A.H.F.S. Category 80:04

Wyeth®
Antivenin (Micrurus fulvius)
(Equine Origin)
North American
Coral Snake Antivenin

Composition
Antivenin (Micrurus fulvius), Wyeth, is a refined, concentrated, and lyophilized preparation of serum globulins obtained by fractionating blood from healthy horses that have been immunized with eastern coral snake (Micrurus fulvius fulvius) venom. Prior to lyophilization, the product contains 0.25% phenol and 0.005% thimerosal (mercury derivative).

Antivenin (Micrurus fulvius), Wyeth, is standardized for potency in mice in terms of its LD_{50} neutralizing capacity per milliliter as determined by intravenous injection of a graded series of Antivenin—M.f. fulvius venom mixtures. Based on this assay system, the reconstituted contents of each vial (10 ml) will neutralize approximately 250 mouse LD_{50} or approximately 2 mg of M.f. fulvius venom.

The results of cross-neutralization tests indicate that Antivenin (Micrurus fulvius), Wyeth, will neutralize the venom of M. fulvius tenere (Texas coral snake) but will NOT neutralize the venom of Micruroides euryxanthus (Arizona or Sonoran coral snake).

INDICATION
Antivenin (Micrurus fulvius) (equine origin) is indicated only for the treatment of envenomation caused by bites of those coral snakes specified in the following paragraph.

Coral Snakes and Bites
Two genera of coral snakes are found in the United States—Micrurus (including the eastern and Texas varieties) and Micruroides (the Sonoran or Arizona variety), found only in southeastern Arizona and southwestern New Mexico.

There are two subspecies of Micrurus fulvius native to the United States: 1) M.f. fulvius, found in the area from eastern North Carolina through the tip of Florida and in the Gulf coastal plain to the Mississippi River; 2) M.f. tenere, the Texas coral snake, found west of the Mississippi River in Louisiana, Arkansas, and Texas. These subspecies can be differentiated by experts but are very similar in appearance. The adult coral snake (M. fulvius) may vary between 20 to 44 inches in length, has a black snout, and yellow, black, and red bands encircling the body. The red and black rings are wider than the INTERPOSED yellow rings. However, melanistic (all black), albino (all white), and partially pigmented forms may be rarely seen. In contrast to the pit vipers (rattlesnakes, copperheads, cottonmouths), coral snakes have round pupils and lack facial pits. They are secretive and rarely bite unless disturbed or HANDLED. The fangs are short, erect, and fixed to the maxilla. Venom flows through the fang from a duct at its base. Pit vipers usually strike and then rapidly withdraw the head after insertion of the fangs. However, coral snakes, with their less efficient biting mechanism, may strike, hold on, and “chew”, presumably so a

sufficient amount of venom can be introduced to immobilize the prey. This “chewing” action may result in more than one “bite”, and the victim MAY recall the colorful snake “hanging on” for a “minute” or so. Permitted to bite under laboratory conditions, M.f. fulvius have yielded 1 to 28 mg of venom.[1, 2] Fix and Minton,[2] after measuring the venom yields of 14 M.f. fulvius and the length of the individual snakes, found a positive linear relationship; six snakes measuring between 29 and 44 inches in length yielded 14 to 28 mg of dried venom, whereas eight measuring 21 to 28 inches in length yielded 2 to 10 mg. The adult human LD_{100} of M.f. fulvius venom has been estimated to be 4 to 5 mg of dried venom. Coral snake venom is chiefly paralytic (neurotoxic) in action, and usually only minimal-to-moderate tissue reaction and pain occur at the site of bite. Most coral snakebites are inflicted upon the upper extremities, especially the hands and fingers. The limited size of the biting apparatus makes it difficult for the coral snake to penetrate clothing or to successfully grasp any part of the body except the hands and feet. Hence, in areas where coral snakes are found, adherence to the simple practices of NEVER picking up colorful snakes, NEVER putting the hands where they cannot be seen (reaching behind rocks, logs, flowers, etc.), and always wearing leather shoes would substantially reduce the chances of a bite.

There are few published reports describing envenomation caused by coral snakebites.[1, 3-7] It has been estimated that only 20±5 coral snakebites occur in the United States each year.[3] Although those persons who exhibit one or more fang punctures seem most likely to develop envenomation, there is NO way to predict which victim may be envenomated by a coral snakebite. Even a reliable observation that the biting snake did or did not "hang on" should NOT be used to predict the likelihood or possible severity of envenomation. Coral snakebites, like bites by crotalids, are not always followed by envenomation. However, in contradistinction to crotalid bites, in which moderate-to-severe envenomation usually can be predicted by rapid onset of the local effects (e.g., pain, discoloration, edema), severe and even fatal envenomation from a coral snakebite can be present without any significant local tissue reaction.

Systemic signs and symptoms of envenomation usually begin from one to seven hours after the bite but may be delayed for as long as 18 hours. If envenomation occurs, the symptoms and signs may progress rapidly and precipitously. Paralysis has been observed within 2-1/2 hours post bite and appears to be of a bulbar type, involving cranial motor nerves. Death from respiratory paralysis has occurred within four hours of the accident.

SYSTEMIC signs and symptoms of envenomation may include euphoria, lethargy, weakness, nausea, vomiting, excessive salivation, ptosis of the eyelids, dyspnea, abnormal reflexes, convulsions, and motor weakness or paralysis, including complete respiratory paralysis. LOCAL signs and symptoms may include scratch marks or fang puncture wounds, no-to-moderate edema, erythema, pain at the bite site, and paresthesia in the bitten extremity.

TREATMENT OF CORAL SNAKEBITE: If practical, immobilize victim immediately and completely. Carry the victim to the nearest hospital as soon as possible. If complete immobilization is not practical, splint the bitten extremity to limit spread of venom. If the biting snake was killed, bring it to the hospital also.

ANY victim of a bite by a coral snake with ANY evidence of a break in the skin caused by the snake's teeth or fangs should be HOSPITALIZED for observation and/or treatment. Cleanse the bite area with germicidal soap and water to remove any venom remaining on the skin. If fang puncture wounds are present, application of a tourniquet and incision and suction over the fang punctures has been recommended,[1, 3] even though there is no evidence to indicate that incision and suction are or are not of value in removing coral snake venom. In addition to maintaining close observation of the patient for 24 hours, which should include checking the respiratory rate every 30 minutes, make sure the following will be available and ready for immediate use should need arise:

– a supply of Antivenin (Micrurus fulvius)

– an oxygen supply

– a mechanical respirator

– facilities and equipment for a tracheostomy

– the services of an anesthesiologist

Appropriate horse-serum sensitivity tests should be done so that, in case administration of Antivenin is subsequently required, a decision on how to proceed will have been made. Parrish and Khan[3] have recommended intravenous administration of coral snake antivenin to patients with one or more fang puncture wounds as soon as possible and before onset of symptoms and signs of envenomation.

If symptoms or signs of envenomation occur in a patient under observation or are already present at the time the patient is first seen, give Antivenin (Micrurus fulvius) promptly by the intravenous route. With vigorous treatment and careful observation, patients with complete respiratory paralysis have recovered, indicating that the respiratory paralysis is reversible.[4, 5] Hemoglobinuria has been observed in experimental animals envenomated by coral snakes. Hence, continuous bladder drainage is recommended with careful attention to urinary output and blood electrolyte balance.

Appropriate tetanus prophylaxis is indicated as for any other potentially contaminated puncture wound.

CONTRAINDICATIONS

For persons with coral snake envenomations threatening life or limb, there are no contraindications to administration of Antivenin. However, administration to persons known to be allergic to horse serum, either by history or as a result of an appropriate sensitivity test, requires careful judgement and considerable experience in the use of antivenoms of equine origin. Healthcare providers must be prepared to manage severe, immediate allergic reactions (anaphylaxis) seen with Antivenins of equine origin.[8,9,10,11]

Antivenin should never be administered prophylactically to asymptomatic patients.[12]

WARNINGS

Patients sensitive to Antivenin or horse serum may develop anaphylaxis. Therefore, it is essential that prior to intravenous (IV) or intramuscular (IM) Antivenin administration a proper skin test be performed, interpreted, and therapy modified if indicated.

There have been isolated reports of cardiac arrest and death associated with use of Antivenin (Crotalidae) Polyvalent (equine origin).[13] Although this experience has not been reported with Antivenin (coral snake), because of the similarity of these Antivenin products, this reaction cannot be ruled out for Antivenin (Micrurus fulvius) (equine origin).

PRECAUTIONS

General

Constant attendance and observation for untoward response is MANDATORY whenever horse serum is administered intravenously so that, should such occur, injection may be discontinued and appropriate treatment instituted immediately.

Those responsible for administration and/or monitoring administration of Antivenin should be familiar with current recommendations for treatment of severe, immediate, systemic reactions (anaphylaxis) associated with use of heterologous sera.

Therapy with beta-adrenergic blockers, including cardioselective agents, has been associated with an increased severity of acute anaphylaxis (see **Drug Interactions**).

Morphine or other narcotics that depress respiration are contraindicated. Sedatives should be used with extreme caution (see **Drug Interactions**).

The physician should be familiar with the package brochure and the pertinent published medical literature concerning envenomation resulting from coral snakebites, as well as the currently acceptable concepts of nonspecific treatment for venomous snakebites.

Precautions to be Taken in Administration of Horse Serum

Before administration of any product prepared from horse serum, appropriate measures must be taken in an effort to detect the presence of dangerous sensitivity: (1) A careful review of the patient's history, including any report of (a) asthma, hay fever, urticaria, or other allergic manifestations; (b) allergic reactions upon exposure to horses; and (c) prior injections of horse serum. (2) A suitable test for detection of sensitivity. A skin test should be performed in every patient prior to administration, regardless of clinical history.

Skin test–Inject intradermally 0.02 to 0.03 ml of a 1:10 dilution of Normal Horse Serum or Antivenin. A control test on the opposite extremity, using Sodium Chloride Injection, USP, facilitates interpretation. Use of larger amounts for the skin-test dose increases the likelihood of false-positive reactions, and in the exquisitely sensitive patient, increases the risk of a systemic reaction from the skin-test dose. A 10% rate of false negative skin test reactions has been reported with the use of Antivenin (Crotalidae) Polyvalent (equine origin).[14] Although this experience has not been reported with Antivenin (coral snake), because of the similarity of these Antivenin products, this reaction cannot be ruled out for Antivenin (Micrurus fulvius) (equine origin).

A 1:100 or greater dilution should be used for preliminary skin testing if the history suggests sensitivity. A positive reaction to a skin test occurs within five to thirty minutes and is manifested by a wheal with or without pseudopodia and surrounding erythema. In general, the shorter the interval between injection and the beginning of the skin reaction, the greater the sensitivity.

If the history is negative for allergy and the result of a skin test is negative, proceed with administration of Antivenin as outlined above. If the history is positive and a skin test is strongly positive, administration may be dangerous, especially if the positive sensitivity test is accompanied by systemic allergic manifestations. In such instances, the risk of administering Antivenin must be weighed against the risk of withholding it, keeping in mind that severe envenomation can be fatal. (See last paragraph of this section.)

A negative allergic history and absence of reaction to a properly applied skin test do not rule out the possibility of an immediate reaction. Also, a negative skin test has no bearing on whether or not delayed serum reactions (serum sickness) will occur after administration of the full dose.

If the history is negative, and the skin test is mildly or questionably positive, administer as follows to reduce the risk of a severe immediate systemic reaction: (a) Prepare, in separate sterile vials or syringes, 1:100 and 1:10 dilutions of Antivenin. (b) Allow at least 15 minutes between injections and proceed with the next dose if no reaction follows the previous dose. (c) Inject subcutaneously, using a tuberculin-type syringe, 0.1, 0.2, and 0.5 ml of the 1:100 dilution at 15-minute intervals; repeat with the 1:10 dilution, and finally undiluted Antivenin. (d) If a systemic reaction occurs after any injection, place a tourniquet proximal to the site of injections and administer an appropriate dose of epinephrine, 1:1000, proximal to the tourniquet or into another extremity. Wait at least 30 minutes before injecting another dose. The amount of the next dose should be the same as the last that did not evoke a reaction. (e) If no reaction occurs after 0.5 ml of undiluted Antivenin has been administered, switch to the intramuscular route and continue doubling the dose at 15-minute intervals until the entire dose has been injected intramuscularly or proceed to the intravenous route as described below under **Dosage and Administration.**

Drug Interactions

Morphine or other narcotics that depress respiration are contraindicated. Sedatives should be used with extreme caution.

Therapy with beta-adrenergic blockers, including cardioselective agents, has been associated with an increased severity of acute anaphylaxis.

Anaphylaxis may be prolonged and resistant to conventional treatment in patients receiving beta-adrenergic blockers. The pharmacotherapeutic actions of epinephrine and other adrenergic agents may be altered, and larger than usual doses may be required.[15]

Dosage and Administration

IMPORTANT: Before administration, read sections on "**CONTRAINDICATIONS, WARNINGS, PRECAUTIONS** and **Adverse Reactions**" Since the possibility of a severe immediate reaction (anaphylaxis) always exists whenever horse serum is administered, appropriate therapeutic agents, such as tourniquet, oxygen supply, epinephrine 1:1000, and another injectable pressor amine (NOT corticosteroids), must be ready for immediate use.

Start an intravenous drip of 250 to 500 ml of Sodium Chloride Injection, USP. If the results of appropriate tests have indicated the patient is not dangerously hypersensitive to horse serum, and depending on the nature and severity of the signs and symptoms of envenomation, administer the contents of 3 to 5 vials (30 to 50 ml) INTRAVENOUSLY by slow injection directly into the intravenous tubing or by adding to the reservoir bottle of the intravenous drip. (If added to reservoir bottle, mix by gentle swirling—DO NOT SHAKE.) In either case, the first 1 or 2 ml should be injected over a 3- to 5-minute period with careful observation of the patient for evidence of allergic reaction. If no signs or symptoms of anaphylaxis appear, continue the injection or intravenous infusion. The rate of delivery is regulated by the severity of signs and symptoms of envenomation and tolerance of Antivenin. However, until the equivalent of 30 to 50 ml of undiluted Antivenin has been given, administer at the maximum safe rate for intravenous fluids, based on body weight and general condition of the patient. For instance, if given by intravenous drip to a previously healthy adult, allow 250 or 500 ml to run in within 30 minutes; in small children, allow the first 100 ml to run in rapidly but then decrease to a rate not to exceed 4 ml per minute. Response to treatment may be rapid and dramatic. Observe the patient carefully and administer additional Antivenin intravenously as required.

According to the data reported by Fix and Minton[2] and cited above concerning venom yields obtained under artificial but probably physiological biting conditions, some envenomated patients may require administration of the contents of 10 or more vials to neutralize the venom dose injected by the biting snake if the entire venom load were delivered by the bite(s).

Snakes' mouths do not harbor *Clostridium tetani*. However, appropriate tetanus prophylaxis is indicated, since tetanus spores may be carried into the fang puncture wounds by dirt present on skin at time of bite or by nonsterile first-aid procedures.

A broad-spectrum antibiotic in adequate dosage is indicated if local tissue damage is evident.

Technique for Reconstituting the Dried Antivenin

Pry off the small metal disc in the cap over the diaphragms of the vials of Antivenin and diluent. Swab the exposed surface of the rubber diaphragms of both vials with an appropriate germicide. With a sterile 10 ml syringe and needle, withdraw the diluent (Sterile Water for Injection, USP) from the vial of diluent and insert the needle through the stopper of the vacuum-containing vial of Antivenin. The vacuum in the Antivenin vial will pull the diluent out of the syringe into the vial. However, delivery of 10 ml of diluent may not always exhaust the vacuum in the Antivenin vial. If all vacuum is not exhausted, reconstitution may be more difficult. Therefore, either disconnect the needle from the syringe and allow room air to be pulled into the Antivenin vial until all vacuum is released from the container or withdraw the syringe with attached needle from the vial, pull 10 ml of room air into the syringe and reinsert needle with attached syringe

containing room air through stopper and repeat, if necessary, to release any remaining vacuum. At the first introduction of diluent into the vaccine vial, it is important for the needle to be pointed at the center of the lyophilized pellet of Antivenin so that the diluent stream will wet the pellet. If the diluent stream is not directed at the pellet but allowed to run down the inside wall of the vial, the pellet will float up and adhere to the stopper thereby rendering complete reconstitution much more difficult. Agitate by swirling, NOT by shaking, for 1 minute, at 5-minute intervals. Gentle agitation will hasten complete dissolution of the lyophilized Antivenin. Shaking causes foaming and if the diluent stream is not properly directed as described earlier, pieces of the pellet may get caught in the foam and will be very difficult to wet. Complete reconstitution usually requires at least 30 minutes.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The color of reconstituted Antivenin may vary from clear to slight yellowish or greenish.

Before each administration, gently swirl the vial to dissolve the contents.

Before any Antivenin is administered, an appropriate horse-serum sensitivity test must be done so that, in case administration of Antivenin is subsequently required, a decision on how to proceed will have been made (see **PRECAUTIONS**).

Adverse Reactions

Immediate systemic reactions (allergic reactions or anaphylaxis) can occur whenever a horse-serum-containing product is administered. An immediate reaction (shock, anaphylaxis) usually occurs within 30 minutes. Symptoms and signs may develop before the needle is withdrawn and may include apprehension, flushing, itching, urticaria; edema of the face, tongue, and throat; cough, dyspnea, cyanosis, vomiting, and collapse. There have been isolated reports of cardiac arrest and death associated with Antivenin (Crotalidae) Polyvalent (equine origin) use. However, serious immediate reactions to Antivenin are rare. In skin-test-negative patients, Antivenin caused a true immediate sensitivity reaction in less than 1 percent of patients.[9] Although this experience has not been reported with Antivenin (coral snake), because of the similarity of these Antivenin products, this reaction cannot be ruled out for Antivenin (Micrurus fulvius) (equine origin).

Serum sickness usually occurs 5 to 24 days after administration and its frequency may be related to the number of Antivenin vials administered.[16] The incubation period may be less than 5 days, especially in those who have received horse-serum-containing preparations in the past. The usual symptoms and signs are malaise, fever, urticaria, lymphadenopathy, edema, arthralgia, nausea, and vomiting. Occasionally, neurological manifestations develop, such as meningismus or peripheral neuritis. Peripheral neuritis usually involves the shoulders and arms. Pain and muscle weakness are frequently present, and permanent atrophy may develop.

HOW SUPPLIED

Each package contains one vacuum vial to yield 10 ml of Antivenin (with preservatives: phenol 0.25% and thimerosal [mercury derivative] 0.005%).

Store original, unused (not reconstituted) vials between 2 and 8 °C (36 and 46 °F).
Do not freeze.

Gently swirl the vial of reconstituted Antivenin before each administration.

References

1. MC COLLOUGH, N. and GENNARO, J.: Coral snakebites in the United States. J. Florida Med. Assn. *49*:968, 1963.

2. FIX, J. and MINTON, S.: Venom extraction and yields from the North American Coral Snake, Micrurus fulvius. Toxicon *14*:143, 1976.

3. PARRISH, H. and KAHN, M.: Bites by coral snakes: Report of 11 representative cases. Am. J. Med. Sci. *253*:561, 1967.

4. MOSELY, T.: Coral snakebite: Recovery following symptoms of respiratory paralysis. Ann. Surg. *163*:943, 1966.

5. RAMSEY, G. and KLICKSTEIN, G.: Coral snakebite. Report of a case and suggested therapy. JAMA *182*:949, 1962.

6. NEILL, W.: Some misconceptions regarding the eastern coral snake, Micrurus fulvius. Herpetologica *13*:111, 1957.

7. RUSSELL, F.: Bites by the Sonoran coral snake, Micruroides euryxanthus. Toxicon *5*:39, 1967.

8. WINGERT, W. and WAINSCHEL, J.: Diagnosis and management of envenomation by poisonous snakes. South. Med. J. *68*:1015, 1975.

9. RUSSEL, F.: Snake venom poisoning. Scholium International, Inc., New York, 1983.

10. LOPRINZI, C. et al: Snake Antivenin administration in a patient allergic to horse serum. South. Med. J. *76*:501, 1983.

11. OTTEN, E. & MCKIMM, D.: Venomous snakebite in a patient allergic to horse serum. Ann. Emerg. Med. *12*:624, 1983.

12. BOWDEN, C. & KRENZELOK, E.: Clinical applications of commonly used contemporary antidotes, a US perspective. Drug Safety *16(1)*:22-24, 1997.

13. Wyeth-Ayerst Data on File.

14. JURKOVICH, G. et al: Complications of Crotalidae Antivenin therapy. The J. of Trauma *28*:7, 1988.

15. TOOGOOD, J.: Beta-blocker therapy and the risk of anaphylaxis. Canc. Med. Assoc. J. *136*:929, 1987.

16. LAWRENCE, W. et al: Pitviper bites: Rational management in which Copperheads and Cottonmouths predominate. Annals of Plastic Surg. *36(3)*:276, 1996.

U.S. Govt. License No. 3

Wyeth Laboratories Inc., Marietta, PA 17547

® CI3280-4 Revised August 31, 2001