



U.S. Food and Drug Administration



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## Mercury in Plasma-Derived Products

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The EPA has raised concerns regarding mercury exposure. These concerns have been in the context of chronic exposure to methyl mercury in milligram amounts. In contrast, blood plasma-derived products (except anti-venoms) containing ethyl mercury are usually given as one or two injections. Furthermore, the ethyl mercury content of these products is in the form of a preservative, thimerosal, which breaks down to form ethyl mercury in microgram amounts.

In the past, plasma-derived products made in multiple-use vials, e.g. Immune Globulin (Human), used for Hepatitis A prophylaxis, contained a preservative, such as ethyl mercury-containing thimerosal, to avoid contamination. This type of multi-dose presentation has been discontinued for all licensed plasma derivative products.

### Rho (D) Immune Globulin (Human) products -

RhoGAM, Ortho Clinical Diagnostics, Inc  
BayRho, Bayer Corporation  
WinRho, Cangene Corporation

#### **RhoGAM, Ortho Clinical Diagnostics, Inc [licensed 1968]**

On April 16, 2001, Ortho Clinical Diagnostics was approved by FDA to produce RhoGAM without thimerosal, and at that time, Ortho agreed to distribute only thimerosal-free product to the US market. The product has a 2-year dating period, so there is no longer any RhoGAM that contains thimerosal that is still in-date.

The following information does not apply to any RhoGAM product currently on the market, but is provided to allow interested individuals to estimate the ethyl mercury content of any RhoGAM treatment that might have been administered in the past, when the thimerosal preservative was still a component of that product.

RhoGAM is manufactured in two doses only: the standard dose of "300 micrograms" of anti-D, and the micro-dose of "50 micrograms" of anti-D. The fill volume for both the standard dose and micro-dose products is typically between 0.6 and 0.8 mL. Preservative-containing RhoGAM contained thimerosal at 0.003%, or 30 micrograms per milliliter. Thimerosal is about 50% ethyl mercury by weight. Hence, a patient who had received a dose of RhoGAM (0.7 ml on average) would have received 10.5 micrograms of ethyl mercury.

There are three indications for which an Rh-negative pregnant woman would receive a significantly larger dose of RhoGAM: a fetal-maternal hemorrhage early in the pregnancy, a fetal-maternal hemorrhage greater than 15 ml of Rh+ red cells, and an Rh+ transfusion. In the first case, a single 300 microgram dose of RhoGAM, is recommended at 12-week intervals. For the second two indications, a procedure exists by which to determine the dose of RhoGAM required, based on the amount of Rho+ red cells in the maternal circulation: the Kleihauer-Betke elution test (see the AABB Technical Manual, 13th ed., pp. 507-8.) The total dose of mercury that would have been received can be calculated by multiplying the number of RhoGAM syringes administered by 10.5 micrograms.

#### **BayRho, Bayer Corporation [licensed 1971]**

The Bayer Corporation makes a Rho (D) Immune Globulin product (BayRho) which in the past contained thimerosal; this product has been manufactured without preservative since 1996, so that no in-date BayRho contains thimerosal. Regarding the previously distributed product, the volume of a single dose of the Bayer product was approximately 0.7 ml. The thimerosal concentration was 0.01%, so the total mercury in a single dose would have been approximately 35 micrograms of ethyl mercury.

#### **WinRho SD, Cangene Corporation [licensed 1996]**

The Cangene Corporation makes a freeze-dried Rho (D) Immune Globulin Intravenous (WinRho SD); this product has never contained a preservative.

In addition, four other plasma-derived products remain on the market that contain or contained ethyl mercury preservatives. They are as follows:

Antivenin (Crotalidae) Polyvalent (Equine); Pit viper snake antivenom, Wyeth Pharmaceuticals Inc  
Antivenin (Micrurus fulvius); Coral snake antivenom (Equine), Wyeth Pharmaceuticals Inc  
Crotalidae Polyvalent Immune Fab (Ovine); Pit viper snake antivenom, Protherics Inc  
Antivenin (Lacrodectus mactans); Black Widow spider antivenom (Equine), Merck & Co, Inc

#### **Pit Viper [Antivenin (Crotalidae) Polyvalent, licensed 1954] and Coral Snake [Antivenin (Micrurus fulvius), licensed 1967] antivenoms by Wyeth**

These products are equine antisera. They are in lyophilized form and when reconstituted contain 0.005% thimerosal (50 micrograms per milliliter). The diluent, WFI, contains the preservative phenylmercuric nitrate at 0.001% concentration (10 micrograms per milliliter). A patient bitten by a snake may receive 15 or more vials (doses of 50 vials have been reported) if the envenomization is severe. A 15 vial dose of this antivenom would contain 4.7 milligrams of mercury.

Wyeth plans to discontinue these products; however, the current supply will last several years, until each lot reaches its expiration date. Rattlesnake bites are dangerous and can cause serious morbidity or mortality. In the interest of the public health these products need to be available until sufficient ethyl mercury-free product can be provided to the public.

#### **Pit Viper antivenom [Crotalidae Polyvalent Immune Fab (Ovine) licensed October 2000, Protherics]**

Mercury is not added to the final product in the form of a preservative, but thimerosal is used to assure that the chromatography columns used in the manufacturing of this product do not become bacterially contaminated with repeated use. The product was approved but the ethyl mercury content was limited to not more than 104.5 micrograms ethyl mercury per vial, with a recommended maximum dose of 18 vials. A patient receiving this product would receive about 1.88 milligrams of mercury.

**Black Widow Spider antivenom [Antivenin (Lactrodectus mactans), licensed 1936, Merck]**

This product is an equine antiserum. The reconstituted product contains 0.1 milligrams of mercury per milliliter, so that the maximum 2-vial dose would contain 0.25 milligrams of mercury. Black Widow Spider bites can be lethal, and the dose is limited to not more than two vials. It has been determined that removal of the product from the market by the FDA would not be in the best interests of public health.

*(Information updated 9/9/2004)*

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