VARICELLA-ZOSTER IMMUNE GLOBULIN (HUMAN)
Liquid Formulation Solvent Detergent Treated

Caution: For Intramuscular Injection Only
Store at 2° C to 8° C (35.6° F to 46.4° F)

Rx ONLY

MASSACHUSETTS PUBLIC HEALTH BIOLOGIC LABORATORIES
Boston, Massachusetts 02130

DESCRIPTION: Varicella-Zoster Immune Globulin (Human) (VZIG) is a sterile 10.0 to 18.0% solution of the globulin fraction of human plasma, primarily immunoglobulin G (IgG) in 0.3M glycine (1). VZIG contains no preservative. VZIG is derived from adult human plasma selected for high titers of varicella-zoster antibodies (2). Plasma pools are fractionated by ethanol precipitation of the proteins according to Methods 6 and 9 of Cohn. A widely utilized solvent-detergent viral inactivation process is also used (3). Each milliliter contains 100 to 180 mg of protein, principally IgG, and trace amounts of IgA and IgM. The product is to be administered by intramuscular injection. The recommended dose is based on body weight.

CLINICAL PHARMACOLOGY: This product contains IgG class varicella-zoster antibodies representative of the contributions of the large number of normal persons who donated plasma to the pool from which the product was derived. Upon absorption into the circulation, the antibodies persist for one month or longer. The precise concentration of varicella-zoster antibodies that must be achieved or maintained in order to attenuate Varicella is not known. In the clinical studies demonstrating its efficacy, VZIG was given within 96 hours of chickenpox exposure (4,5). When administered as described below, the product has been shown to significantly reduce mortality and morbidity from varicella among immunodeficient children. Lack of treatment of such patients has been associated with a mortality of 7%, a pneumonia rate of 25%, an encephalitis rate of 5%, and widespread pox (more than 100 pox) in 87% (6,7). Clinical studies have shown that Varicella-Zoster Immune Globulin (Human) was able to significantly modify the expected severity of chickenpox, and that the observed frequencies of death (1%), pneumonia (6%), encephalitis (0%), and widespread pox (27%) were less than one quarter of those observed in the past when hyperimmune globulin was not given (4). Although controlled clinical studies of VZIG efficacy in susceptible neonates, infants and healthy adults have not been done to date, it is expected that VZIG will also attenuate VZV infection in these groups (8).

INDICATIONS AND USAGE: Varicella-Zoster Immune Globulin (Human) is intended for the passive immunization of exposed, susceptible individuals who are at greater risk of complications from varicella than healthy children. High-risk groups include immunocompromised children, newborns of mothers with varicella shortly before or after delivery, premature infants, immunocompromised adults and normal susceptible adults (8) and may also include susceptible highrisk infants less than a year of age.

Immunocompromised Children. VZIG is recommended for passive immunization of susceptible, immunocompromised children after significant exposure to chickenpox or zoster. These children include those with primary cellular immune deficiency disorders or neoplastic diseases and those currently receiving immunosuppressive treatments. Although VZIG administration has been shown to reduce the severity of disease and decrease the rate of complications, severe varicella and death may still occur in exposed immunocompromised children despite VZIG administration. Antiviral chemotherapy should be considered if significant clinical varicella develops after VZIG administration.

Newborns of Mothers with Varicella Shortly Before or After Delivery.VZIG is indicated for newborns of mothers who develop chickenpox within 5 days before or within 48 hours after delivery (9-11). Despite VZIG administration some of these neonates may still develop varicella

(10-15) which can be severe or fatal (8). Antiviral chemotherapy should be considered in neonates who develop clinical varicella following VZIG administration.

Premature Infants. Although the risk of post-natally acquired varicella in the premature infant is unknown, it has been judged prudent to administer Varicella-Zoster Immune Globulin (Human) to exposed premature infants of 28 weeks gestation or more if their mothers have a negative or uncertain history of varicella (8). Premature infants of less than 28 weeks gestation or birth weight of less than 1000 g should be considered for VZIG regardless of maternal history since they may not yet have acquired transplacental maternal antibody.

Full Term Infants Less Than 1 Year of Age. Mortality from varicella in the first year of life is 4 times higher than that in older children, but lower than mortality in immunocompromised children or normal adults (16,17). The decision to administer VZIG to infants less than one year of age should be evaluated on an individual basis. After careful evaluation of the type of exposure, susceptibility to varicella including maternal history of varicella and zoster, and presence of underlying disease, VZIG may be administered to selected infants.

Immunocompromised Adults. The complication rate for immunocompromised adults who contract varicella is likely to be substantially greater than for normal adults. Approximately 90% of immunocompromised adults with negative or unknown histories of prior varicella are likely to be immune. After a careful evaluation, which might include the measurement of antibody to Varicella-Zoster virus by a reliable and sensitive assay such as Fluorescent Antibody to Membrane Antigen (FAMA), adults who are believed susceptible should receive VZIG.

Healthy Adults. Chickenpox can be severe in normal adults. The decision to administer VZIG to an adult should be evaluated on an individual basis. Approximately 90% of adults with negative or uncertain histories of varicella will be immune. The objective is to modify rather than prevent illness in hopes of inducing lifelong immunity. The clinician should consider the patient's health status, type of exposure, and likelihood of previous unrecognized varicella infection in deciding whether to administer VZIG. Adults who are older siblings of large families and adults whose children have had varicella are more likely to be immune. If reliable and sensitive tests for varicella antibody are available, they might be used to determine susceptibility, if time permits. If, after careful evaluation, a normal adult with significant exposure to varicella is believed susceptible, VZIG may be administered.

Pregnant Women. Pregnant women may be at higher risk of complications of chickenpox than healthy adults (18). They should be evaluated the same way as other adults. There is no evidence that administration of VZIG to a susceptible, pregnant woman will prevent viremia, fetal infection or congenital varicella syndrome. Therefore the primary indication for VZIG in pregnant women is to prevent complications of varicella in a susceptible adult patient rather than to prevent intrauterine infection. Pregnant women should be evaluated for type of exposure and history of previous infection as described for healthy adults.

Timing of VZIG After Varicella or Zoster Exposure. Greatest effectiveness of treatment is to be expected when it is begun within 96 hours after exposure; treatment after 96 hours is of uncertain value. There is no evidence that established infections with Varicella-Zoster virus can be modified by Varicella-Zoster Immune Globulin (Human). There is no indication for the prophylactic use of Varicella-Zoster Immune Globulin (Human) in immunodeficient children or adults when there is a past history of varicella, unless the patient has undergone bone marrow transplantation.
Multiple Exposures. The duration of protection from a single dose of VZIG is not known. Therefore a second dose of VZIG should be considered when high risk patients have second exposures to Varicella-Zoster.

CONTRAINDICATIONS: A history of prior severe reaction associated with the administration of human immune globulin, or severe thrombocytopenia.

WARNING: This product is made from human plasma and like other plasma products carries the possibility for transmission of blood-borne viral agents, e.g., viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. The risk for transmission of recognized blood-borne viruses (i.e. HIV-1, HIV-2, Hepatitis-B Virus, and Hepatitis C Virus) is considered to be extremely low because of the viral inactivation and removal properties inherent in the Cohn cold-ethanol precipitation procedure used for purification of immune globulin products (19-21). Until 1993, cold ethanol manufactured immune globulins licensed in the U.S. had not been documented to transmit any viral agent. However, during a brief period in late 1993 to early 1994, an intravenous immune globulin made by one U.S. manufacturer was associated with transmission of Hepatitis C virus (22). This was determined to be an isolated incident only related to one product not specifically treated by a viral inactivation process (23). To further reduce the risk of enveloped viruses like Hepatitis C Virus, VZIG is also treated with a widely utilized solvent-detergent viral inactivation process (3). Because new blood-borne viruses may yet emerge, VZIG like other blood products should be given only if a benefit is expected. All infections should be reported directly to your physician and to the Regulatory Affairs Department at Massachusetts Public Health Biologic Laboratories at (617)983-6400. Please discuss the risks and benefits of this product with your physician.

The parenteral administration of any biologic should be surrounded by every precaution for the prevention and arrest of allergic and other untoward reactions.

Persons with immunoglobulin A deficiency have the potential for developing antibodies to immunoglobulin A and could have anaphylactic reactions to subsequent administration of blood products that contain immunoglobulin A. Therefore Varicella-Zoster Immune Globulin (Human) should be given to such persons only if the expected benefits outweigh the potential risks.

PRECAUTIONS: Prepare the skin with 70% alcohol. Inject Varicella-Zoster Immune Globulin (Human) intramuscularly. NEVER ADMINISTER THIS MATERIAL INTRAVENOUSLY. Draw back on the plunger of the syringe to be certain that the needle is not in a blood vessel. A separate sterile disposable syringe and needle should be used for each individual patient to prevent the transmission of hepatitis viruses or other infectious agents from one person to another. Although systemic allergic reactions are rare (see Adverse Reactions, below) epinephrine should be available for treatment of acute symptoms.

Antibodies present in immune globulin preparations may interfere with the immune response to live virus vaccines such as measles, mumps, and rubella. Therefore vaccination with live virus vaccines should be deferred until approximately five months after administration of Varicella-Zoster Immune Globulin (Human). Persons who received Varicella-Zoster Immune Globulin (Human) within 14 days of live virus vaccination should be revaccinated with the live virus vaccine 5 months later (24).

Administration of VZIG will result in false-positive tests for immunity to VZV for approximately two months after receiving VZIG. Therefore serodiagnostic tests to determine immunity to VZV should not be performed within 2 months of VZIG administration.
"Pregnancy Category C. Animal reproduction studies have not been conducted with Varicella-Zoster Immune Globulin (Human). It is also not known whether Varicella-Zoster Immune Globulin (Human) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Varicella-Zoster Immune Globulin (Human) should be given to a pregnant woman only if clearly needed." [21CFR 201.57 (f)] (8).

Although pregnant women have not received the product in controlled studies, clinical use of other immunoglobulin preparations such as Rh immune globulin administered during pregnancy suggests that there are no known adverse effects on the fetus from the immune globulin itself.

ADVERSE REACTIONS: The most frequent adverse reaction to Varicella-Zoster Immune Globulin (Human) is local discomfort at injection site. Pain, redness, or swelling occur at the

injection site in about one in 100 patients. Less frequent adverse reactions are gastrointestinal symptoms, malaise, headache, rash and respiratory symptoms, which occur in approximately 1 in 500 patients. Severe reactions such as angioneurotic edema and anaphylactic shock are rare (less than 1 in 1000 patients). Varicella-Zoster Immune Globulin (Human) is prepared in the same manner as Immune Globulin (Human) and other immune globulins, and may be expected to resemble these globulins in ability to stimulate allotypic or other antiglobulin antibodies, and to react with such antibodies generated in response to prior injection of human globulin, or in response to transfusion of blood (25).

DOSAGE AND ADMINISTRATION: Administer the product by deep intramuscular injection in the gluteal muscle, or in a physician-directed site if there are contraindications to the gluteal site. NEVER ADMINISTER THIS MATERIAL INTRAVENOUSLY. The recommended dose of Varicella-Zoster Immune Globulin (Human) is based on body weight according to the following schedule:

WEIGHT OF PATIENTS DOSE
Kilograms Pounds Units Number of Vials
0-10 0-22 125 1 @ 125 units
10.1-20 22.1-44 250 2 @ 125 units
20.1-30 44.1-66 375 3 @ 125 units
30.1-40 66.1-88 500 4 @ 125 units
Over 40 Over 88 625 1 @ 625 units or 5 @ 125 units

Since VZIG does not contain a preservative administer the entire contents of each vial. Each 125 unit vial contains 125 units of antibody to varicella-zoster virus in a volume of approximately 1.25 ml and each 625 unit vial contains 625 units of antibody in a volume of approximately 6.25 ml. For patients weighing 10 kilograms or less, 125 units (1.25 ml) may be given in a single injection site. For patients weighing more than 10 kilograms, we recommend that no more than 2.5 ml be given in a single injection site, however some clinicians elect to give larger or smaller volumes. The number of units required to prevent pneumonia and death and to reduce the number of pox is unknown. The proposed dosage regimen was found to be effective in significantly modifying the expected severity of chickenpox and reducing the observed frequency of death, pneumonia and encephalitis to less than 25% of the expected rate without treatment.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

To prevent the transmission of hepatitis viruses or other infectious agents from one person to another, a separate sterile disposable syringe and needle should be used for each individual patient.

OVERDOSAGE: Although no data are available, clinical experience with other immunoglobulin preparations suggests that the only manifestations would be pain and tenderness at the injection site.

HOW SUPPLIED: The product is supplied in glass vials in two single use dosage forms:
NDC 52769-574-11 at 125 units/vial (in a volume of approximately 1.25 ml) and
NDC 52769-574-66 at 625 units/vial (in a volume of approximately 6.25 ml).

STORAGE: The product should be stored between 2° C and 8° C (35.6° F to 46.4° F). DO NOT FREEZE.

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