effect Rates on Study Day 5 or Study Day 8**

<b>Experienced Coagulopathic Effect on Either Day 5 or Day 8</b>	<b>Group 1 ANAVIP/ANAVIP (n=39)</b>	<b>Group 2 ANAVIP/Placebo (n=38)</b>	<b>Group 3 Comparator product (n=37)</b>
<b>Yes</b>	4 (10.3%)	2 (5.3%)	11 (29.7%)
<b>No</b>	35 (89.7%)	36 (94.7%)	26 (70.3%)
<b>Treatment Group (vs. Group 3) Odds Ratio (95% CI<sup>1</sup>)</b>	0.275 (0.058, 1.048)	0.135 (0.014, 0.686)	

<sup>1</sup>CI= confidence interval

FDA conducted a post hoc analysis to assess the outcomes of the patients who presented with or without baseline coagulopathic effect in the three treatment groups. Using the pre-specified criteria for coagulopathic effect, it was found that ANAVIP/ANAVIP (Group 1) had the highest percentage of baseline coagulopathic subjects among the three groups [41.5% compared with 17.5% and 32.5% for the ANAVIP/Placebo (Group 2) and Comparator product (Group 3), respectively]. Thirty-three percent (33%) of all baseline coagulopathic subjects also experienced coagulopathic effect on either Day 5 or 8, compared to only 6% for baseline non-coagulopathic subjects. Only 18% of the subjects with baseline coagulopathic effect in Group 1 continued to remain coagulopathic at Days 5 or 8 compared to 58% in Group 3 (Table 6).

**Table 6. Coagulopathy by Treatment Group and Baseline Coagulopathy**

<b>Baseline Coagulopathy and Experienced coagulopathy on either Day 5 or 8</b>	<b>Group 1 ANAVIP/ANAVIP</b>	<b>Group 2 ANAVIP/Placebo</b>	<b>Group 3 Comparator product</b>	<b>Total</b>
<b>Number of subjects</b>	n=17	n=7	n=12	n=36
<b>Yes</b>	3 (17.65%)	2 (28.57%)	7 (58.33%)	12 (33.3%)
<b>No</b>	14 (82.35%)	5 (71.43%)	5 (41.67%)	24 (66.7%)
<b>No Baseline Coagulopathy and Experienced coagulopathy on either Day 5 or 8</b>	<b>Group 1 ANAVIP/ANAVIP</b>	<b>Group 2 ANAVIP/Placebo</b>	<b>Group 3 Comparator product</b>	<b>Total</b>
<b>Number of Subjects</b>	n=22	n=31	n=25	n=78
<b>Yes</b>	1 (4.55%)	0 (0%)	4 (16%)	5 (6.4%)
<b>No</b>	21 (95.45%)	31 (100%)	21 (84%)	73 (93.6%)

An exact logistic regression analysis adjusting for baseline coagulopathic effect and region was conducted and showed that treatment effect for both Groups 1 and 2 is statistically significant (Table 7). This analysis provides supportive evidence of the efficacy of ANAVIP.

**Table 7. Comparison Coagulopathic Effect Rates Adjusted for Baseline Coagulopathy**

	<b>Group 1 ANAVIP/ANAVIP (n=39)</b>	<b>Group 2 ANAVIP/Placebo (n=38)</b>
<b>Treatment Group (vs Comparator product)</b>	0.184 (0.033, 0.794)	0.121 (0.010, 0.764)
<b>Odds ration (95% CI<sup>1</sup>)</b>		

<sup>1</sup>CI= confidence interval

Analysis by snakebite type was performed but was limited due to the number of unknown snakebite types (n=43). However, 57 subjects who were envenomated by rattlesnakes showed more severe coagulopathic effects and resolution of these effects after treatment with ANAVIP as compared to 21 subjects who were envenomated by copperhead snakes. Due to limited coagulopathic effects in the copperhead snake bite subgroup, efficacy outcomes for late coagulopathies could not be evaluated.

## 15 REFERENCES

1. Seifert SA and Boyer LV: Recurrence phenomena after immunoglobulin therapy for snake envenomation: Part 1. Pharmacokinetics and pharmacodynamics of immunoglobulin antivenoms and related antibodies. Annals of Emergency Medicine 37(2):189-195; 2001.
2. Boyer LV, Seifert SA and Cain JS: Recurrence phenomena after immunoglobulin therapy for snake envenomation: Part 2. Guidelines for clinical management with crotaline Fab antivenom. Annals of Emergency Medicine 37(2):196-201; 2001.
3. Sanchez EE, Galan JA, Perez JC, et al. The efficacy of two antivenoms against the venom of North American snakes, Toxicon 41: 357-365; 2003.
4. Gold BS, Dart RC and Barish RA: Bites of venomous snakes. New England Journal of Medicine 347(5):347-56; 2002.
5. Boyer LV, Seifert SA, Clark RF, et al: Recurrent and persistent coagulopathy following Pit Viper envenomation. Archives of Internal Medicine 159:706-710; 1999.
6. Boyer LV, Chase PB, Degan JA, et al: Subacute coagulopathy in a randomized, comparative trial of Fab and F(ab')<sub>2</sub> antivenoms. Toxicon 74: 101-108; 2013.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

ANAVIP is supplied as a sterile, lyophilized preparation in a single-dose vial. When reconstituted with 10 mL of 0.9% NaCl solution, each vial contains not more than 12 mg per mL of protein, and will neutralize not less than 780 times the LD<sub>50</sub> of *Bothrops asper* (Terciopelo or fer-de-lance) venom and 790 times the LD<sub>50</sub> of *Crotalus simus* (formerly *Crotalus durissus*) (Central American Rattlesnake) venom, 244 times the LD<sub>50</sub> of *Crotalus adamanteus* (Eastern Diamondback Rattlesnake) venom, 147 times the LD<sub>50</sub> of *Crotalus atrox* (Western Diamondback Rattlesnake) venom, 185 times the LD<sub>50</sub> of *Crotalus scutulatus* (Mohave Rattlesnake) venom, 28 times the LD<sub>50</sub> of *Agkistrodon contortrix* (Copperhead) venom and 61 times the LD<sub>50</sub> of *Agkistrodon piscivorus* (Cottonmouth or Water Moccasin) venom in a mouse neutralization assay.

Each carton NDC 66621-0790-2 contains 1 vial of ANAVIP NDC 66621-0790-1.

- Store at room temperature (up to 25 °C (77 °F)). Brief temperature excursions are permitted up to 40 °C (104°F).
- DO NOT FREEZE.

- Use within 6 hours after reconstitution.
- Discard partially used vials.

## 17 PATIENT COUNSELING INFORMATION

- Advise patients to contact their physician immediately if they experience unusual bruising or bleeding (e.g., nosebleeds, excessive bleeding after brushing teeth, the appearance of blood in stools or urine, excessive menstrual bleeding, petechiae, excessive bruising or persistent oozing from superficial injuries) after hospital discharge.<sup>5</sup>
- Serious Allergic Reactions
  - o Advise patients to contact their physician immediately if they experience any signs and symptoms of delayed allergic reactions or serum sickness (e.g., rash, fever, myalgias, arthralgia, pruritus, urticaria) after hospital discharge [see *Hypersensitivity (5.1)*].<sup>4</sup>

### Manufactured by:

Laboratorios Silanes S.A. de C.V.

Toluca, Estado de Mexico, Mexico

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### Manufactured for:

Rare Disease Therapeutics, Inc.

2550 Meridian Blvd., Suite 150

Franklin, TN 37067

[www.raretx.com](http://www.raretx.com)

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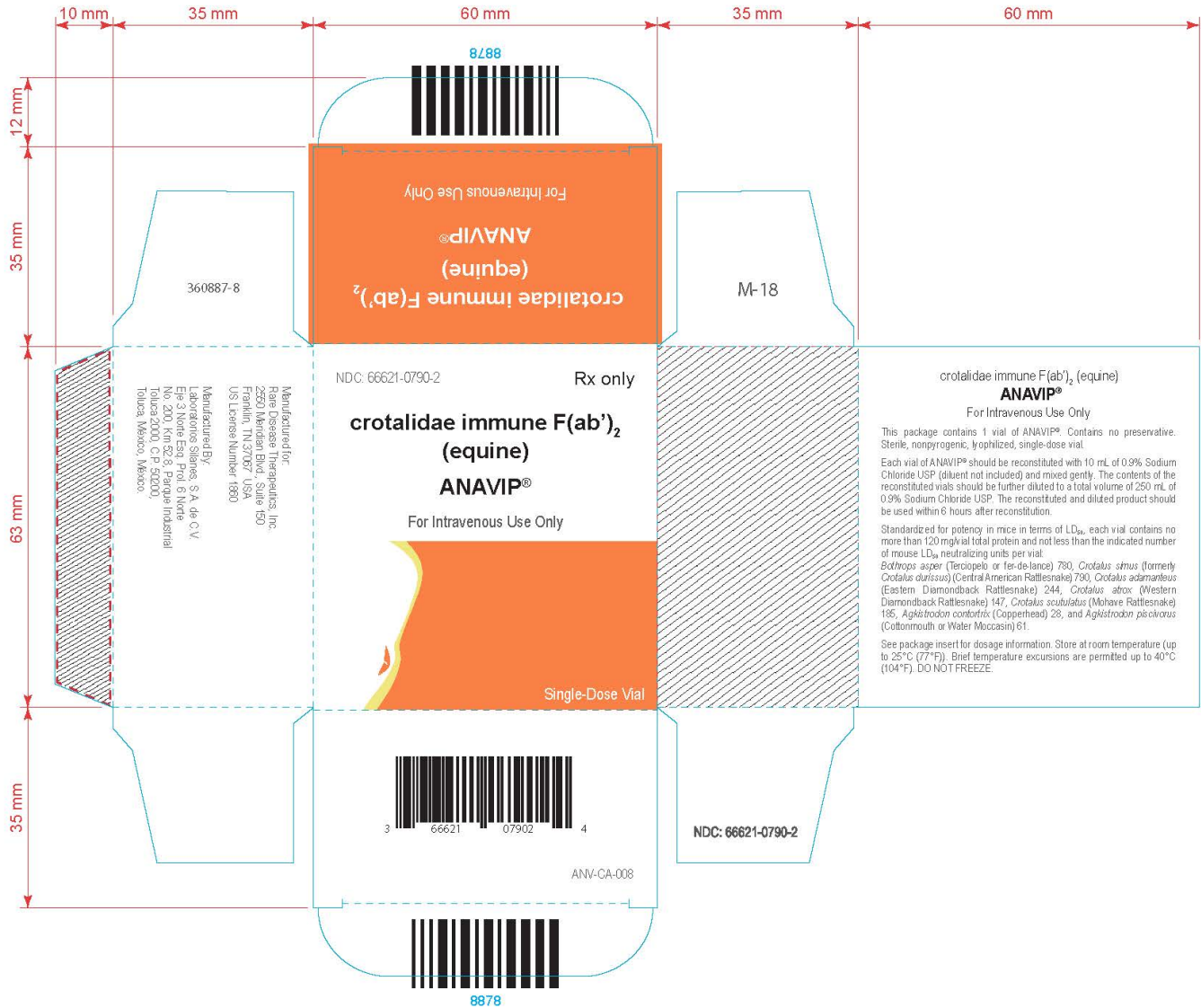


RDT Part No. ANV-PI-009

Silanes Part number: 360893-8

**PACKAGE LABEL**

**Anavip Carton label**



Panel de Control (Original Mecánico para someter)						
Tipo de Material:		Caja <input checked="" type="checkbox"/>	Etiqueta <input type="checkbox"/>	Aluminio <input type="checkbox"/>	Instructivo <input type="checkbox"/>	Otro <input type="checkbox"/>
Descripción: Cja Anavip Sol Iny Liof						
Dimensiones:		X= 60 mm	Y= 63 mm	Z= 35 mm	No. de Suaje:	M-18
				Escala:	100 %	
Código Interno (AR):		ANAVIP SOL INY-SEC-V.1		Tipo de barniz:		BAACBRPL
Fecha de Solicitud (AR):		ANV-CA-008 12 SEP 2023		Área sin barniz:		35 x 63 mm
Fecha de Elaboración:		27 SEP 2023		Digrama:		
Elaboró:		Ricardo Villavicencio Decaro		Pantones y acabados especiales:		Pantone 164 C Black C 80% Pantone Process Black C <input type="checkbox"/> Línea de Corte <input checked="" type="checkbox"/> Línea de Precorte <input type="checkbox"/> Línea de DobleZ <input checked="" type="checkbox"/> Área sin barniz
				Países a los que aplica:		<input checked="" type="checkbox"/> USA

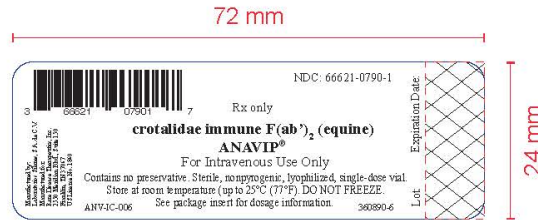
PNO-LOG-000012 F6 (V.1.0)

## Serialization Example of Anavip Carton label

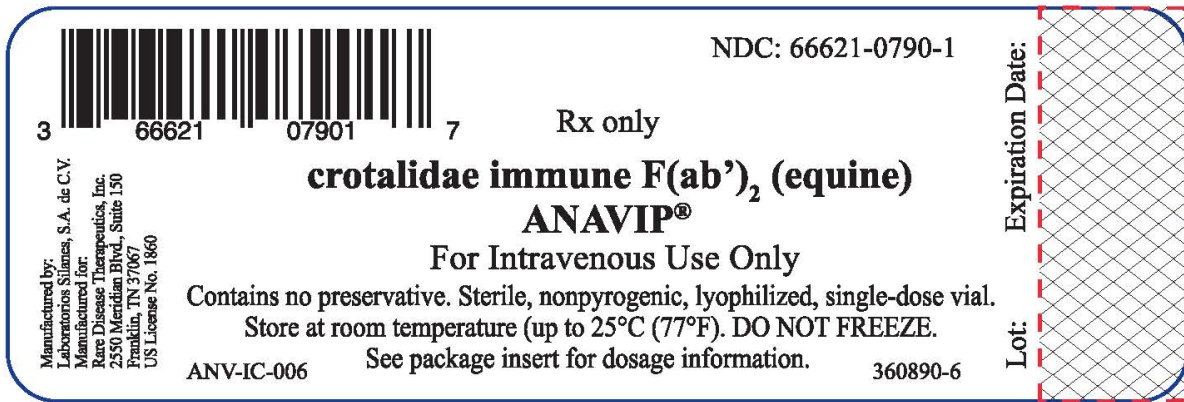




**Anavip Vial label**



Esc. 100%



Esc. 250%

Panel de Control para Original Mecánico			
Tipo de Material:	Caja <input type="checkbox"/> Etiqueta <input checked="" type="checkbox"/> Aluminio <input type="checkbox"/> Instructivo <input type="checkbox"/> Otro <input type="checkbox"/>	Pantones y acabados especiales:	
Descripción:	Etq Anavip	<input checked="" type="checkbox"/> Pantone Process Black C <input type="checkbox"/> Línea de Corte <input checked="" type="checkbox"/> Área sin barniz	
Dimensiones:	X= 72 mm Y= 24 mm	No. de Suaje:	No Aplica
Código de documento:	OM-000209 (3.0)	Escala:	100 %
Código del dibujo:	360890-6	C. Pharma:	No Aplica
Fecha de Marbete:	ANV-IC-006 APR 2021	Tipo de barniz:	<input checked="" type="checkbox"/> Barniz UV
Fecha de Elaboración:	08 MAR 2021	Área sin barniz:	<input checked="" type="checkbox"/> 9 x 24 mm
Elaboró:	Ricardo Villavicencio Decaro	Digrama:	
		Razón del Cambio No Aplica.	

PNO-LOG-000012 F1 (V. 1.0)

crotalidae immune f(ab)2(equine) injection, powder, lyophilized, for solution

### Product Information

<b>Product Type</b>	PLASMA DERIVATIVE	<b>Item Code (Source)</b>	NDC:66621-0790
<b>Route of Administration</b>	INTRAVENOUS		

### Active Ingredient/Active Moiety

<b>Ingredient Name</b>	<b>Basis of Strength</b>	<b>Strength</b>
<b>PIT VIPER (CROTALINAE) IMMUNE GLOBULIN ANTIVENIN (EQUINE)</b> (UNII: 92VV7G83ED) (PIT VIPER (CROTALINAE) IMMUNE GLOBULIN ANTIVENIN (EQUINE) - UNII:92VV7G83ED)	PIT VIPER (CROTALINAE) IMMUNE GLOBULIN ANTIVENIN (EQUINE)	12 mg in 1 mL

### Packaging

<b>#</b>	<b>Item Code</b>	<b>Package Description</b>	<b>Marketing Start Date</b>	<b>Marketing End Date</b>
1	NDC:66621-0790-2	1 in 1 CARTON		
1	NDC:66621-0790-1	10 mL in 1 VIAL; Type 0: Not a Combination Product		

### Marketing Information

<b>Marketing Category</b>	<b>Application Number or Monograph Citation</b>	<b>Marketing Start Date</b>	<b>Marketing End Date</b>
BLA	BLA125488	05/06/2015	

**Labeler** - Rare Disease Therapeutics, Inc (966133100)

**Registrant** - Rare Disease Therapeutics, Inc (966133100)

### Establishment

<b>Name</b>	<b>Address</b>	<b>ID/FEI</b>	<b>Business Operations</b>
Laboratorios Silanes S.A. de C.V.		588387584	manufacture(66621-0790)

Revised: 4/2024

Rare Disease Therapeutics, Inc