

IMPORTANT SAFETY INFORMATION

INDICATION

ANAVIP® [Crotalidae Immune F(ab')₂ (Equine)] is an equine-derived antivenin indicated for the management of adult and pediatric patients with North American rattlesnake envenomation.

CONTRAINDICATIONS

None.

ADVERSE REACTIONS

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

WARNINGS AND PRECAUTIONS

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.

Transmissible Infectious Agents

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

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.

Please see accompanying Full Prescribing Information for additional safety information.



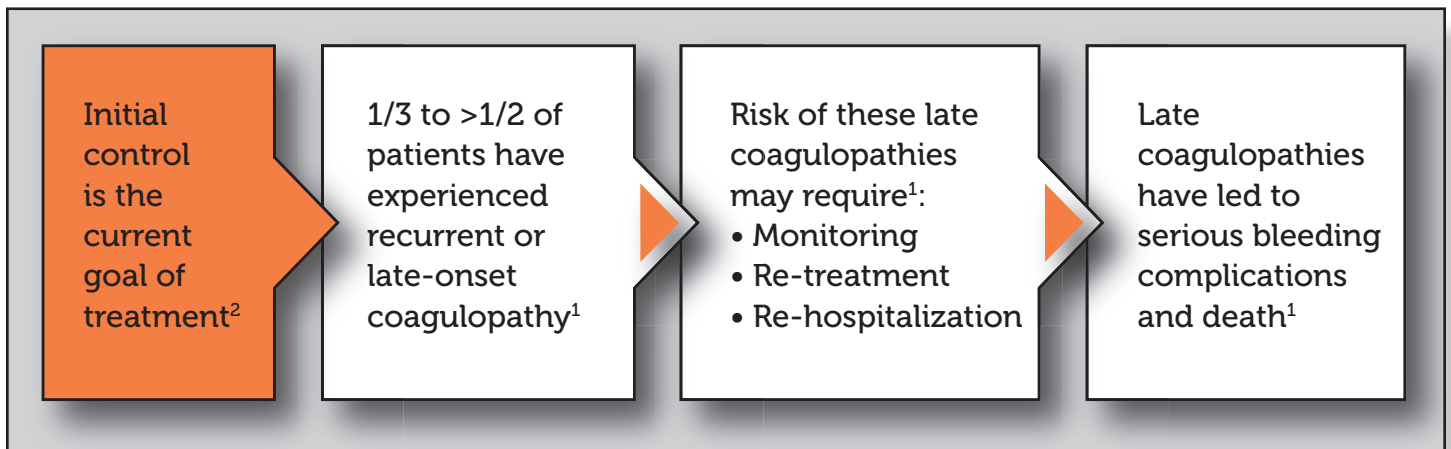
ANAVIP™

Crotalidae Immune F(ab')₂ (Equine)

Venom Has Met Its Match¹

Treating N.A. rattlesnake envenomation has both short-term and long-term concerns^{1,2}

Patients treated with a single Fab antivenom remain at risk after initial control¹



A PK mismatch may lead to late coagulopathy¹

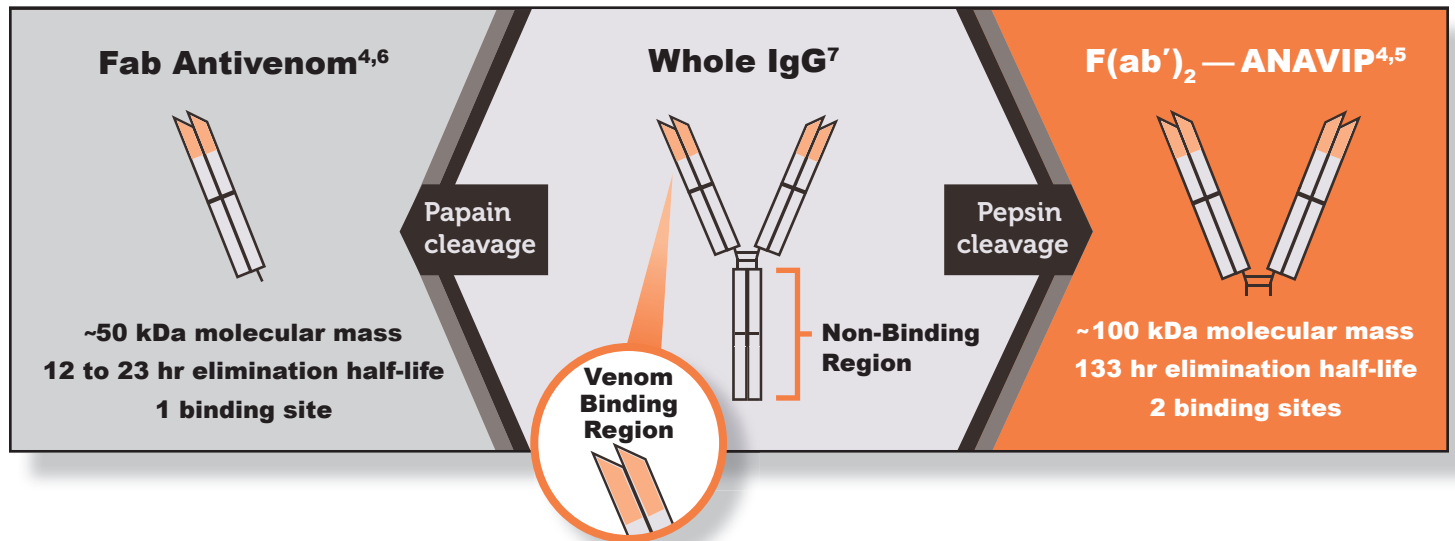
- ◆ Some venom components take significantly longer to clear than unbound single Fab antivenom fragments³
- ◆ A depot of unneutralized venom can remain in the body after initial control, resulting in prolonged absorption³
- ◆ Late coagulopathy can be as severe or worse than the presenting coagulopathy¹

Late coagulopathy is a persistent threat with single Fab antivenom^{1,4}

N.A.=North American; short-term=acute phase rattlesnake; long-term=subacute phase rattlesnake envenomation; Late coagulopathy=recurrent or late-onset coagulopathy; PK=pharmacokinetic; envenomation.

ANAVIP—a F(ab')₂ antivenom designed to circulate for weeks⁵

F(ab')₂ antivenom and single Fab antivenom have fundamental PK differences^{1,3,4}



ANAVIP—a PK profile optimized to match N.A. rattlesnake venom^{1,3,4}

- ◆ Elimination half-life for ANAVIP is 5.5 days, compared with <1 day with a single Fab antivenom^{5,6}
- ◆ A difference in half-life has been attributed to molecular mass^{4,7}
 - ❖ Unbound antivenom <70 kDa is more likely to be eliminated renally³

ANAVIP has distinct PK advantages over a single Fab antivenom^{4,6}

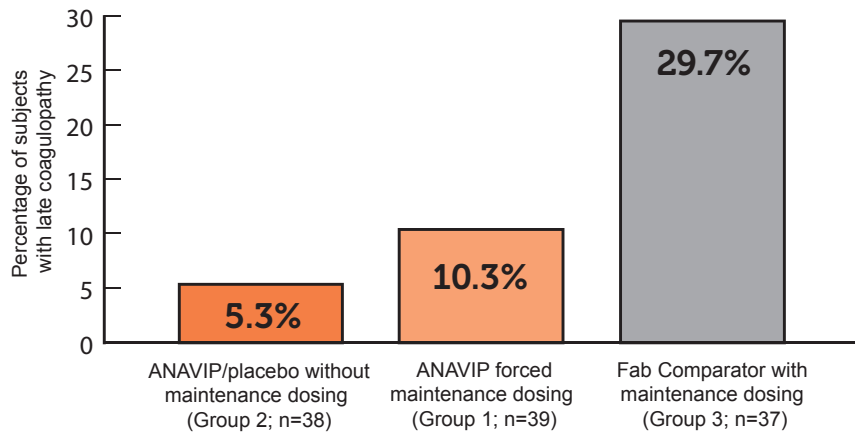
Please see front cover for full Important Safety Information and enclosed Full Prescribing Information for ANAVIP.

ANAVIPTM
Crotalidae Immune F(ab')₂ (Equine)

90% to 95% of people administered ANAVIP avoided late coagulopathy^{1,5}

ANAVIP without maintenance dosing significantly outperformed Fab Comparator^{1,a,b,e}

Incidence of late coagulopathy at Day 5 or Day 8^{1,5}



Lower risk of late coagulopathy after initial control¹

Study design: In a randomized, prospective, blinded, controlled, multicenter study of 121 patients experiencing envenomation in the United States, two ANAVIP regimens were compared with the approved regimen for the Fab Comparator. After achieving initial control, maintenance dosing was administered every 6 hr with either blinded study drug (Group 1 and Group 3) or placebo (Group 2). The efficacy endpoint was the proportion of patients experiencing a coagulopathic effect (defined as absolute platelet levels <150,000/mm³, fibrinogen levels <150 mg/dL, or clinical coagulopathy requiring intervention) on Day 5 or Day 8.⁵

- ◆ Late coagulopathy was seen at 1 study site using ANAVIP and 7 study sites using Fab Comparator¹
- ◆ ANAVIP significantly improved lowest mean platelet count^c and lowest mean fibrinogen level^d vs Fab Comparator¹
- ◆ ANAVIP required a 3.5- to 6-fold lower maximum protein load than Fab Comparator to neutralize toxins¹
- ◆ Treatment effect for ANAVIP was statistically significant in an exact logistic regression analysis adjusting for baseline coagulopathic effect and region^{5,b}

ANAVIP reduced the risk of late coagulopathy seen with Fab Comparator¹

^ap<0.05, Fisher's exact test, Group 1 and Group 2 compared with Group 3.

^bOdds ratio adjusted for baseline coagulopathy vs Group 3 (95% confidence interval) for Group 1 was 0.184 (0.033, 0.794) and for Group 2 was 0.121 (0.010, 0.764).

^cMean platelet nadir (253.4 +/- 80.3 [10³/mm³] for Group 1 and 247.5 +/- 62.6 [10³/mm³] for Group 2 vs 208 +/- 76.9 [10³/mm³] for Group 3; p<0.05).

^dMean fibrinogen nadir (340.0 +/- 70.0 mg/dL for Group 1 and 367.8 +/- 93.9 mg/dL for Group 2 vs 309.9 +/- 116.4 mg/dL for Group 3; p<0.05). Significance was only demonstrated in Group 2.

^eThe 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 rattlesnake envenomation.

ANAVIP safety profile⁵

Pooled adverse reaction data by body system (N=86)⁵

65 (76%) Patients reporting at least one adverse event

47 (55%) Skin and subcutaneous tissue disorders

37 (43%) Pruritus

10 (12%) Rash

4 (5%) Blister

3 (4%) Erythema

28 (33%) Gastrointestinal disorders

20 (23%) Nausea

5 (6%) Vomiting

19 (22%) Musculoskeletal and connective tissue disorders

9 (11%) Arthralgia

6 (7%) Myalgia

5 (6%) Pain in extremity

21 (24%) General disorders and administration site conditions

7 (8%) Edema, peripheral

3 (4%) Chills

4 (5%) Pyrexia

12 (14%) Nervous system disorders

5 (6%) Headache

4 (5%) Psychiatric disorders

2 (2%) Anxiety

2 (2%) Insomnia

4 (5%) Metabolism and nutrition disorders

2 (2%) Dehydration

5 (6%) Respiratory, thoracic, and mediastinal disorders

1 (1%) Dyspnea

2 (2%) Blood and lymphatic system disorders

1 (1%) Thrombocytopenia

No drug-related serious adverse reactions seen in clinical trials¹

◆ While 9 patients experienced serious adverse reactions after receiving ANAVIP, all were considered unrelated to ANAVIP¹

Comparable safety profile with low incidence of immune reactions¹

◆ In the Phase 3 trial, the plasma source and molecular structure were not associated with an increase in immune reactions or miscellaneous adverse reactions¹

❖ 1 patient in each study group experienced acute serum reaction. All 3 patients tolerated subsequent doses after resolution¹

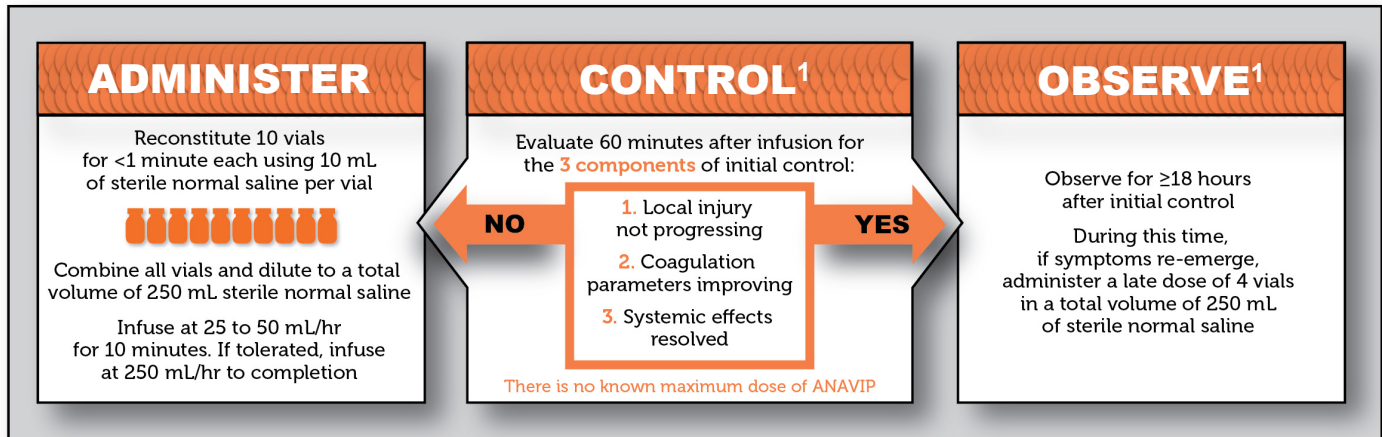
❖ 1 patient in each study group experienced symptoms suggestive of serum sickness. No immune reaction was severe¹

Please see front cover for full Important Safety Information and enclosed Full Prescribing Information for ANAVIP.

ANAVIPTM
Crotalidae Immune F(ab')₂ (Equine)

ANAVIP eliminates scheduled maintenance dosing after initial control^{1,5}

Reconstitutes quickly with standardized dosing⁵



See accompanying Full Prescribing Information for complete dosage and administration instructions.

ANAVIP is a long-lasting antivenom that could replace a single Fab antivenom where indicated^{1,5}

≥5.5x longer half-life^{5,6}

Significantly lower odds of late coagulopathy⁵

Comparable safety profile with no increase in immune reactions¹

Quick reconstitution with no scheduled maintenance dosing^{1,5}

References: 1. Bush SP, Ruha A-M, Seifert SA, et al. Comparison of F(ab)₂ versus Fab antivenom for pit viper envenomation: a prospective, blinded, multicenter, randomized clinical trial. *Clin Tox.* 2015;53(1):37-45. 2. Lavonas EJ, Ruha A-M, Banner W, et al. Unified treatment algorithm for the management of crotaline snakebite in the United States: results of an evidence-informed consensus workshop. *BMC Emerg Med.* 2011;11(2):1-15. 3. Seifert SA, Boyer LV. Recurrence phenomena after immunoglobulin therapy for snake envenomations: part 1. Pharmacokinetics and pharmacodynamics of immunoglobulin antivenoms and related antibodies. *Ann Emerg Med.* February 2001;37:189-195. 4. World Health Organization. WHO guidelines for the production, control, and regulation of snake antivenom immunoglobulins; 2016. http://www.who.int/biologicals/expert_committee/Antivenom_WHO_Guidelines_DJW_DEB_mn_cp.pdf. Accessed January 7, 2019. 5. ANAVIP [Crotalidae Immune F(ab)₂ (Equine)] Prescribing Information. Rare Disease Therapeutics, Inc.; Franklin, TN. June 2019. 6. CroFab [crotalidae polyvalent immune fab (ovine)] Prescribing Information. BTG International Inc.; West Conshohocken, PA. August 2018. 7. Gutierrez JM, Leon G, Lomonte B. Pharmacokinetic-pharmacodynamic relationships of immunoglobulin therapy for envenomation. *Clin Pharmacokinet.* 2003;42(8):721-741.

Please see front cover for full Important Safety Information and enclosed Full Prescribing Information for ANAVIP.

ANAVIPTM
Crotalidae Immune F(ab)₂ (Equine)

Poison Control Center: 1-800-222-1222
To report suspected adverse reactions,
call: 1-877-851-1902
To order ANAVIP, call: 1-866-830-7350



www.ANAVIP.com

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®

crotalidae immune F(ab')₂ (equine) Lyophilized Powder for Solution for Injection For Intravenous Use Only

Initial U.S. Approval: 2015

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

Intravenous use only

Dose	No. of Vials	Infusion Rate
Initial dose	10 vials	Infuse intravenously over 60 minutes. (2)
Additional dose(s) to achieve initial control	10 vials (as needed)	Infuse intravenously over 60 minutes. (2)
Observation and late dosing	4 vials	Infuse intravenously over 60 minutes. (2)

- Initiate administration as soon as possible after rattlesnake bite in patients who develop signs of envenomation (e.g., local injury, coagulation abnormality, or systemic signs of envenomation).
- 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

FULL PRESCRIBING INFORMATION: CONTENTS*

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*Sections or subsections omitted from the full prescribing information are not listed.

Each vial contains a sterile, lyophilized preparation containing not more than 120 milligrams total protein and not less than the indicated number of mouse LD₅₀ neutralizing units (3):

Snake Species Used for Standardization	Minimum Mouse LD ₅₀ Units per Vial
<i>Bothrops asper</i>	780
<i>Crotalus durissus</i>	790

-----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.

-----USE IN SPECIFIC POPULATIONS-----
Pregnancy: No human or animal data. Use only if clearly needed. (8.1)

See Section 17 for PATIENT COUNSELING INFORMATION.

Revised: 06/2020

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

For intravenous use only.

Administer ANAVIP as soon as possible after rattlesnake 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 rattlesnake 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. Poison Control Centers are a helpful resource for individual treatment advice.
- 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 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.
- Use reconstituted and diluted product within 6 hours.
- Discard partially or unused reconstituted and diluted product.

Additional Dosing to Achieve Initial Control

- Administer additional 10 vial doses if needed to arrest the progressive symptoms and repeat every hour. There is no known maximum dose.
- Repeat above steps for *initial dose* as many times as needed until local signs of envenomation are not progressing, systemic symptoms are resolved and coagulation parameters have normalized or are trending toward normal.
- Prepare as described above for the 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 for 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 LD₅₀ neutralizing units:

Snake Species Used for Standardization	Minimum Mouse LD₅₀ Units per Vial
<i>Bothrops asper</i>	780
<i>Crotalus durissus</i>	790

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.⁴

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 1 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 1. Incidence of Adverse Events in Clinical Studies of ANAVIP by Body System

	ANAVIP [N=86] (%)
Patients Reporting at Least One Adverse Event	65 (76%)
Skin and subcutaneous tissue disorders	47 (55%)
Pruritus	37 (43%)
Rash	10 (12%)
Blister	4 (5%)
Erythema	3 (4%)
Gastrointestinal disorders	28 (33%)
Nausea	20 (23%)
Vomiting	5 (6%)
Musculoskeletal and connective tissue disorders	19 (22%)
Arthralgia	9 (11%)
Myalgia	6 (7%)
Pain in extremity	5 (6%)
General disorders and administration site conditions	21 (24%)
Edema peripheral	7 (8%)
Chills	3 (4%)
Pyrexia	4 (5%)
Nervous system disorders	12 (14%)
Headache	5 (6%)
Psychiatric disorders	4 (5%)
Anxiety	2 (2%)
Insomnia	2 (2%)
Metabolism and nutrition disorders	4 (5%)
Dehydration	2 (2%)
Respiratory, thoracic and mediastinal disorders	5 (6%)
Dyspnea	1 (1%)
Blood and lymphatic system disorders	2 (2%)
Thrombocytopenia	1 (1%)

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. ANAVIP should be given to a pregnant woman only if clearly needed.

8.2 Lactation

Risk Summary

It is not known whether ANAVIP is excreted in human breast milk. Because many drugs are excreted in human milk, caution should

be exercised when ANAVIP is administered to a nursing woman.

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 the 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')₂ (equine)] is a sterile, lyophilized, polyvalent preparation of equine immunoglobulin F(ab')₂ fragments, manufactured from the plasma of horses immunized with venom of *Bothrops asper* and *Crotalus durissus*. The product is obtained by pepsin digestion of horse plasma to remove the F_c portion of immunoglobulin, followed by fractionation and purification steps. The F(ab')₂ 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, 18.2-85.8 mg of sucrose, and 16.2-51.8 mg of glycine as stabilizers. Trace amounts of pepsin (≤ 160 ng/vial), cresol (≤ 0.058 mg/vial), borates (≤ 1 mg/vial), and sulfates (≤ 1.7 mg/vial) may be present from the manufacturing process. Each vial contains no more than 120 mg of protein and will neutralize not less 780 times the LD₅₀ of *Bothrops asper* venom and 790 times the LD₅₀ of *Crotalus durissus* 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')₂ fragments of immunoglobulin G (IgG) that bind and neutralize venom toxins, facilitating redistribution away from target tissues and elimination from the body.^{1,2}

12.3 Pharmacokinetics

Fourteen healthy volunteers each received one vial of intravenous (IV) dose (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 2.

Table 2. Pharmacokinetic Parameters of the ANAVIP Antivenin Following a Single IV Dose to Healthy Volunteers (n=13)

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

13 NONCLINICAL TOXICOLOGY

In a published non-GLP study³, ANAVIP and another licensed pit viper antivenin were tested and cross-reactivity to the venoms of multiple different pit vipers including rattlesnakes was demonstrated in rabbits and mice. Animal studies to determine a NOAEL were unsuccessful due to technical limitations that prevented determination of a systemically toxic dose.

14 CLINICAL STUDIES

Study 1 was a randomized, prospective, open-label, controlled, comparative, multicenter study conducted in 12 patients aged 18 to 70 years of age with signs of pit viper envenomation.⁶ The subjects received either a licensed 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/mm³, and all 6 had fibrinogen levels above 150 mg/dL. During the follow-up phase two patients exhibited platelets below 150,000/mm³ 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/mm³. One subject's platelets were 114,000/mm³ 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/mm³, with no downward trend; 1 subject's platelet counts was 127,000/mm³ on follow-up Day 1, reached 160,000/mm³ on Day 4 and continued trending upward. All 6 subjects in 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 pit viper antivenin (comparator) conducted in patients with 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/mm³ as measured on either Study Day 5 (±1 day) or 8 (±1 day); absolute fibrinogen levels <150 mg/dL as measured on either Study Day 5 (±1 day) or 8 (±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 3. 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 rattlesnake envenomation.

Table 3. Comparison of Coagulopathic Effect Rates on Study Day 5 or Study Day 8

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

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 4).

Table 4. Coagulopathy by Treatment Group and Baseline Coagulopathy

Baseline coagulopathy	Experienced coagulopathy on either Day 5 or 8	ANAVIP/ANAVIP	ANAVIP/Placebo	Comparator product	Total
Yes	Number of subjects	N=17	N=7	N=12	N=36
	Yes	3 (17.65%)	2 (28.57%)	7 (58.33%)	12 (33.3%)
	No	14 (82.35%)	5 (71.43%)	5 (41.67%)	24 (66.7%)
No	Number of subjects	N=22	N=31	N=25	N=78
	Yes	1 (4.55%)	0 (0%)	4 (16%)	5 (6.4%)
	No	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 5). This analysis provides supportive evidence of the efficacy of ANAVIP.

Table 5. Comparison of Coagulopathic Effect Rates Adjusted for Baseline Coagulopathy

	Group 1 (N=39) ANAVIP/ANAVIP	Group 2 (N=38) ANAVIP/Placebo
Treatment Group (vs. Comparator product)		
Odds Ratio (95% CI ¹)	0.184 (0.033, 0.794)	0.121 (0.010, 0.764)

¹CI= 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. Efficacy outcomes could not be evaluated in the copperhead snake bite subgroup due to these limited coagulopathic effects.

15 REFERENCES

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3. Sanchez EE, Galan JA, Perez JC, et al. The efficacy of two antivenoms against the venom of North American snakes. Toxicol 41: 357-365; 2003.
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16 HOW SUPPLIED/STORAGE AND HANDLING

ANAVIP is supplied as a sterile lyophilized preparation in a single-use vial. When reconstituted with 10mL of 0.9% NaCl solution, each vial contains not more than 12 mg per mL of protein, and will neutralize not less 780 times the LD₅₀ of *Bothrops asper* venom and 790 times the LD₅₀ of *Crotalus durissus* 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.⁵
- Serious Allergic Reactions
 - 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)*].⁴

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