January 2011

# BioSupply Trends

Special Focus: PLASMA

Quarterly

# Plasma Therapies

## *Where Are We Now?*

**Hyperimmune Globulins: Understanding Their Role**

Managing and Treating Diabetes

Myths & Facts: Measles and Mumps

**Specialty Drugs: The Next Frontier**

The Mysterious Tale of von Willebrand Disease — Page 64

# Developed Specifically for the Treatment of von Willebrand Disease

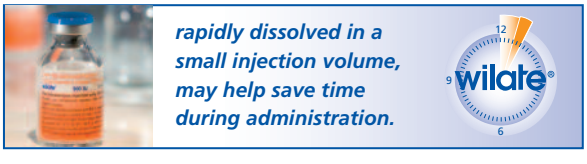
wilate®

von Willebrand Factor/Coagulation Factor VIII Complex (Human)

- **High purity VWF/FVIII complex**
- **Double virus inactivated**
- **Physiologic 1:1 ratio of VWF and FVIII**
- **Parallel pharmacokinetic profiles for FVIII and VWF**
- **Clinical efficacy, safety, and tolerability proven in adult and pediatric populations**
- **Rapidly dissolved in a small volume**
- **Convenient dosing**

## Two convenient vial sizes

- **450 IU VWF:RCo and 450 IU FVIII activities in 5 mL**
- **900 IU VWF:RCo and 900 IU FVIII activities in 10 mL**
- **Includes Mix2Vial™ transfer device**




**Important safety information:**
wilate® is contraindicated for individuals with a history of anaphylactic or severe systemic reaction to human plasma-derived products, any ingredient in the formulation, or components of the container. Thromboembolic events have been reported in VWD patients receiving coagulation factor replacement therapies. FVIII activity should be monitored to avoid sustained excessive FVIII levels. wilate® is made from human plasma. The risk of infectious agents, including viruses and, theoretically, the Creutzfeldt-Jakob disease agent, cannot be completely eliminated. The most common adverse reactions to treatment with wilate® in patients with VWD have been urticaria and dizziness. The most serious adverse reactions to treatment with wilate® in patients with VWD have been hypersensitivity reactions.

wilate® is a von Willebrand Factor/Coagulation Factor VIII Complex (Human) indicated for the treatment of spontaneous and trauma-induced bleeding episodes in patients with severe von Willebrand disease (VWD), as well as patients with mild or moderate VWD in whom the use of desmopressin is known or suspected to be ineffective or contraindicated.

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octapharma
For the safe and optimal use of human proteins

## HIGHLIGHTS OF PRESCRIBING INFORMATION

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

**Wilate, von Willebrand Factor/Coagulation Factor VIII Complex (Human), Powder for Solution, for Intravenous Use Only. Initial U.S. Approval: 2009**

## INDICATIONS AND USAGE

- Wilate is a von Willebrand Factor/Coagulation Factor VIII Complex (Human) indicated for the treatment of spontaneous and trauma-induced bleeding episodes in patients with severe von Willebrand disease (VWD) as well as patients with mild or moderate VWD in whom the use of desmopressin is known or suspected to be ineffective or contraindicated.
- Wilate is not indicated for the prophylaxis of spontaneous bleeding episodes, or the prevention of excessive bleeding during and after surgery in VWD patients.
- Wilate is also not indicated for Hemophilia A

## DOSAGE FORMS AND STRENGTHS

- Wilate is a sterile, lyophilized powder for reconstitution for intravenous injection, provided in the following nominal strengths per vial:

  o 450 IU VWF:RCo and 450 IU FVIII activities in 5 mL

  o 900 IU VWF:RCo and 900 IU FVIII activities in 10 mL

## CONTRAINDICATIONS

- Hypersensitivity with known anaphylactic or severe systemic reaction to human plasma-derived products, any ingredient in the formulation, or components of the container.

## WARNINGS AND PRECAUTIONS

- Hypersensitivity reaction
- Thromboembolic events associated with von Willebrand factor/Coagulation Factor FVIII (VWF/FVIII) products: plasma levels of FVIII activity should be monitored to avoid sustained excessive FVIII levels, which may increase the risk of thrombotic events
- Potential for inducing antibodies to Factor VIII (inhibitors) and antibodies to VWF, especially in VWD type 3 patients
- Theoretical risk of infectious agents transmission as the product is made from human plasma

## ADVERSE REACTIONS

The most common adverse reactions in clinical studies on VWD were urticaria and dizziness (each 2.2%) (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Octapharma USA Inc. at phone # 866-766-4860 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

## DRUG INTERACTIONS

- None known.

## USE IN SPECIFIC POPULATIONS

- Pregnancy: No human or animal data. Use only if clearly needed.

## DOSAGE AND ADMINISTRATION

### For Intravenous Use after Reconstitution

- Treatment should be initiated under the supervision of a physician experienced in the treatment of coagulation disorders.
- Each vial of Wilate contains the labeled amount in International Units (IU) of von Willebrand factor (VWF) activity as measured with the Ristocetin cofactor assay (VWF:RCo), and coagulation factor VIII (FVIII) activity measured with the chromogenic substrate assay.
- The number of units of VWF:RCo and FVIII activities administered is expressed in IU, which are related to the current WHO standards for VWF and FVIII products. VWF:RCo and FVIII activities in plasma are expressed either as a percentage (relative to normal human plasma) or in IU (relative to the International Standards for VWF:RCo and FVIII activities in plasma).

### Dosage in von Willebrand Disease

The ratio between VWF:RCo and FVIII activities in Wilate is approximately 1:1.

The dosage should be adjusted according to the extent and location of the bleeding. In VWD type 3 patients, especially in those with gastro-intestinal (GI) bleedings, higher doses may be required.

### Dosing Schedule

Physician supervision of the treatment regimen is required. A guide for dosing in the treatment of major and minor hemorrhages is provided in Table 1.

The careful control of replacement therapy is especially important in life-threatening hemorrhages. **When using a FVIII-containing VWF product, the treating physician should be aware that continued treatment may cause an excessive rise in FVIII activity.**

Table 1 Guide to Wilate Dosing for Treatment of Minor and Major Hemorrhages

| Type of Hemorrhages | Loading Dosage (IU VWF:RCo /kg BW) | Maintenance Dosage (IU VWF:RCo /kg BW) | Therapeutic Goal |
|---|---|---|---|
| Minor Hemorrhages | 20-40 IU/kg | 20-30 IU/kg every 12-24 hours* | VWF:RCo and FVIII activity through levels of >30% |
| Major Hemorrhages | 40-60 IU/kg | 20-40 IU/kg every 12-24 hours* | VWF:RCo and FVIII activity through levels of >50% |

Treatment guidelines apply to all VWD types

*This may need to be continued for up to 3 days for minor hemorrhages and 5-7 days for major hemorrhages

Repeat doses are administered for as long as needed based upon repeat monitoring of appropriate clinical and laboratory measures.

Although dose can be estimated by the guidelines above, it is highly recommended that whenever possible, appropriate laboratory tests should be performed on the patient's plasma at suitable intervals to assure that adequate VWF:RCo and FVIII activity levels have been reached and are maintained.

In the unlikely event that a patient who is actively bleeding should miss a dose, it may be appropriate to adopt a dosage depending on the level of coagulation factors measured, extent of the bleeding, and patient's clinical condition.

## HOW SUPPLIED/STORAGE AND HANDLING

| NDC Number | Size | Protein Amount |
|---|---|---|
| 67467-181-01 | 450 IU VWF:RCo and 450 IU FVIII activities in 5 mL | ≤ 7.5 mg |
| 67467-181-02 | 900 IU VWF:RCo and 900 IU FVIII activities in 10 mL | ≤ 15.0 mg |

- Wilate is supplied in a package with a single-dose vial of powder and a vial of diluent (Water for Injection with 0.1% Polysorbate 80), together with a Mix2Vial™ transfer device, a 10-mL syringe, an infusion set and two alcohol swabs.
- Each vial of Wilate contains the labeled amount of IU of VWF:RCo activity as measured using a manual agglutination method, and IU of FVIII activity measured with a chromogenic substrate assay.
- Components used in the packaging of Wilate contain no latex.

### Shelf life

- Store Wilate for up to 36 months at +2°C to +8°C (36°F to 46°F) protected from light from the date of manufacture. Within this period, Wilate may be stored for a period of up to 6 months at room temperature (maximum of +25°C or 77°F). The starting date of room temperature storage should be clearly recorded on the product carton. Once stored at room temperature, the product must not be returned to the refrigerator. The shelf-life then expires after the storage at room temperature, or the expiration date on the product vial, whichever is earliest. Do not freeze.
- Do not use after the expiration date.
- Store in the original container to protect from light.
- Reconstituted the Wilate powder only directly before injection. Use the solution immediately after reconstitution. Use the reconstituted solution on one occasion only, and discard any remaining solution.

## PATIENT COUNSELING INFORMATION

- Inform patients of the early signs of hypersensitivity reactions including hives, generalized urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis. If allergic symptoms occur, patients should discontinue the administration immediately and contact their physician.
- Inform patients that undergoing multiple treatments with Wilate may increase the risk of thrombotic events thereby requiring frequent monitoring of plasma VWF:RCo and FVIII activities.
- Inform patients that there is a potential of developing inhibitors to VWF, leading to an inadequate clinical response. Thus, if the expected VWF activity plasma levels are not attained, or if bleeding is not controlled with an adequate dose or repeated dosing, contact the treating physician.
- Inform patients that despite procedures for screening donors and plasma as well as those for inactivation or removal of infectious agents, the possibility of transmitting infective agents with plasma-derived products cannot be totally excluded.


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For the safe and optimal use of human proteins

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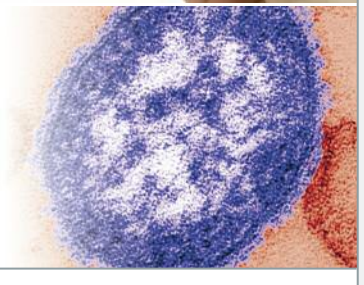
## Features

Special Focus: Plasma







## Up Front



## BioTrends Watch



## BioFocus



## BioSources



**About BioSupply Trends Quarterly**
*BioSupply Trends Quarterly* is the definitive source for industry trends, news and information for healthcare professionals in the biopharmaceuticals marketplace.

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# Precious Proteins

**IN MY NOW** more than 22 years as a specialty distributor of plasma derivatives, there are two things I've noticed consistently about our manufacturing partners: an obsession with safety, and a dedication to saving lives. The connection to patient outcomes and passion for continuous improvement are constants in an industry affected by a multitude of interconnected, difficult-to-control variables. These fragile proteins hold the miraculous ability to save lives and restore health, yet the process of bringing them to market is long and arduous, with unusual complexities that affect supply and demand. In our feature, Plasma Therapies: Where Are We Now? we explore such variables as raw material, manufacturing bandwidth and reimbursement — all components that can make the plasma market volatile, and patients and their healthcare providers vulnerable. As our cover illustration depicts, a roll of the dice can move the game forward or back.

To truly understand the miraculous role these precious proteins play, it is necessary to look at the sometimes obscure and varied disease states they treat. In our article, The Role of Hyperimmune Globulins, we take an in-depth look at those plasma derivatives with high titers of antibody against a specific organism, as well as the role they play in treating specific diseases through passive immunity. Hyperimmunes are used when an individual is exposed to a disease and has not been previously immunized with the vaccine. What really drives home the wondrous nature of these specialized immune globulins is the understanding that many people who contract the serious diseases that they treat would otherwise die without them.

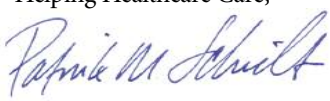
Our Industry Insight column takes a look at von Willebrand disease (VWD) — a mysterious disorder named after physician Erik von Willebrand. The defective protein, which scientists were able to identify some 50 years after Dr. von Willebrand first alerted the world about this strange disease, turns out to be the largest protein found in human plasma. It is fascinating to note the progress made in the diagnosis and treatment of this disease that affects roughly 1 percent of the general population. Now, nearly nine decades after von Willebrand's first observations, physicians have several very effective treatment options for those affected with VWD, with the promise of still better ones to come.

In our article, Specialty Drugs on the Rise, we explore the changing landscape of fragile biologics such as plasma-derived therapeutics, as well as other high-cost pharmaceuticals that require special preparation, handling and monitoring. It is truly one of the great frontiers in healthcare, and while specialty pharmaceuticals have traditionally been limited to treating rare diseases such as immune-mediated diseases and hemophilia, that is changing. As the specialty drug category has recently expanded to include oral medications and drugs with alternative and new delivery systems, additional and improved options for individuals with more common chronic conditions become available.

We also take a step away from the plasma market to look at the diabetes epidemic in our article, The Highs and Lows of Managing and Treating Diabetes. That prevention and lifestyle changes can have a significant impact on this disease is promising, but it is also clear that there is no quick fix. Efforts to educate and provide intervention have clearly taken on a more focused effort among all stakeholders.

As always, we hope you find the content and resources in this issue of *BioSupply Trends Quarterly* relevant and helpful as we embark on a new year. ❖

Helping Healthcare Care,



Patrick M. Schmidt
Publisher

BioSupply Trends Quarterly

Our mission is to serve as the industry's leading resource for timely, newsworthy and critical information impacting the biopharmaceuticals marketplace, while providing readers with useful tips, trends, perspectives and leading indicators on the topics pertinent to their business.

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# An Update on Specialty Drug Tiers

Prior to the Medicare Modernization Act of 2003 and the development of the Medicare Part D drug benefit plan, specialty therapies were covered under the traditional drug tiers: Tier I for generic drugs, Tier II for preferred brand-name drugs and Tier III for non-preferred brand-name drugs. But, the Part D drug benefit plan created two new drug tiers: Tier IV, which is now found in most insurers' plans, and Tier V, which is found in just a few. Depending upon the plan, specialty drugs that cost more than $600 per year can now be classified under Tier IV or Tier V. These lifesaving therapies tend to be infusibles/injectables to treat autoimmune/inflammatory diseases (Crohn's disease, lupus, multiple sclerosis, psoriasis, rheumatoid arthritis, etc.), HIV/AIDS, cancer, hepatitis C, anemia, enzyme disorders (Gaucher disease), pulmonary arterial hypertension, immune disorders other than primary immune deficiency disease (PIDD) that rely on intravenous immune globulin (IVIG), osteoporosis, and the list continues to grow.

As of 2011, 90 percent of Part D plans will classify IVIG as a Tier IV drug, requiring beneficiaries to pay, on average, 33 percent of the cost of the drug until they reach the doughnut hole.* After that, beneficiaries will be required to pay 5 percent of the cost of IVIG for the remainder of the calendar year. And, according to a report by Avalere Health (www.avalerehealth.net), it is estimated that 50 percent of private medical plans will have a Tier IV plan in place in 2011.

*Some states are reforming the way insurance companies can do business to ensure patients still have access to needed therapies.*

While tier pricing can be a money-saver for patients when paying premiums, these new tiers, instituted by either private insurers or Medicare, are pricing patients out of treatments. As a result, some states are reforming the way insurance companies can do business to ensure patients still have access to needed therapies. In 2010, the governor of New York signed into law legislation that prohibits private health insurers from creating specialty tiers with their prescription drug formularies in the state (see the related story in the October 2010 issue of *BioSupply Trend Quarterly*'s Washington Report.) The state of New York found that specialty tiering is contrary to the original purpose of insurance, which is to spread the costs; instead, it creates a structure in which those who are most sick pay more, and the insurance companies pay less.

On Oct. 14, 2010, the Senate Banking, Commerce and Insurance Committee held an interim study review on insurers' prescription fee practices with the goal to work on a revised version of LB1017, the specialty tier legislation introduced in 2010 in Nebraska to eliminate specialty tiers and coinsurance, and cap out-of-pocket expenses for prescription medications at $1,000 for an individual policy and $2,000 for a group policy. The goal is to reintroduce LB1017 in 2011 with no opposition. Progress has been made in Arizona, California, Florida, Maryland and Minnesota, and at least another dozen states are getting ready to introduce legislation modeled after Nebraska's legislation. ❖

*Hargrave, E, Hoadley, J, and Merrell, K. Drugs on Specialty Tiers. MedPAC, February 2009, No. 09-1.

# Hospital Outpatient Reimbursement Increased for 2011

In August, the Centers for Medicare and Medicaid Services (CMS) proposed to change the reimbursement rate of separately payable, non-pass-through drugs and biologicals, which include most plasma protein therapies, such as intravenous immune globulin, as well as alpha-1 proteinase inhibitors and blood clotting factors. The increase from average sales price (ASP) plus 4 percent to ASP plus 5 percent paid in 2010 was proposed to be effective on Jan. 1, 2011. However, this is not a permanent change, and CMS can change the reimbursement up or down in 2012. To learn more about this rule, refer to page 46281 of the CMS proposed rule document at http://edocket.access.gpo.gov/2010/pdf/2010-16448.pdf. ❖

# Massachusetts Moves Forward to Implement ACOs

A key part of the healthcare reform law enacted in 2010 encourages the development of Accountable Care Organizations (ACOs) that would allow doctors to team up with each other and hospitals in new ways to provide medical services. ACOs are defined as organizations of healthcare providers that agree to be accountable for the quality, cost and overall care of Medicare beneficiaries who are enrolled in the traditional fee-for-service program. The goal of ACOs is to improve the quality of care for Medicare beneficiaries and reduce unnecessary costs.

*A key part of the healthcare reform law enacted in 2010 encourages the development of Accountable Care Organizations (ACOs) that would allow doctors to team up with each other and hospitals in new ways to provide medical services.*

One state that is rapidly moving forward with ACOs is Massachusetts. A panel of state officials and healthcare executives drafted a first-in-the-nation blueprint for scrapping current fee-for-service payments. The new system, called global payments, would require doctors, hospitals and other providers to band together into ACOs that would split the payments and better coordinate patient care, thereby improving quality. These provider groups generally would get a flat per-patient fee, along with incentives for high-quality care, which, it is hoped, will eliminate unnecessary tests and procedures and encourage greater focus on preventive care.

However, the Massachusetts health panel still must agree on a number of contentious issues, such as how much power state regulators will have over the prices paid to providers, the rules for forming ACOs, and whether providers — many of which profit from the fee-for-service system — will have seats on the board that eventually oversees the potential dismantling of that system.

One example of an ACO is the Alternative Quality Contract created by Blue Cross Blue Shield of Massachusetts, which the Becker's Hospital Review calls one of the most advanced versions yet. April Greene, director of payment reform at Massachusetts Blue Cross, said benefits include allowing both physicians and hospitals to join, granting contracts with providers for five years, creating a collegial relationship rather than the traditional managed care contracting, giving providers freedom to create their own approaches to improve quality and reduce costs, and offering providers data on utilization of services and referral patterns so they can gain insight into their performance.

Under the health reform law, the ACO program will become fully operational in 2012. On Oct. 5, 2010, the Centers for Medicare & Medicaid Services (CMS), the Federal Trade Commission (FTC) and Office of the Inspector General (OIG) of the Department of Health and Human Services hosted a workshop on legal issues related to ACOs. The workshop focused on the interactions of ACOs with the antitrust, physician self-referral, anti-kickback and civil monetary penalty laws.

Despite successes thus far of both Blue Cross and the Massachusetts legislature to implement ACOs, the nation as a whole may not be ready for such a payment revolution. According to Kaiser Health News: "The current payment system is so profitable for most medical providers that they are not inclined to change it. National conversion to such a system would require a major change in the attitude of providers and in the political climate." ❖

**MICHELLE VOGEL**, *MPA, is executive director for the Alliance for Plasma Therapies, Washington, DC. She can be reached at (888) 331-2196 or mvogel@plasmaalliance.org.*

*Disease*

# CDC Revises Flu Death Estimate

The number of annual flu deaths, consistently reported to be 36,000 by the U.S. Centers for Disease Control and Prevention (CDC), has been revised. The CDC says that during the past 30 years, the number of annual flu-related deaths in the U.S. has ranged from a low of about 3,300 to a high of about 49,000. The new range of numbers takes into account deaths from the 1976-77 flu season through the 2006-07 season, while the old number looked only at the 1990s, when the influenza A (H3N2) was a dominant strain. In the 31 seasons reflected in the new numbers, about 90 percent of deaths occurred in adults 65 and older.

The update underscores the moving-target nature of influenza, and that there is no average flu season. "We want to point out the incredible variability of influenza seasons," says Dr. David Shay, lead author of a report appearing in the Aug. 27, 2010, issue of the *Morbidity and Mortality Report*. "There are at least four factors that affect mortality in any given year: the specific influenza strain, the length of the season, how many people get sick and who gets sick — whether it's hitting younger or older people differentially." ❖

*Research*

# Treatment Under Development for Autoimmune Diseases

Setpoint Medical, a startup company based in Boston, is developing a nerve stimulator designed to dampen the out-of-control immune system that triggers autoimmune diseases such as inflammatory bowel disease and rheumatoid arthritis. The technology is based on a decade of research that shows how the brain controls the immune system, particularly inflammation. That research has shown that inflammation is controlled in part by the vagus nerve, which carries signals between the brain and a number of visceral organs. For immune function, it makes direct connections to the spleen, which houses different types of immune cells poised for release at times of infection.

Stimulating the vagus nerve can put a brake on the immune system, stopping the rapid recruitment of immune cells to the site of injury or infection, according to numerous animal studies. The effect is similar to that of a popular class of drugs called TNF alpha blockers, used to treat arthritis and other autoimmune diseases, which block the release of an immune-signaling molecule that is central to inducing inflammation. However, while

these drugs work effectively in 50 percent to 70 percent of patients, they can lose their effectiveness over time and have been linked to serious side effects such as infection and cancer.

The treatment being developed by Setpoint Medical has not yet been tested in patients, but based on animal research, scientists hope it will provide an alternative treatment that is more effective and has fewer side effects. According to James Broderick, interim president at Setpoint Medical, preliminary tests using the company's first-generation device in 12 healthy volunteers show that the effect is potent in humans and comparable to that seen in animal research. ❖

*Vaccines*

# CDC Says Most U.S. Teens Get Vaccinated

More U.S. teens are getting recommended vaccines against certain cancers, meningitis and infectious diseases, according to a survey of 20,000 teens ages 13 to 17 conducted by the U.S. Centers for Disease Control and Prevention (CDC).

The survey found that 56 percent of teens had at least one dose of tetanus-diphtheria-acellular pertussis vaccine (Tdap), an increase of 15 points since 2008. Fifty-four percent of teens got at least one dose of meningococcal conjugate vaccine, up 12 points. And, 44 percent of girls had received at least one dose of human papillomavirus (HPV), an increase of seven percentage points. Only 27 percent of girls got all three doses of the HPV vaccine, up nine points from 2008.

"We can see that more parents of adolescents are electing to protect their children from serious diseases such as pertussis, meningitis and cervical cancer, but there is clear room for improvement in our system's ability to reach this age group," says the CDC's Dr. Anne Schuchat. ❖

*Research*

## Genetic Link Found Between Parkinson's and Immune System

A study conducted by the Neuro Genetics Research Consortium, an international team of researchers, has discovered new evidence that Parkinson's disease may have an infectious or autoimmune origin. The study, which involved more than 2,000 Parkinson's disease patients and 2,000 healthy volunteers from clinics in Oregon, Washington, New York and Georgia, assessed clinical, genetic and environmental factors that might contribute to the development and progression of Parkinson's disease and its complications. Researchers found a new association between Parkinson's and the human leukocyte antigen (HLA) region, which contains a large number of genes related to immune system function in humans. HLA genes are essential for recognizing foreign invaders from the body's own tissues. It is hoped that pursuing the connection between Parkinson's disease and inflammation, especially in the context of variable genetic makeup, may lead to better, more selective drugs for treating Parkinson's disease. The study appears online in *Nature Genetics*. ❖

*Vaccines*

## Vaccines Sales Growing

Global sales of vaccines grew by 16 percent in 2009, according to healthcare market research publisher Kalorama Information, and researchers are forecasting sales to rise at a compound annual rate of 9.7 percent during the next five years, which would push sales to roughly $35 billion. This will be fueled by wider use of current vaccines and the introduction of new ones.

The world's top five drug makers by revenue also dominate the vaccine market: Pfizer, Merck, Novartis AG, Sanofi-Aventis SA's Sanofi Pasteur unit and GlaxoSmithKline, in descending order. Besides developing new vaccines, they are working to boost vaccine sales in heavily populated emerging markets, including China and India. ❖

*Industry*

## Company to Provide In-Home Clinical Trials

FlexCare Clinical Research LLC is a new niche clinical service provider focused on providing study visits in the home or alternative site settings via a network of skilled clinicians. The company was created to meet growing demand from the biopharmaceuticals industry to accelerate clinical trials and streamline study processes, as well as to boost patient recruitment and retention, which is often a challenge at traditional investigative sites at hospitals or clinics. Services offered include study drug administration, blood draws and other biologic sample collections, clinical assessments, questionnaires and training. The company's chief executive officer is Gail Adinamis who has three decades of comprehensive Phase I through IV clinical trials experience. ❖

*Industry*

## Kaiser Foundation Launches Health Reform Source Site

The Kaiser Family Foundation has launched an online gateway providing access to new and comprehensive resources on the health reform law. The Health Reform Source (healthreform.kff.org) provides explanations of the basics of the law, in-depth analysis of policy issues in implementation, and quick and easy access to relevant data, studies and developments.

Some initial features of the site include "Health Reform Hits Main Street," a new animated short movie with three major sections that explain problems in the current healthcare system, short-term changes that will take place between now and 2014, and major provisions that will take effect in 2014; "The Scan," a daily feed of easily digestible summaries of the latest research and studies from the foundation and others, as well as official actions and other developments related to the health law; the foundation's Twitter entries on healthcare reform and links to Kaiser Health News stories; a customizable "Implementation Timeline," which presents a detailed list of major provisions that can be viewed by year or by topic; and a lot more. ❖

### Did You Know?

"Since the development of the two vaccines for rotavirus, the first in 2006 and the second in 2008, hospitalization rates had dropped by 16 percent in 2007 and by 45 percent in 2008."

— Centers for Disease Control and Prevention

*Research*

## Serum Albumin Levels Linked to Multiple Myeloma Severity

A new study shows that lower levels of serum albumin are associated with greater disease severity in multiple myeloma patients. The study, published in *Annals of Hematology*, retrospectively examined 373 multiple myeloma patients in Seoul, Korea. Patients were split into two groups: those with serum albumin greater than 3.5 g/dL and those with serum albumin less than 3.5 g/dL. Patients in the lower serum albumin group were, on average, older with a median age of 62 years, compared with 58 years for the higher serum albumin group.

Results showed that the lower serum albumin group had lower levels of hemoglobin, the protein found in red blood cells that helps transport oxygen throughout the body. Low hemoglobin levels means that the bone marrow is overcrowded with myeloma cells and cannot produce the number of red blood cells that the body needs, resulting in symptoms such as fatigue and shortness of breath. Patients with low serum albumin levels also had higher levels of serum beta2-microglobulin, M proteins and bone marrow plasma cells at the time they were diagnosed — all indicative of increased disease severity and cancer progression. The study did not, however, determine why the relationship exists between low serum albumin levels and increased disease severity. ❖

*Vaccines*

## Vaccine May Fight Cancer and HIV

Researchers at the University of Oklahoma Health Sciences Center have found a way to create a vaccine using T cells that activate a distinct part of the immune system. The vaccine could have potential treatment and prevention applications for cancer, tuberculosis and several viral diseases, including HIV.

Until now, vaccines have focused on generating antibodies to keep people from getting sick. While many of these antibody (B cell) vaccines work well, the dependence on antibodies has prompted some viruses to skirt antibody immunity, making vaccines less effective or not effective at all for some viruses. A T-cell vaccine, however, would activate another arm of the immune system to target a specific virus in the body and kill it.

The researchers first created a vaccine using the West Nile virus as its target and are now working to develop vaccines for other diseases, such as cancer, where activating T cells can be difficult. The research appears in the May issue of *The Journal of Immunology*. ❖

*Research*

## Gene Therapy Tested for Hemophilia B

Amsterdam Molecular Therapeutics has begun a Phase I/II exploratory clinical trial with a gene therapy product for hemophilia B. The trial is an open-label dose-escalation study using a vector-gene combination developed at St. Jude Children's Research Hospital. The hemophilia B gene therapy, administered once, will introduce the functional gene for the Factor IX protein into the patient's liver cells with the goal to restore blood clotting functionality long-term. In pre-clinical studies, Factor IX gene therapy resulted in long-term production of Factor IX protein at a therapeutically significant level after a single administration.

If this approach is successful, the long-term efficacy of one-time administered hemophilia B gene therapy is expected to be perceived as a significant advance over the current regular dosing of recombinant Factor IX. In addition, the efficacy profile of this gene therapy is anticipated to exceed that of current therapy, as the gene therapy will lead to stable Factor IX levels, whereas recombinant protein treatment causes peaks and troughs. ❖

*Research*

## Benlysta Benefits Lupus Patients in Drug Trial

Benlysta, an experimental lupus drug from GlaxoSmithKline chemically known as belimumab, significantly reduced patients' symptoms in a recent drug trial. Conducted by Human Genome Sciences Inc., the 865-patient study, known as Bliss-52, found that a higher dose of Benlysta started benefiting patients 16 weeks into the trial, and improvement was sustained for both a higher and lower dose from weeks 24 and 28, respectively, for the duration of the 52-week test.

Patients in the study received one of two doses of the drug or a placebo. At a lower dose, 51.4 percent of patients showed improved symptoms, compared with 43.6 percent who took the placebo. At a higher dose, 57.6 percent had improved symptoms. Symptoms included pain, hair loss and skin rash.

Approximately 320,000 lupus patients in the U.S. are managed by rheumatologists, and about two-thirds of those patients (those who have stopped responding to standard therapies) would be candidates for the drug. ❖

*Research*

## Teva Launches Lupus Clinical Trial

Teva Pharmaceutical Industries Ltd. is investigating whether its drug Laquinimod, which is in a Phase III clinical trial for treating multiple sclerosis, also is suitable for treating lupus. Patients are being recruited for a Phase IIa clinical trial for Laquinimod for treating lupus nephritis, which affects the kidneys, and lupus arthritis, which affects joints.

Teva is developing Laquinimod with Swedish company Active Biotech. The drug is being investigated for fast-track approval by the U.S. Food and Drug Administration and could be approved for marketing by 2012. The approval will be for only MS, but there are indications that Laquinimod is effective for treating other autoimmune diseases, such as Crohn's disease, arthritis and rheumatoid arthritis, as well as lupus. ❖

*Medicine*

## FDA OKs Prolastin-C for AAT Deficiency

Prolastin-C has been approved by the Food and Drug Administration for the treatment of alpha1-antitrypsin (AAT) deficiency, a genetic condition in which low levels of this essential protein can result in emphysema. Manufactured by Talecris Biotherapeutics, Prolastin-C's active protein increases or "augments" protein levels in AAT-deficient patients. Clinical studies have shown that Prolastin-C and Prolastin are equally effective at raising AAT levels in the blood, and that the adverse event profile of Prolastin-C is consistent with that of Prolastin. However, Prolastin-C delivers twice the active protein per milliliter as Prolastin, cutting infusion volume and time in half when given at a recommended rate of 0.08 mL/kg/min. ❖

## People and Places in the News

### FDA APPROVALS

**Octapharma USA** has received orphan drug exclusivity from the U.S. Food and Drug Administration (FDA) for Wilate (von Willebrand Factor/Factor VIII Concentrate, Human), the replacement therapy developed specifically for von Willebrand disease.

The FDA has approved a new one-vial formulation of **Sanofi-Aventis U.S.** chemotherapeutic agent Taxotere (docetaxel) Injection Concentrate, which is available to cancer treatment clinics and hospitals nationwide in both 80 mg and 20 mg dosages. Introduced more than 14 years ago, Taxotere is approved by the FDA for use in treating patients at specific stages of five types of cancer, but it was previously available in only a two-vial formulation.

**Pfizer Inc.** has received 510(k) clearance by the FDA for its prefilled dual-chamber syringe used to reconstitute and administer antihemophilic factor (recombinant) plasma/albumin-free intravenous infusion (Xyntha) in patients with hemophilia A. The all-in-one syringe is the first to supply freeze-dried albumin-free recombinant factor VIII and also the diluent (0.9% sodium chloride), eliminating the reconstitution transfer step and improving patient convenience.

**Fenwal Inc.** has been given a new 510(k) clearance by the FDA for its Amicus blood cell separator. The new clearance involves the use of the Amicus separator with InterSol platelet additive solution, which Fenwal introduced earlier this year. InterSol is an electrolyte-based fluid that replaces 65 percent of the human plasma previously needed as a storage solution for donated platelets. Blood centers can collect the plasma replaced by InterSol and provide it to hospitals where it is used to treat patients.

### APPOINTMENTS

Tolerx Inc., a biopharmaceutical company developing novel therapies to treat autoimmune diseases and cancer by modulating T-cell activity, has appointed Antonin de Fougerolles, PhD, as chief scientific officer. Dr. deFougerolles has 15 years of biotech research and development experience in immunology.

University of California, Irvine, professors **Michael Cahalan**, **Greg Duncan** and **Susan Trumbore** have been elected to the National Academy of Sciences. They are among 72 new members and 18 foreign associates from 14 countries chosen in recognition of their distinguished and continuing achievements in original research. ❖

*Legal Issue*

# Vaccines Court Rejects Mercury-Autism Link

In March 2010, the federal vaccines court ruled in three separate cases that the mercury-containing preservative thimerosal does not cause autism. More than 5,300 parents had filed claims with the vaccines court, a branch of the U.S. Court of Federal Claims, seeking damages because they believed their children had developed autism as a result of vaccinations. Largely because of parental fears, thimerosal was removed from all childhood vaccines by 2001, except for multidose vials of influenza vaccine. Despite that action, the prevalence of autism has continued to grow, and it is now thought to affect as many as one in every 100 children, according to the Centers for Disease Control and Prevention.

The vaccines court was established in 1986 because vaccine manufacturers were facing many liability suits that threatened their ability to continue manufacturing the medicines. The court holds no-fault hearings to determine whether a child has been harmed by a vaccine. Compensation comes from a $2.5 billion fund based on a 75-cent surcharge on each dose of vaccine. The court has made many awards to parents who successfully showed that their children were damaged neurologically or otherwise by vaccines, but has refused to accept claims that autism is caused by vaccination. ❖

## Vaccine Update

Antigenics has had promising results of its experimental **herpes** vaccine in a Phase I clinical trial. The drug, called AG-707, is used to treat herpes simplex virus-2, which causes genital herpes.

Scientists at Stanford University are working on a **stress** vaccine that would help people relax without slowing them down. The vaccine contains a tailored herpes virus that carries engineered "neuro-protective" genes into the brain to counteract glucocorticoid hormones before they can harm the brain. The vaccine has been proven to work on rats, but human trials still need to be carried out.

An experimental vaccine appears to be safe and effective in protecting people against **hepatitis E** infection. A Phase III clinical trial in China involved 97,356 healthy participants, half of whom received the vaccine and the other half a placebo. None of those who received the vaccine became infected with the virus, while 15 of those given the placebo did.

Australian researchers are moving toward producing the first-ever vaccine for **dengue fever**, the potentially life-threatening infection spread by mosquitoes in the tropics. Late-stage clinical trials are under way for the vaccine, which will protect against all four known strains of the disease. Participants are being recruited in Perth, Adelaide and Brisbane.

A **flu vaccine patch** that has tiny microneedles that inject the vaccine into the skin could be possible in the future. The patch, which was developed in collaboration by researchers at Georgia Tech and Emory University, is placed on the skin and left for five minutes to 15 minutes and can remain longer without doing any damage. When tested on mice, the microneedles delivered a correct dose of the flu vaccine.

Another **vaccine patch** is being developed at the University of Queensland. Called the Nanopatch, it induces a similarly protective immune response as a vaccine delivered by needle and syringe, but uses 100 times less vaccine. According to the scientists, the patch targets specific antigen-presenting cells found in a narrow layer just beneath the skin surface, and results are 10 times better than those achieved by other delivery methods.

Researchers at the Scripps Research Institute have discovered a potential new way to stimulate the immune system to prevent or clear a **viral infection**, which could increase the effectiveness of human vaccines designed to prevent viral infections. The researchers found that by blocking a protein called interleukin-10 (IL-10), they can significantly boost immune memory in mice. And, because not all vaccines are 100 percent effective, they

*Legal Issue*

# Supreme Court Accepts Appeal Over Vaccine Safety

In March 2010, the U.S. Supreme Court agreed to decide whether drug makers can be sued outside a special judicial forum, known as the vaccines court, set up by Congress in 1986 to address specific claims about safety. The questions in the latest case are whether such liability claims can proceed if the vaccine-related injuries could have been avoided by better product design and if federal officials had approved another allegedly safer drug. Oral arguments in the dispute were held in the fall.

The lawsuit was brought by the parents of Hannah Bruesewitz, a girl who was in good health as an infant in 1992, but who began having seizures and became disabled after being given a series of DPT (diphtheria, pertussis and tetanus) shots. The Bruesewitzes alleged Wyeth Laboratories failed to adequately warn them and other parents of the risks associated with the vaccine. The vaccines court rejected the initial claim, and then the case went to a federal appeals court that eventually ruled for Wyeth, now owned by Pfizer Inc. However, despite the victory, the company urged the high court to hear the case, seeking final resolution on broader legal questions.

Wyeth and other drug manufacturers say their products are generally safe, but side effects can occur in very rare cases. They also say that the vaccine industry is generally not profitable, but that the health benefits for society in general have kept them in the business. For that, they say, legal protection provided by Congress is essential to ensure such drugs are widely available and affordable. Lawmakers acknowledged the vaccine supply was suffering under rising company costs from potential liability claims. The vaccines court created under the legislation was a liability shield, designed to be a reliable, relatively quick, no-fault solution to various claims. However, unresolved is whether and when certain exceptions to liability should be in play in specific cases. ❖

hope to enhance vaccination by using this approach. More information can be found at www.pnas.org/content/early/2010/01/20/0914500107.abstract.

Merck & Co. has provided U.S. regulators with new information needed for approval to market its Gardasil cervical cancer vaccine to women between the ages of 27 and 45. Gardasil was approved in 2006 for preventing **cervical cancer** and genital warts in females between ages 9 and 26.

An **inhalable measles vaccine** called carbondioxide assisted nebulization has been developed by researchers at the University of Colorado. Trials in animals have been successful, and human trials, to be conducted in Pune, India, will be conducted in three phases.

Researchers at the Cleveland Clinic have had positive results in tests on a new vaccine that could be used to protect against **breast cancer**. The vaccine works by forcing the immune system to tackle a protein found in breast cancer cells and the mammary tissue of women who are breastfeeding. In the study, half of the genetically cancer-prone mice that were vaccinated with α-lactalbumin failed to develop breast cancer, while the other half that were administered a vaccine without the antigen all developed breast cancer. Human trials are planned.

The U.S. Food and Drug Administration has granted orphan drug status to BioSante Pharmaceuticals' experimental **cancer vaccine** called GVAX CML for the treatment of chronic myeloid leukemia. This is the company's third vaccine to get orphan designation after pancreatic cancer and acute myeloid leukemia vaccines. ❖

*Research*

# Pay-for-Performance Effective Incentive

A study published in the January/February 2010 issue of the *Journal for Healthcare Quality* reveals that pay-for-performance (P4P) programs are effective in incentivizing low-performing physicians. The study investigated the impact of P4P in a preferred provider organization (PPO) on low-performing physicians over a four-year period. Results showed that the P4P program improved quality of care especially for selected quality measures, such as mammography, cervical cancer screening and childhood immunization measures. The low-performing physicians using P4P improved significantly more than the comparison group that did not implement a P4P program. In addition, the study found that the positive benefit of the P4P program may not be realized until the third or fourth year, highlighting the importance of sustaining P4P over longer periods of time. ❖

# Reimbursement FAQs

Some commonly held misunderstandings about reimbursement are clarified.

**I have read that primary immune deficient patients should start with a loading dose of intravenous immune globulin (IVIG) before switching to subcutaneous immune globulin (SCIG). But, I fear that asking the insurance company for a change in therapy before the date of reauthorization will trigger a review, causing more paperwork for my staff and unnecessary stress for my patient. Is there evidence that shows patients can safely and successfully start out on SCIG rather than IVIG?**

Yes, there is research showing a patient can be treated with SCIG without using a loading dose of IVIG. One such article, titled Improvement in Quality of Life Measurements in Newly Diagnosed Patients with Primary Immunodeficiency Receiving Directly Initiated Subcutaneous Replacement Therapy with Vivaglobin, was printed in the February 2010 edition of *The Journal of Allergy and Clinical Immunology*. According to the article's authors, "Therapy can be successfully initiated with a SCIG loading phase in newly diagnosed PID[D] patients, challenging the widespread recommendation for an initial intravenous IgG phase, and resulting in substantial improvement in HRQL [health related quality of life] indicators."[1]

**I have a patient who has maxed out COBRA options and is considering conversion options. One plan being considered places this patient's Vivaglobin under the pharmacy benefit for self-injectables. But, all medications in this particular category have a 30 percent copayment with none of the patient's responsibility going toward the yearly out-of-pocket maximum. There is no way a patient of normal means can afford that. What other options does this patient have?**

It's possible that the insurance representative in this case is a salesperson who has no knowledge of particular medications. This patient should first ask for a written copy of the drug formulary to confirm the placement of Vivaglobin under the pharmacy benefit. If Vivaglobin does fall under the pharmacy benefit and none of the costs go toward the yearly out-of-pocket maximum, then it is unlikely a patient of normal means will be able to afford the medication. In this case, the patient has two options. Option one would be to choose a different plan. Option two would involve exploring with the prescribing physician whether changing from subcutaneous infusions to intravenous infusions is an option. If so, the benefit would most likely then fall under the medical portion of the plan. Once under the medical portion, the patient would qualify to meet the out-of-pocket maximum and eventually have infusions covered at 100 percent.

## What classifies a Medicare patient as homebound? And, who can certify a patient as homebound?

For a patient to receive services in the home, a physician must certify that patient as homebound. It is not necessary for the patient to be confined to bed or even completely to the home to obtain homebound status. For instance, if leaving the home requires a great deal of effort, he or she may qualify for homebound status. And, once certified homebound, a patient may still leave the home for purposes such as infrequent family outings, medical appointments and church services. Specifically, the Medicare benefit policy states:

"It is expected that in most instances, absences from the home that occur will be for the purpose of receiving health care treatment. However, occasional absences from the home for nonmedical purposes, e.g., an occasional trip to the barber, a walk around the block or a drive, attendance at a family reunion, funeral, graduation, or other infrequent or unique event would not necessitate a finding that the patient is not homebound if the absences are undertaken on an infrequent basis or are of relatively short duration and do not indicate that the patient has the capacity to obtain the health care provided outside rather than in the home."[2]

## I would like to prescribe Hizentra, but because the package insert recommends prescribing at 153 percent of the intravenous dose, it seems unreasonably expensive. Is that prescribing dose necessary?

The U.S. Food and Drug Administration (FDA)-approved labeling for Hizentra does state that the recommended dose of Hizentra is 153 percent of the intravenous dose. However, several well-respected immunologists prescribe one-to-one dosing for their primary immune deficient patients. According to data released from a Phase III study at a meeting of the European Society for Immunodeficiencies, "Hizentra (IgPro20) provides primary immunodeficiency (PI) patients with a safe and effective alternative to other immunoglobulin therapies when given in equivalent doses."[3]

## I have a patient who insists her insurance company will approve only one brand of IVIG, but she does not respond well to that particular brand. Are insurance companies now dictating which brands of IVIG can be used?

Because there is no generic IVIG, insurers generally do not specify a particular brand. I checked several major insurer IVIG policies and formularies, and none of them specified a preference for a particular brand of IVIG. However, infusion providers do enter into exclusive contracts for certain brands as a cost-saving measure. So, your patient is most likely being informed by her provider that she can be treated with only one particular brand of IVIG. If this is the case, she is either misunderstanding or is being misled by her provider. I suggest your patient call her insurer directly and ask whether her preferred IVIG is covered. It may be necessary for her to change providers. ❖

### Ask Our Experts

*Have a reimbursement question? Our experts are ready to answer them. Email us at editor@BSTQuarterly.com.*

Sources:

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**KRIS MCFALLS** *is the patient advocate for* IG Living *magazine, directed to patients who rely on immune globulin and their caregivers.*

*Editor's Note: The content of this article is intended to provide a general guide to the subject matter. Specialist advice should be sought about your specific circumstances.*

# Plasma Therapies

## *Where Are We Now?*

Several key variables play a role in the promising possibilities for lifesaving plasma protein therapies.

By Kris McFalls

As the market for plasma protein therapies continues to grow at a steady pace, the possibilities for these precious lifesaving proteins seem endless. Patients long for that one treatment to return them to the quality of health and life they once had. Scientists, in turn, are dedicated to providing the safest, most effective product possible. And the manufacturers' desire to make it all happen is indisputable.

However, the plasma protein market contains difficult-to-control variables that have a skewing effect on the laws of supply and demand. Limited natural resources, long processing time, increasing costs for expensive plasma testing, few manufacturers, costly but necessary government regulations and low reimbursement rates can make the plasma market particularly vulnerable to prolonged and painful market swings.


## The Plasma Variable

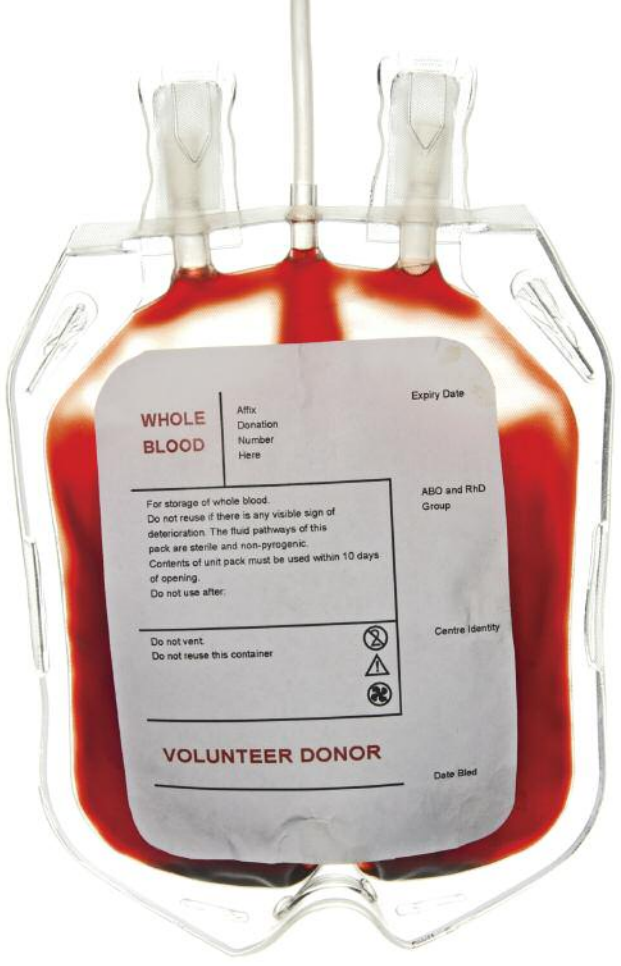
As the demand for plasma-based therapies continues to increase, several manufacturers are exploring new indications for these lifesaving therapies. But an increase in demand for these products first necessitates an increase in the raw product: plasma.

In the United States alone, there were roughly 22 million donations of plasma collected in 2009, according to the Plasma Protein Therapy Association (PPTA). This represents an approximate increase of 4.5 million donations over 2008. Most of the world's plasma was collected in about 400 plasma donation centers scattered throughout the U.S., the majority of which are owned by Baxter's BioLife Plasma Services, CSL Behring, Talecris Plasma Resources, Octapharma Plasma Inc. and Grifol's Biomat USA Inc.

*Several industry and patient organizations continue to press Medicare for a change in the current reimbursement model.*

Increasing the number of plasma donors to meet the increased product demand is challenging at best. And, regulations set forth by the U.S. Food and Drug Administration (FDA) to ensure the safety of the blood supply limits how much plasma can be collected. This raises the need for exploring safe and reliable ways to increase the donor pool.

This past year, the Health and Human Services' Advisory Committee on Blood Safety and Availability (ACBSA) considered relaxing the rules banning gay and bisexual men from donating blood or plasma. Current policy dictates that all men who have had sex with other men since 1977 be deferred as donors. Both patient and industry groups recognize that the HIV epidemic had disproportionally impacted both gay men and the plasma user community. The American Red Cross, America's Blood Centers and Advanced Transfusion and Cellular Therapies Worldwide were in favor of changing the ban to a temporary 12-month deferral after the last sexual encounter. But, several patient organizations, including the PPTA, released statements in favor of retaining the ban until further research into the matter could be attained because current data did not sufficiently support a change to the donor deferral policy. On June 10, 2010, the ACBSA found that data did not support changing the current policy and, therefore, did not recommend a change. The committee, however, did recommend researching the matter further.




### The Manufacturer Variable

Even when the plasma supply is robust, there is a risk of a sudden shortage of plasma protein therapies due to a limited number of manufacturers. This is especially true in the immune globulin (IG) market, where current science is unable to develop a production method for manufacturing a recombinant product. And, because most of the manufacturers provide products for the worldwide market, a shortage creates a domino effect on the worldwide supply.

Those who have been in the IG business for a long time remember the mid- to late-1990s, when IG products were in very short supply. Some patients were forced to go without treatment or extend the intervals between treatments. Brand choice was limited, and many patients were forced to take whatever product was available due to shortages caused by plant shutdowns, viral contamination and discontinued products due to mergers. Since that time, manufacturing processes and safety continue to improve. Most products are now liquid, the result of a manufacturing process that produces a higher yield. Safety procedures are more stringent, and the blood supply is safer as evidenced by the significantly fewer number of recalls.

Yet, with so few manufacturers, recalls and withdrawals continue to pose a risk to the worldwide supply of IG. Recently, the market experienced a complete withdrawal of Octagam (immune globulin intravenous [human] 5% liquid preparation). Even though Octapharma is not one of the top-three producers of IG for the U.S., the voluntary withdrawal still affected the U.S. market since supplies from all markets were needed to fill the void of the loss of Octagam from the U.S., Australia and Europe. And, even with improved manufacturing efficiency, it still takes approximately nine months to transform a plasma donation into a vial of ready-to-infuse IG. Therefore, even a rapid increase of production by the other manufacturers may not be able to meet the demands caused by a sudden withdrawal of any one brand of IG.

While there is currently not a shortage of IG, history has shown that recalls and withdrawals can cause sudden and unexpected shortages at any time, and to be complacent and unprepared for such possibilities is to put patients' lives in danger. "The wonderful thing about IVIG [intravenous IG] is its unwavering path toward dozens of undiscovered areas of therapeutic promise for thousands of patients globally," says Chris Ground, FFF Enterprises' vice president of national accounts. "This is precisely why we must make every effort to be vigilant surrounding the global supply-and-demand ratio of IVIG and to work to try to keep those factors in balance. Being out of balance creates challenges either way. This, of course, is easier said than done, given the always present possibility of manufacturing issues. Yet, this is an inextricable fact of the plasma industry. We must strive to nurture demand, while delicately balancing this with managed increases in manufacturers' global capacity."

***In the United States alone, there were roughly 22 million donations of plasma collected in 2009, according to the Plasma Protein Therapy Association (PPTA). This represents an approximate increase of 4.5 million donations over 2008.***

**CSL Behring**

**BRIEF SUMMARY OF PRESCRIBING INFORMATION**

# Hizentra, Immune Globulin Subcutaneous (Human), 20% Liquid

**Before prescribing, please consult full prescribing information, a brief summary of which follows. Some text and references refer to full prescribing information.**

## 1 INDICATIONS AND USAGE

Hizentra is an Immune Globulin Subcutaneous (Human) (IGSC), 20% Liquid indicated as replacement therapy for primary humoral immunodeficiency (PI). This includes, but is not limited to, the humoral immune defect in congenital agammaglobulinemia, common variable immunodeficiency, X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.

## 4 CONTRAINDICATIONS

Hizentra is contraindicated in patients who have had an anaphylactic or severe systemic reaction to the administration of human immune globulin or to components of Hizentra, such as polysorbate 80.

Hizentra is contraindicated in patients with hyperprolinemia because it contains the stabilizer L-proline (*see Description [11]*).

Hizentra is contraindicated in IgA-deficient patients with antibodies against IgA and a history of hypersensitivity (*see Description [11]*).

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Hypersensitivity

Severe hypersensitivity reactions may occur to human immune globulin or components of Hizentra, such as polysorbate 80. In case of hypersensitivity, discontinue the Hizentra infusion immediately and institute appropriate treatment.

Individuals with IgA deficiency can develop anti-IgA antibodies and anaphylactic reactions (including anaphylaxis and shock) after administration of blood components containing IgA. Patients with known antibodies to IgA may have a greater risk of developing potentially severe hypersensitivity and anaphylactic reactions with administration of Hizentra. Hizentra contains ≤50 mcg/mL IgA (*see Description [11]*).

### 5.2 Reactions Reported to Occur With IGIV Treatment

The following reactions have been reported to occur with IGIV treatment and may occur with IGSC treatment.

**Renal Dysfunction/Failure**

Renal dysfunction/failure, osmotic nephropathy, and death may occur with use of human immune globulin products. Ensure that patients are not volume depleted and assess renal function, including measurement of blood urea nitrogen (BUN) and serum creatinine, before the initial infusion of Hizentra and at appropriate intervals thereafter.

Periodic monitoring of renal function and urine output is particularly important in patients judged to have a potential increased risk of developing acute renal failure.[1] If renal function deteriorates, consider discontinuing Hizentra. For patients judged to be at risk of developing renal dysfunction because of pre-existing renal insufficiency or predisposition to acute renal failure (such as those with diabetes mellitus or hypovolemia, those who are overweight or use concomitant nephrotoxic medicinal products, or those who are over 65 years of age), administer Hizentra at the minimum rate practicable.

**Thrombotic Events**

Thrombotic events may occur with use of human immune globulin products[2-4]. Patients at increased risk may include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, hypercoagulable disorders, prolonged periods of immobilization, and/or known or suspected hyperviscosity. Because of the potentially increased risk of thrombosis, consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies. For patients judged to be at risk of developing thrombotic events, administer Hizentra at the minimum rate practicable.

**Aseptic Meningitis Syndrome (AMS)**

AMS may occur with use of human immune globulin products.[5] The syndrome usually begins within several hours to 2 days following IGIV treatment. AMS is characterized by signs and symptoms including severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, nausea, and vomiting. Cerebrospinal fluid (CSF) studies frequently show pleocytosis up to several thousand cells per cubic millimeter, predominantly from the granulocytic series, with elevated protein levels up to several hundred mg/dL. AMS may occur more frequently in association with high doses (2 g/kg) and/or rapid infusion of IGIV.

Conduct a thorough neurological examination, including CSF studies, to rule out other causes of meningitis in patients exhibiting signs and symptoms of AMS. Discontinuation of IGIV treatment has resulted in remission of AMS within several days without sequelae.

**Hemolysis**

Hizentra can contain blood group antibodies that may act as hemolysins and induce *in vivo* coating of red blood cells (RBCs) with immunoglobulin, causing a positive direct antiglobulin (Coombs') test result and hemolysis.[6-8] Delayed hemolytic anemia can develop subsequent to immune globulin therapy due to enhanced RBC sequestration, and acute hemolysis, consistent with intravascular hemolysis, has been reported.[9]

Monitor recipients of Hizentra for clinical signs and symptoms of hemolysis. If these are present after a Hizentra infusion, perform appropriate confirmatory laboratory testing. If transfusion is indicated for patients who develop hemolysis with clinically compromising anemia after receiving Hizentra, perform adequate cross-matching to avoid exacerbating on-going hemolysis.

**Transfusion-Related Acute Lung Injury (TRALI)**

Noncardiogenic pulmonary edema may occur in patients administered human immune globulin products.[10] TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever. Typically, it occurs within 1 to 6 hours following transfusion. Patients with TRALI may be managed using oxygen therapy with adequate ventilatory support.

Monitor Hizentra recipients for pulmonary adverse reactions. If TRALI is suspected, perform appropriate tests for the presence of anti-neutrophil antibodies in both the product and patient's serum.

### 5.3 Transmissible Infectious Agents

Because Hizentra is made from human plasma, it may carry a risk of transmitting infectious agents (e.g., viruses, and theoretically, the Creutzfeldt-Jakob disease [CJD] agent). The risk of infectious agent transmission has been reduced by screening plasma donors for prior exposure to certain viruses, testing for the presence of certain current virus infections, and including virus inactivation/removal steps in the manufacturing process for Hizentra.

Report all infections thought to be possibly transmitted by Hizentra to CSL Behring Pharmacovigilance at 1-866-915-6958.

### 5.4 Laboratory Tests

Various passively transferred antibodies in immunoglobulin preparations may lead to misinterpretation of the results of serological testing.

## 6 ADVERSE REACTIONS

The most common adverse reactions (ARs), observed in ≥5% of study subjects receiving Hizentra, were local reactions (i.e., swelling, redness, heat, pain, and itching at the injection site), headache, vomiting, pain, and fatigue.

### 6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, AR rates observed in clinical studies of a product cannot be directly compared to rates in the clinical studies of another product and may not reflect the rates observed in clinical practice.

The safety of Hizentra was evaluated in a clinical study for 15 months in subjects with PI who had been treated previously with IGIV every 3 or 4 weeks. The safety analyses included 49 subjects in the intention-to-treat (ITT) population. The ITT population consisted of all subjects who received at least one dose of Hizentra (*see Clinical Studies [14]*).

Subjects were treated with Hizentra at weekly doses ranging from 66 to 331 mg/kg body weight during the wash-in/wash-out period and from 72 to 379 mg/kg during the efficacy period. The 49 subjects received a total of 2264 weekly infusions of Hizentra.

No deaths or serious ARs occurred during the study. Two subjects withdrew from the study due to ARs. One subject experienced a severe injection-site reaction one day after the third weekly infusion, and the other subject experienced moderate myositis. Both reactions were judged to be "at least possibly related" to the administration of Hizentra.

Table 2 summarizes the most frequent adverse events (AEs) (experienced by at least 4 subjects), *irrespective of causality*. Included are all AEs and those considered temporally associated with the Hizentra infusion, i.e., occurring during or within 72 hours after the end of an infusion. Local reactions were the most frequent AEs observed, with injection-site reactions (i.e., swelling, redness, heat, pain, and itching at the site of injection) comprising 98% of local reactions.

**Table 2: Incidence of Subjects With Adverse Events (AEs)* (Experienced by 4 or More Subjects) and Rate per Infusion, *Irrespective of Causality* (ITT Population)**

| AE (≥4 Subjects) | All AEs* | | AEs* Occurring During or Within 72 Hours of Infusion | |
|---|---|---|---|---|
| | Number (%) of Subjects (n=49) | Number (Rate†) of AEs (n=2264 Infusions) | Number (%) of Subjects (n=49) | Number (Rate†) of AEs (n=2264 Infusions) |
| Local reactions‡ | 49 (100) | 1340 (0.592) | 49 (100) | 1322 (0.584) |

**Table 2: (Continued)**

| AE (≥4 Subjects) | All AEs* | | AEs* Occurring During or Within 72 Hours of Infusion | |
|---|---|---|---|---|
| | Number (%) of Subjects (n=49) | Number (Rate†) of AEs (n=2264 Infusions) | Number (%) of Subjects (n=49) | Number (Rate†) of AEs (n=2264 Infusions) |
| Other AEs: | | | | |
| Headache | 13 (26.5) | 40 (0.018) | 12 (24.5) | 32 (0.014) |
| Cough | 8 (16.3) | 9 (0.004) | 5 (10.2) | 6 (0.003) |
| Diarrhea | 7 (14.3) | 8 (0.004) | 5 (10.2) | 6 (0.003) |
| Fatigue | 6 (12.2) | 6 (0.003) | 4 (8.2) | 4 (0.002) |
| Back pain | 5 (10.2) | 11 (0.005) | 4 (8.2) | 5 (0.002) |
| Nausea | 5 (10.2) | 5 (0.002) | 4 (8.2) | 4 (0.002) |
| Abdominal pain, upper | 5 (10.2) | 5 (0.002) | 3 (6.1) | 3 (0.001) |
| Rash | 5 (10.2) | 7 (0.003) | 2 (4.1) | 3 (0.001) |
| Pain in extremity | 4 (8.2) | 7 (0.003) | 4 (8.2) | 6 (0.003) |
| Migraine | 4 (8.2) | 5 (0.002) | 3 (6.1) | 4 (0.002) |
| Pain | 4 (8.2) | 5 (0.002) | 3 (6.1) | 4 (0.002) |
| Epistaxis | 4 (8.2) | 6 (0.003) | 2 (4.1) | 3 (0.001) |
| Pharyngolaryngeal pain | 4 (8.2) | 6 (0.003) | 2 (4.1) | 2 (<0.001) |
| Arthralgia | 4 (8.2) | 5 (0.002) | 2 (4.1) | 3 (0.001) |

* Excluding infections.
† Rate of AEs per infusion.
‡ Includes injection-site reactions as well as bruising, scabbing, pain, irritation, cysts, eczema, and nodules at the injection site.

The ratio of infusions with temporally associated AEs, including local reactions, to all infusions was 1338 to 2264 (59.1%; upper 95% confidence limit of 62.4%). Excluding local reactions, the corresponding ratio was 173 to 2264 (7.6%; upper 95% confidence limit of 8.9%).

Table 3 summarizes the most frequent ARs (i.e., those AEs considered by the investigators to be "at least possibly related" to Hizentra administration) experienced by at least 2 subjects.

**Table 3: Incidence of Subjects With Adverse Reactions (Experienced by 2 or More Subjects) to Hizentra and Rate per Infusion (ITT Population)**

| Adverse Reaction (≥2 Subjects) | Number (%) of Subjects (n=49) | Number (Rate*) of Adverse Reactions (n=2264 Infusions) |
|---|---|---|
| Local reactions† | 49 (100) | 1338 (0.591) |
| Other ARs: | | |
| Headache | 12 (24.5) | 36 (0.016) |
| Vomiting | 3 (6.1) | 3 (0.001) |
| Pain | 3 (6.1) | 4 (0.002) |
| Fatigue | 3 (6.1) | 3 (0.001) |
| Contusion | 2 (4.1) | 3 (0.001) |
| Back pain | 2 (4.1) | 3 (0.001) |
| Migraine | 2 (4.1) | 3 (0.001) |
| Diarrhea | 2 (4.1) | 2 (<0.001) |
| Abdominal pain, upper | 2 (4.1) | 2 (<0.001) |
| Nausea | 2 (4.1) | 2 (<0.001) |
| Rash | 2 (4.1) | 2 (<0.001) |
| Arthralgia | 2 (4.1) | 2 (<0.001) |

* Rate of ARs per infusion.
† Includes injection-site reactions as well as bruising, scabbing, pain, irritation, cysts, eczema, and nodules at the injection site.

Table 4 summarizes injection-site reactions based on investigator assessments 15 to 45 minutes after the end of the 683 infusions administered during regularly scheduled visits (every 4 weeks).

**Table 4: Investigator Assessments* of Injection-Site Reactions by Infusion**

| Injection-Site Reaction | Number† (Rate‡) of Reactions (n=683 Infusions§) |
|---|---|
| Edema/induration | 467 (0.68) |
| Erythema | 346 (0.50) |
| Local heat | 108 (0.16) |
| Local pain | 88 (0.13) |
| Itching | 64 (0.09) |

* 15 to 45 minutes after the end of infusions administered at regularly scheduled visits (every 4 weeks).
† For multiple injection sites, every site was judged, but only the site with the strongest reaction was recorded.
‡ Rate of injection-site reactions per infusion.
§ Number of infusions administered during regularly scheduled visits.

Most local reactions were either mild (93.4%) or moderate (6.3%) in intensity.

### 6.2 Postmarketing Experience

*Because postmarketing reporting of adverse reactions is voluntary and from a population of uncertain size, it is not always possible to reliably estimate the frequency of these reactions or establish a causal relationship to product exposure.*

The following adverse reactions have been identified and reported during the postmarketing use of IGIV products[11]:

- *Infusion reactions:* Hypersensitivity (e.g., anaphylaxis), headache, diarrhea, tachycardia, fever, fatigue, dizziness, malaise, chills, flushing, urticaria or other skin reactions, wheezing or other chest discomfort, nausea, vomiting, rigors, back pain, myalgia, arthralgia, and changes in blood pressure
- *Renal:* Acute renal dysfunction/failure, osmotic nephropathy
- *Respiratory:* Apnea, Acute Respiratory Distress Syndrome (ARDS), TRALI, cyanosis, hypoxemia, pulmonary edema, dyspnea, bronchospasm
- *Cardiovascular:* Cardiac arrest, thromboembolism, vascular collapse, hypotension
- *Neurological:* Coma, loss of consciousness, seizures, tremor, aseptic meningitis syndrome
- *Integumentary:* Stevens-Johnson syndrome, epidermolysis, erythema multiforme, dermatitis (e.g., bullous dermatitis)
- *Hematologic:* Pancytopenia, leukopenia, hemolysis, positive direct antiglobulin (Coombs') test
- *Gastrointestinal:* Hepatic dysfunction, abdominal pain
- *General/Body as a Whole:* Pyrexia, rigors

To report SUSPECTED ADVERSE REACTIONS, contact CSL Behring Pharmacovigilance at 1-866-915-6958 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

## 7 DRUG INTERACTIONS

### 7.1 Live Virus Vaccines

The passive transfer of antibodies with immunoglobulin administration may interfere with the response to live virus vaccines such as measles, mumps, rubella, and varicella (*see Patient Counseling Information [17]*).

### 7.2 Serological Testing

Various passively transferred antibodies in immunoglobulin preparations may lead to misinterpretation of the results of serological testing.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Pregnancy Category C. Animal reproduction studies have not been conducted with Hizentra. It is not known whether Hizentra can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Hizentra should be given to pregnant women only if clearly needed.

### 8.3 Nursing Mothers

Hizentra has not been evaluated in nursing mothers.

### 8.4 Pediatric Use

Hizentra was evaluated in 10 pediatric subjects (3 children and 7 adolescents) with PI. No pediatric-specific dose requirements were necessary to achieve the desired serum IgG levels.

Hizentra was not evaluated in neonates or infants.

### 8.5 Geriatric Use

Of the 49 subjects evaluated in the clinical study of Hizentra, 6 subjects were 65 years of age or older. No overall differences in safety or efficacy were observed between these subjects and younger subjects.

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**BRIEF SUMMARY OF PRESCRIBING INFORMATION**

# Vivaglobin®

## Immune Globulin Subcutaneous (Human) 16% Liquid

**Before prescribing, please consult prescribing information, a brief summary of which follows. Some text and references refer to full prescribing information.**

### 1 INDICATIONS AND USAGE

Vivaglobin is an Immune Globulin Subcutaneous (Human) (IGSC), 16% Liquid indicated as replacement therapy for primary humoral immunodeficiency (PI). This includes, but is not limited to, the primary immunodeficiency in common variable immunodeficiency (CVID), X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.

### 4 CONTRAINDICATIONS

Vivaglobin is contraindicated in patients who have had an anaphylactic or severe systemic reaction to the administration of Immune Globulin (Human).

Vivaglobin is contraindicated in IgA-deficient patients with antibodies against IgA or a history of hypersensitivity (*see Description [11]*).

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 Hypersensitivity Reactions

Severe hypersensitivity reactions may occur (*see Patient Counseling Information [17.2]*). In case of hypersensitivity, discontinue the Vivaglobin infusion immediately and institute appropriate treatment. Epinephrine should be immediately available to treat any acute severe hypersensitivity reactions.

Individuals with IgA deficiency can develop anti-IgA antibodies and anaphylactic reactions (including anaphylaxis and shock) after administration of blood components containing IgA. Patients with known antibodies to IgA may have a greater risk of developing potentially severe hypersensitivity and anaphylactic reactions. Vivaglobin contains ≤1.7 mg/mL IgA (*see Description [11]*). The minimum concentration of IgA that will provoke a hypersensitivity reaction is not known; therefore all IgG preparations carry the risk of inducing an anaphylactic reaction to IgA.

#### 5.2 Aseptic Meningitis Syndrome (AMS)

AMS has been reported to occur infrequently with IGIV treatment[5] and with Vivaglobin treatment. The syndrome usually begins within several hours to 2 days following IGIV treatment. AMS is characterized by signs and symptoms including severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, nausea, and vomiting. Cerebrospinal fluid (CSF) studies frequently show pleocytosis up to several thousand cells per cubic millimeter, predominantly from the granulocytic series, and with elevated protein levels up to several hundred mg/dL. AMS may occur more frequently in association with high doses (2 g/kg) and/or rapid infusion of IGIV.

Patients exhibiting such signs and symptoms should receive a thorough neurological examination, including CSF studies, to rule out other causes of meningitis. Discontinuation of IGIV treatment has resulted in remission of AMS within several days without sequelae.

#### 5.3 Reactions Reported with IGIV Treatment

The following reactions have been reported to occur with IGIV treatment and may occur with IGSC treatment.

**Renal Dysfunction/Failure**

Renal dysfunction/failure, osmotic nephropathy, and death may occur with use of human immune globulin products. Ensure that patients are not volume depleted and assess renal function, including measurement of blood urea nitrogen (BUN) and serum creatinine, before the initial infusion of Vivaglobin and at appropriate intervals thereafter.

Periodic monitoring of renal function and urine output is particularly important in patients judged to have a potential increased risk of developing acute renal failure.[1] If renal function deteriorates, consider discontinuing Vivaglobin. For patients judged to be at risk of developing renal dysfunction because of pre-existing renal insufficiency or predisposition to acute renal failure (such as those with diabetes mellitus or hypovolemia, those who are overweight or use concomitant nephrotoxic medicinal products, or those who are over 65 years of age), administer Vivaglobin at the minimum rate practicable.

**Thrombotic Events**

Thrombotic events may occur with use of human immune globulin products.[2-4] Patients at risk may include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, hypercoagulable disorders, prolonged periods of immobilization, and/or known or suspected hyperviscosity. Because of the potentially increased risk of thrombosis, consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies. For patients judged to be at risk of developing thrombotic events, administer Vivaglobin at the minimum rate practicable.

**Hemolysis**

Vivaglobin may contain blood group antibodies that may act as hemolysins and induce *in vivo* coating of red blood cells (RBCs) with immunoglobulin, causing a positive direct antiglobulin (Coombs') test result and hemolysis.[6-8] Delayed hemolytic anemia can develop subsequent to immune globulin therapy due to enhanced RBC sequestration, and acute hemolysis, consistent with intravascular hemoylysis, has been reported.[9]

Monitor recipients of Vivaglobin for clinical signs and symptoms of hemolysis. If these are present after Vivaglobin infusion, perform appropriate confirmatory laboratory testing. If transfusion is indicated for patients who develop hemolysis with clinically compromising anemia after receiving Vivaglobin, perform adequate cross-matching to avoid exacerbating on-going hemolysis.

**Transfusion-Related Acute Lung Injury (TRALI)**

Noncardiogenic pulmonary edema may occur in patients administered human immune globulin products.[10] TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever. Typically, it occurs within 1 to 6 hours following transfusion. Patients with TRALI may be managed using oxygen therapy with adequate ventilatory support.

Monitor recipients of Vivaglobin for pulmonary adverse reactions. If TRALI is suspected, perform appropriate tests for the presence of anti-neutrophil antibodies in both the product and patient's serum.

#### 5.4 Transmissible Infectious Agents

Because Vivaglobin is made from human plasma, it may carry a risk of transmitting infectious agents, e.g., viruses and, theoretically, the Creutzfeldt-Jakob (CJD) agent. No cases of transmission of viral diseases or CJD have been associated with the use of Vivaglobin. Report all infections thought possibly to have been transmitted by Vivaglobin to the CSL Behring Pharmacovigilance Department at 1-866-915-6958 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*. The physician should discuss the risks and benefits of this product with the patient before prescribing or administering it to the patient (*see Patient Counseling Information [17.2]*).

#### 5.5 Laboratory Tests

After infusion of IgG, the transitory rise of the various passively transferred antibodies in the patient's blood may yield positive serological testing results, with the potential for misleading interpretation. Passive transmission of antibodies to erythrocyte antigens (e.g., A, B, and D) may cause a positive direct or indirect antiglobulin (Coombs') test.

### 6 ADVERSE REACTIONS

The most common adverse reactions (those AEs considered by the investigator to be at least possibly related to Vivaglobin administration) observed in ≥5% of study subjects receiving Vivaglobin were local injection-site reactions (swelling, redness, and itching), headache, nausea, rash, asthenia, and gastrointestinal disorder.

#### 6.1 Clinical Studies Experience

*Because clinical studies 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 practice.*

**US-Canada Study**

The safety of Vivaglobin was evaluated in a clinical study in the US and Canada for 12 months in 65 subjects with PI who had been previously treated with IGIV every 3 or 4 weeks (*see Clinical Studies [14.1]*). After 3 months, subjects were switched from IGIV to weekly subcutaneous administration of Vivaglobin for 12 months. Subjects were treated weekly with Vivaglobin at a mean dose of 158 mg/kg body weight (range: 34 to 352 mg/kg). The 65 subjects received a total of 3,656 infusions of Vivaglobin.

Table 2 shows the number of subjects who withdrew from the US-Canada study due to adverse events (AEs) and the AEs leading to discontinuation.

**Table 2: Subjects with Adverse Events (AEs) Leading to Discontinuation, US-Canada Study**

| AEs | Subjects with AEs *At Least Possibly Related* | Subjects with AEs *Irrespective of Causality* | Total Number (%) of Subjects |
|---|---|---|---|
| Subjects with at least 1 AE leading to discontinuation | 4 | 1 | 5 (8%) |
| Injection-site reaction | 3 | – | 3 (5%) |
| Intestinal obstruction | – | 1 | 1 (2%) |
| Hyperventilation | 1* | – | 1 (2%) |
| Tachycardia | 1* | – | 1 (2%) |

* One subject experienced hyperventilation and tachycardia.

Table 3 summarizes the most frequent AEs (experienced by more than 5% of subjects), *irrespective of causality*. It includes all AEs and those considered temporally associated with the Vivaglobin infusion, i.e., occurring during the infusion or within 72 hours after the end of the infusion.

**Table 3: Incidence of Subjects With Adverse Events (AEs)* (Experienced by >5% of Subjects) and Rate† per Infusion, *Irrespective of Causality*, in the US-Canada Study**

| AEs* (>5% of Subjects) | All AEs | | AEs Occurring During or Within 72 Hours of Infusion | |
|---|---|---|---|---|
| | Number (%) of Subjects (n=65) | Number (Rate†) of AEs per Infusion (n=3656) | Number (%) of Subjects (n=65) | Number (Rate†) of AEs Per Infusion (n=3656) |
| AEs at the injection site‡ | 60 (92%) | 1789 (0.49) | 60 (92%) | 1767 (0.4848) |
| Other AEs | | | | |
| Headache | 31 (48%) | 159 (0.04) | 30 (46%) | 104 (0.033) |
| Gastrointestinal disorder | 24 (37%) | 35 (0.01) | 18 (28%) | 24 (0.007) |
| Fever | 16 (25%) | 28 (0.008) | 12 (8%) | 20 (0.005) |
| Nausea | 12 (18%) | 18 (0.005) | 11 (17%) | 15 (0.004) |
| Rash | 11 (17%) | 22 (0.006) | 10 (15%) | 16 (0.004) |
| Sore throat | 10 (15%) | 17 (0.005) | 8 (12%) | 11 (0.003) |
| Allergic reaction | 7 (11%) | 8 (0.002) | 5 (8%) | 5 (0.001) |
| Pain | 6 (9%) | 8 (0.002) | 4 (6%) | 4 (0.001) |
| Diarrhea | 6 (9%) | 6 (0.002) | 5 (8%) | 5 (0.001) |
| Cough increased | 6 (9%) | 6 (0.002) | 5 (8%) | 5 (0.001) |
| Gastrointestinal pain | 5 (8%) | 6 (0.002) | 4 (6%) | 5 (0.001) |
| Migraine | 5 (8%) | 5 (0.001) | 2 (3%) | 2 (0.001) |
| Skin disorder | 5 (8%) | 7 (0.002) | 3 (5%) | 5 (0.001) |
| Asthma | 5 (8%) | 8 (0.002) | 3 (5%) | 4 (0.001) |
| Arthralgia | 4 (6%) | 4 (0.001) | 3 (5%) | 3 (0.001) |
| Asthenia | 4 (6%) | 4 (0.001) | 2 (3%) | 2 (0.001) |
| Malaise | 4 (6%) | 5 (0.001) | 2 (3%) | 2 (0.001) |

* Excluding infections. † Rate, number of AEs per infusion. ‡ Includes injection-site inflammation.

The total number of AEs, *irrespective of causality,* including injection-site reactions, that began during or within 72 hours after the end of an infusion was 2262 (a rate of 0.62 AEs per infusion); excluding injection-site reactions, the rate of AEs per infusion was 0.14.

Table 4 summarizes the severity of local AEs by infusion, *irrespective of causality*.

**Table 4: Severity of Local Adverse Events (AEs) by Infusion, *Irrespective of Causality*, in the US-Canada Study**

| AEs (Number of infusions: 3656) | Number (Rate*) of AEs | Number (Rate*) of AEs Occurring During or Within 72 Hours of Infusion |
|---|---|---|
| AEs at the injection site | 1789 (0.49) | 1767 (0.48) |
| Mild† | 1112 (0.30) | 1100 (0.30) |
| Moderate‡ | 601 (0.16) | 593 (0.16) |
| Severe§ | 65 (0.02) | 64 (0.02) |
| Unknown severity | 11 (<0.01) | 10 (<0.01) |
| Discontinuations due to AEs at the injection site | 3 subjects | |

* Rate, number of AEs per infusion.
† Defined as those reactions that did not interfere with routine activities.
‡ Defined as those reactions that interfered with routine activities.
§ Defined as those reactions that made it impossible to perform routine activities.

Of the three subjects who discontinued the study due to injection-site reactions, one withdrew on Day 1 (Infusion 1) of the wash-in/wash-out period after a moderate injection-site reaction and a mild headache; one withdrew on Day 22 (Infusion 4) of the wash-in/wash-out period following severe injection-site reactions for two weeks; and one withdrew on Day 78 following a mild injection-site reaction.

Local reactions decreased substantially after repeated use.

Table 5 summarizes the most frequent adverse reactions (experienced by at least 3% of subjects) and considered by the investigator to be *at least possibly related* to Vivaglobin administration.

**Table 5: Incidence of Subjects With Adverse Reactions (Experienced in ≥3% of Subjects) and Rate* Per Infusion in the US-Canada Study**

| Related Adverse Reactions (≥3% Subjects) | Number (%) of Subjects (n=65) | Number (Rate*) of Adverse Reactions per Infusion (n=3656) |
|---|---|---|
| Adverse reactions at the injection site† | 60 (92%) | 1787 (0.49) |
| Other Adverse reactions | | |
| Headache | 21 (32%) | 59 (0.016) |
| Nausea | 7 (11%) | 9 (0.002) |
| Rash | 4 (6%) | 9 (0.002) |
| Asthenia | 3 (5%) | 3 (0.001) |
| Gastrointestinal disorder | 3 (5%) | 3 (0.001) |
| Fever | 2 (3%) | 2 (0.001) |
| Skin disorder | 2 (3%) | 3 (0.001) |
| Tachycardia | 2 (3%) | 2 (0.001) |
| Urine abnormality | 2 (3%) | 3 (0.001) |

***** Rate, number of adverse reactions per infusion. † Includes injection-site inflammation.

**Europe-Brazil Study**

In a clinical study conducted in Europe and Brazil, the efficacy and safety of Vivaglobin were evaluated for 10 months in 60 subjects with PI. Subjects were treated weekly with Vivaglobin at a mean dose of 89 mg/kg body weight (range: 51 to 147 mg/kg), which was 101% of their previous weekly IGIV or IGSC dose (*see Clinical Studies [14.2]*). Study subjects received a total of 2,297 infusions of Vivaglobin.

The AEs and their rates reported in this study were similar to those reported in the US-Canada study, with two exceptions: no episodes of headache were reported; and 18 (a rate of 0.008 per infusion) episodes of fever were judged to be related to the administration of Vivaglobin. One subject discontinued due to repeated local reactions of moderate severity.

### 6.2 Postmarketing Experience

*Because postmarketing reporting of adverse reactions is voluntary and from a population of uncertain size, it is not always possible to reliably estimate the frequency of these reactions or establish a causal relationship to product exposure.*

**Vivaglobin**

Adverse reactions identified during worldwide postmarketing use of Vivaglobin for treatment of PI are allergic-anaphylactic reactions (including dyspnea, pruritus, urticaria, rash, edema and other cutaneous reactions, wheezing, syncope, hypotension, and throat swelling), generalized reactions (including flu-like symptoms, myalgia, chills, fever, tachycardia, arthralgia, nausea and vomiting, diarrhea, gastrointestinal cramping, stomach pain, back pain, headache, headache possibly caused by increased blood pressure, and chest tightness), migraine, and injection-site reactions.

**General**

The following adverse reactions have been identified and reported during the postmarketing use of IGIV products[11]:

- *Renal:* Acute renal dysfunction/failure, osmotic nephropathy
- *Respiratory:* Apnea, Acute Respiratory Distress Syndrome (ARDS), TRALI, cyanosis, hypoxemia, pulmonary edema, dyspnea, bronchospasm
- *Cardiovascular:* Cardiac arrest, thromboembolism, vascular collapse, hypotension
- *Neurological:* Coma, loss of consciousness, seizures, tremor, aseptic meningitis syndrome
- *Integumentary:* Stevens-Johnson syndrome, epidermolysis, erythema multiforme, bullous dermatitis
- *Hematologic:* Pancytopenia, leukopenia, hemolysis, positive direct antiglobulin (Coombs') test
- *General/Body as a Whole:* Pyrexia, rigors
- *Musculoskeletal:* Back pain
- *Gastrointestinal:* Hepatic dysfunction, abdominal pain

## 7 DRUG INTERACTIONS

### 7.1 Live Virus Vaccines

The passive transfer of antibodies with immunoglobulin administration may interfere with the response to live virus vaccines such as measles/mumps/rubella and varicella (*see Patient Counseling Information [17.2]*).

### 7.2 Serological Testing

Various passively transferred antibodies in immunoglobulin preparations may lead to misinterpretation of the results of serological testing.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Pregnancy Category C. Animal reproduction studies have not been conducted with Vivaglobin. It is also not known whether Vivaglobin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Vivaglobin should be given to a pregnant woman only if clearly needed.

### 8.3 Nursing Mothers

Vivaglobin has not been evaluated in nursing mothers.

### 8.4 Pediatric Use

- In the US-Canada study, Vivaglobin was evaluated in 6 children (ages 5 through 11) and 4 adolescents (ages 13 through 16). In the Europe-Brazil study, Vivaglobin was evaluated in 16 children (ages 3 through 11) and 6 adolescents (ages 13 through 16).
- The safety and efficacy of Vivaglobin were not studied in pediatric subjects under 2 years of age.
- There were no differences in the safety and efficacy profiles as compared with adult subjects.
- No pediatric-specific dosing requirements were necessary to achieve the desired serum IgG levels.
- For recommendations on the number of simultaneous injection sites for pediatric patients who weigh less than 45 kg (99 pounds), *see Administration (2.4)*.

### 8.5 Geriatric Use

The clinical studies of Vivaglobin did not include sufficient numbers of subjects 65 years of age and older to determine whether they respond differently from younger subjects. For recommendations on the number of simultaneous injection sites for geriatric patients, see *Administration (2.4)*.

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Based on April 2010 Revision.

## The Reimbursement Variable

Even in stable markets, reimbursement rates continue to pose a risk to plasma-derived therapies. Several industry and patient organizations continue to press Medicare for a change in the current reimbursement model. In its public comments to the Centers for Medicare and Medicaid Services (CMS), the PPTA supported the "CMS proposal to set the payment level of separately payable non-pass-through drugs and biologicals, which include most plasma protein therapies, at average sales price (ASP) plus 6 percent. [However, the PPTA raised objections to] the policy of using hospital claims data that includes drugs and biologicals sold as part of the heavily discounted 340B Drug Pricing Program when setting Outpatient Prospective Payment System (OPPS) payment rates." Additionally, several patient organizations continue to press hard for changes in the Medicare payment system to allow patients equal access to care both in a home and clinical setting.

Some states are trying to ensure patient access to care by targeting private insurers' policies. A few states have either passed or are considering legislation to disallow private insurers from moving plasma therapies into a high tier-level program with copayments as high as 50 percent of the cost of the medication. Included in the same legislation is a proposal that also would limit the yearly out-of-pocket maximum patients must pay. With decreasing reimbursement rates and increased patient liability, legislation will continue to play a key role in patient access to care.

## Possibilities and Responsibilities

As the plasma therapy market continues to evolve and grow, so will the possibilities and responsibilities. It is clear that the industry is excited about the promises these lifesaving products bring to patients worldwide. Yet, while focused on fulfilling this potential, all participants also are working very hard to not lose sight of their responsibilities for doing it right. ❖

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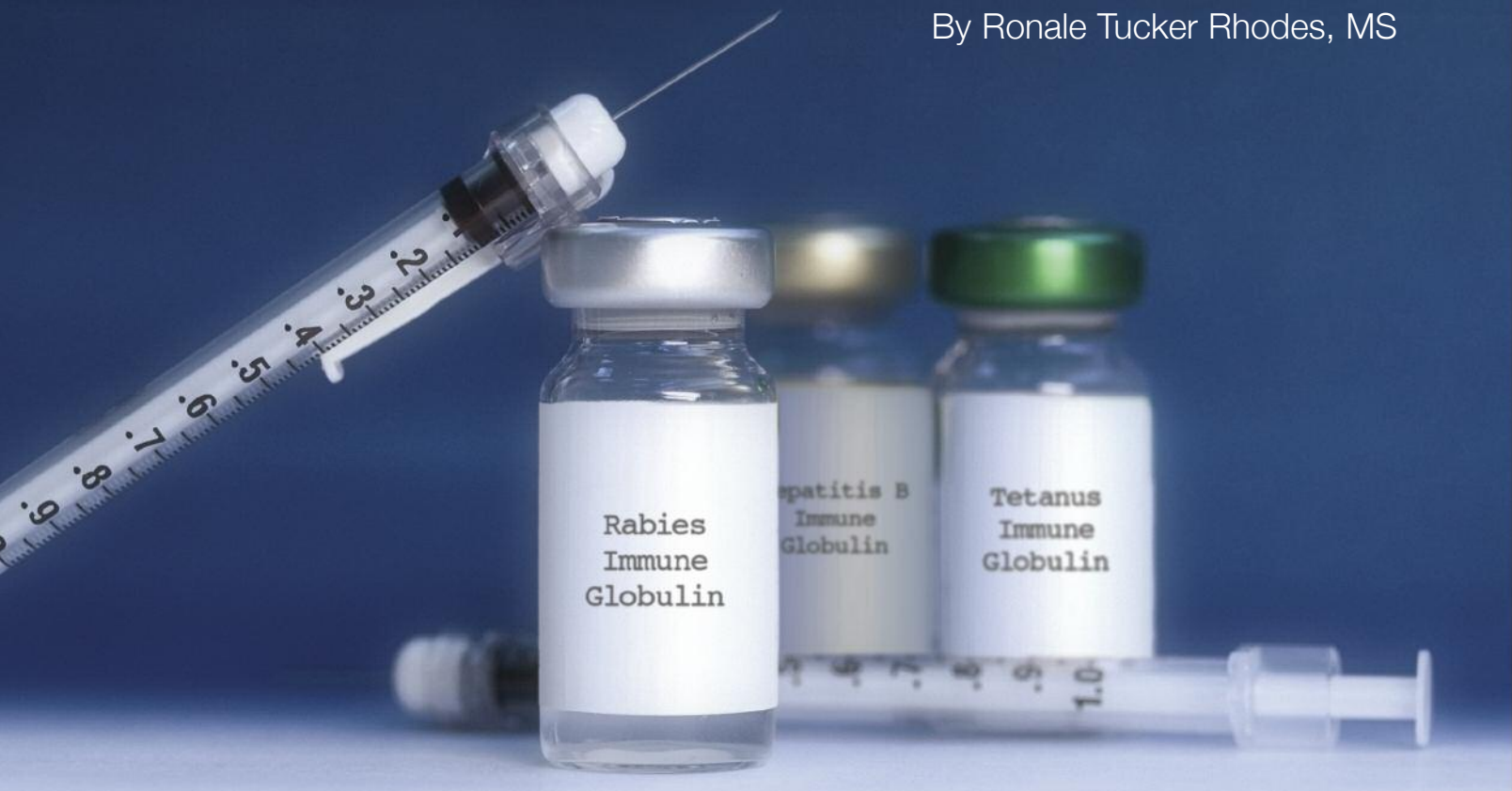
# THE ROLE OF HYPERIMMUNE

By Ronale Tucker Rhodes, MS




While these obscure, life-saving treatments are used to treat vastly different diseases, the common denominator they share is that each is made from plasma with a specialized high-titer antibody that provides short-term passive immunity.

Several years ago, I was awakened in the early morning hours by my husband screaming outside on our back patio. I rushed outside, turned the patio light on and saw him with blood covering his arms, chest and neck. He had heard a small animal desperately trying to get out of our pool, and while trying to rescue it, he was severely scratched and bitten. After he flung it out of the pool, the animal took off into the night, leaving us clueless about what kind of animal it was and worse, whether it was diseased. What that meant, of course, was that without being able to identify the animal and then test it to determine that it wasn't rabid, my husband had to endure treatment for rabies. It was a month-long series of shots, beginning with a hyperimmune globulin. But, in the end, my husband was healthy and didn't contract the rabies virus.

# GLOBULINS

Our story is a familiar one for many, most of which have a similar happy ending. But, that's not always what happens, as in the case of Ed Hurley, III, a 25-year-old who in 2003 developed a low-grade fever. His family thought he was coming down with the flu. But for 10 days he just couldn't seem to shake the fever. On the 11th day, he was slurring his words and had trouble keeping his balance. Four days later, he went into a coma, and with his brain no longer functioning, he died.[1] Unfortunately for Hurley, he never knew he had been infected with rabies, so he was unaware he needed treatment.

Rabies immune globulin is but one of several hyperimmune globulins. Some others are tetanus, hepatitis B (HBV), cytomegalovirus (CMV) used after solid organ and bone marrow transplants, and $Rh_oD$ immune globulin, classically used to prevent hemolytic disease of the newborn (HDN). Without judicious and timely administration of the appropriate hyperimmune globulin, patients with a range of conditions can face serious injury or death. Understanding the role these plasma-derived treatments play, then, is crucial.

## What Are Hyperimmune Globulins?

Hyperimmunes are immune globulin preparations that are high in antibodies that protect against specific diseases by providing passive immunity. Passive immunity is achieved by administration of purified antibodies that provide immediate, but short-term, protection against the disease. Active immunity, on the other hand, occurs when a person is exposed to a live pathogen or when they are injected with a substance that contains the antigen such as the rabies vaccine (artificially acquired active immunity) — both of which cause the individual to become immune to the disease as a result of the primary immune response.[2]

Passive immunization with hyperimmune globulin may be appropriate in the following circumstances: when the patient cannot synthesize antibody; when the patient has been exposed to a disease to which they cannot mount an adequate immune response or that is likely to cause complications; or when the patient has contracted a disease and the effects of an associated toxin must be ameliorated.[3]

Passive immunity also can occur naturally or artificially. Naturally acquired passive immunity occurs during pregnancy when certain antibodies are passed from the maternal into the fetal bloodstream.[2] Artificially acquired passive immunity occurs when antibodies that are not produced by the recipient are introduced through an injection. This is the case with most hyperimmune globulins.

## How Are Hyperimmunes Manufactured?

All hyperimmune globulins are made from donated plasma from people with high titers of antibody against a specific organism or antigen. These donors were either naturally exposed or infected at some time in the past or they were artificially immunized.[3]

There are 380 U.S. Food and Drug Administration (FDA)-licensed and International Quality Plasma Program (IQPP)-certified plasma collection centers located throughout the United States, most of which are owned exclusively by plasma therapy manufacturers. Donors can provide plasma much more frequently than whole blood donors — as much as two times per week for plasma, versus once every eight weeks for blood.[4]

Hyperimmunes are immune globulin preparations that are high in antibodies that protect against specific diseases.

Plasma is collected through a process called plasmapheresis, which withdraws small amounts of whole blood and then spins it in a centrifuge to separate the plasma. To identify donors with a high antibody concentration, or "titer," against a particular pathogen, collected units from conventional plasma donors may be screened using licensed assays run on automated testing equipment. A well-done video of the plasmapheresis process can be viewed at http://www.youtube.com/watch?v=eDsqlfd6cRQ.[5]

Once this special "hyperimmune plasma" is collected, it goes through a process called fractionation that separates and collects the individual proteins to manufacture the various plasma products, including hyperimmune globulins.[4]

### How Are Hyperimmunes Used to Treat Diseases?

Hyperimmunes can save lives, and it should be noted that hyperimmunes are needed only in certain circumstances, for example, when an individual has not been previously immunized with the vaccine.

**Rabies**. After an animal bite or other exposure to a rabid animal, or if one is thought to have the potential to have transmitted rabies, rabies post-exposure prophylaxis is given. Treatment includes both passive and active immunization for those who have not previously been immunized against the disease. Passive immunity is provided by human rabies immune globulin (HRIG). HRIG is given at the time post-exposure prophylaxis is initiated, and is injected around the bite wound to neutralize any rabies virus that may be present. Any dosage that cannot be injected at the bite site is injected into the gluteal area. Active immunity includes five doses of rabies vaccine, with the first dose given on the day post-exposure (called day 0) and additional doses given on days three, seven, 14 and 28. Individuals who have received a pre-exposure rabies vaccine series should not receive HRIG.[6]

To prevent CMV and to treat CMV pneumonitis in patients who have had solid organ and bone marrow transplants, intravenous human CMV immune globulin (CMV-IGIV) is often used in combination with antiviral drug therapy.

**Tetanus**. Everyone should be vaccinated against tetanus. The schedule for active immunization for tetanus for children is a series of five DTap (tetanus, diphtheria and pertussis) vaccinations, generally started at 2 months of age and completed at approximately 5 years of age. A booster vaccination is then recommended at 11 years of age with Tdap and a follow-up booster is recommended every 10 years thereafter. An individual would receive the tetanus immunoglobulin vaccination when wounded and either early symptoms of tetanus appear or the tetanus booster status is unknown or significantly out of date. Tetanus immunoglobulin is given into the muscle surrounding the wound, and the remainder of the dose is given in the gluteal area.[7]

**Hepatitis B Virus (HBV)**. Individuals who have not been vaccinated against HBV risk being infected if exposed to the virus. The HBV vaccine is given in three doses over a six- to 12-month period, and it provides protection for 15 years and possibly much longer. Those individuals not vaccinated against HBV who believe they have been exposed to the virus should get both the HBV vaccine and the hepatitis B immune globulin (HBIG) within 24 hours to prevent infection.[8] By far, the biggest use of HBIG is for prevention of reinfection of hepatitis B-positive patients following liver transplantation, and it accounts for nearly all of the use of the Nabi-HB vaccine.

However, newborns whose mothers are HBV infected also are very susceptible to contracting HBV. These newborns should get three HBV injections, the first within 12 hours of birth, the second at 1 to 2 months old and the third at 6 months old. In addition, babies born to infected mothers should receive the HBIG within 12 hours of delivery. All women should be screened for hepatitis B surface antigen during pregnancy to determine if they are a carrier (chronically affected) of HBV. Without intervention, 90 percent of babies born to infected mothers will become chronically infected, reducing their life expectancy.[8]

**Cytomegalovirus (CMV) after solid organ and bone marrow transplants**. While CMV is a common virus that infects most people worldwide and is relatively harmless in healthy individuals, those with weakened immune systems do risk contracting CMV disease, which can cause serious, potentially life-threatening illnesses. Symptoms include fever, pneumonia, liver infection and anemia, and the illnesses can last for weeks or months and can be fatal.[9]

To prevent CMV and to treat CMV pneumonitis in patients who have had solid organ and bone marrow transplants, intravenous human CMV immune globulin (CMV-IGIV) is often used in combination with antiviral drug therapy. Different dosing schedules are recommended for kidney versus liver, pancreas, lung or heart transplant patients. Clinical studies have shown a 50 percent to 56 percent reduction in primary CMV disease and serious CMV disease for renal and liver transplant patients, respectively, who were administered CMV-IGIV, as well as an improved survival rate for liver transplant patients.[10]

**$Rh_O$(D) and hemolytic disease of the newborn (HDN)**. $Rh_O$(D) hyperimmunes are used frequently for treating patients with idiopathic thrombocytopenic purpura (ITP).

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GRIFOLS

## Hyperimmune Globulins and What They Treat

| Product | Brand | Manufacturer | Virus/Disease |
|---|---|---|---|
| Rabies Immune Globulin (Human) | HyperRAB S/D | Talecris Biotherapeutics | Rabies |
| Rabies Immune Globulin (Human) | Imogam Rabies – HT | Sanofi Pasteur | Rabies |
| Tetanus Immune Globulin (Human) | HyperTET S/D | Talecris Biotherapeutics | Tetanus |
| Hepatitis B Immune Globulin (Human) (HBIG) | HyperHEP B S/D | Talecris Biotherapeutics | Hepatitis B |
| Hepatitis B Immune Globulin (Human) (HBIG) | Nabi-HB | Biotest Pharmaceuticals | Hepatitis B |
| Hepatitis B Immune Globulin Intravenous (Human) | HepaGam B | Cangene bioPharma | Hepatitis B |
| Cytomegalovirus (CMV) Immune Globulin Intravenous (Human) (CMV-IGIV) | Cytogam | CSL Behring | Cytomegalovirus (CMV) |
| $Rh_0$(D) Immune Globulin (Human) | HyperRHO S/D | Talecris Biotherapeutics | Hemolytic disease of the newborn (HDN) |
| $Rh_0$(D) Immune Globulin (Human) | RhoGAM | Ortho-Clinical Diagnostics | Hemolytic disease of the newborn (HDN) |
| $Rh_0$(D) Immune Globulin (Human) | MICRhoGAM | Ortho-Clinical Diagnostics | Hemolytic disease of the newborn (HDN) |
| $Rh_0$(D) Immune Globulin Intravenous (Human) | Rhophylac | CSL Behring | Hemolytic disease of the newborn (HDN) & Idiopathic thrombocytopenic purpura (ITP) |
| $Rh_0$(D) Immune Globulin Intravenous (Human) | WinRho SDF Liquid | Cangene bioPharma | Idiopathic thrombocytopenic purpura (ITP) |

But, HDN also occurs when there is an incompatibility between the blood types of the mother and baby, typically when an Rh-negative mother has a second or later pregnancy with an Rh-positive fetus. When the baby's red blood cells carry the Rh antigen inherited from the father, and the baby's red blood cells cross the placental barrier into the circulation of the Rh negative mother, the mother's immune system responds by developing antibodies to fight and destroy these foreign-appearing cells, and the mother is said to be "Rh sensitized." In a first pregnancy, Rh sensitization is not likely, but it usually becomes a problem in a future pregnancy with another Rh positive baby when the mother's anti-Rh antibodies cross the placenta. These antibodies proceed to destroy Rh-positive red blood cells in the baby's circulation, making the baby anemic, which can dangerously limit vital oxygenation of the developing baby's organs and tissues.[11]

The risk of future sensitization can be greatly reduced by giving all unsensitized mothers anti-Rh (also called anti-D) IG, which "mops up" any fetal red blood cells that may have leaked into the maternal circulation, reducing the risk of first-time exposure to the Rh antigen. Usually, Rh-negative mothers receive an injection of anti-Rh IG at about 28 weeks gestation, about the time when fetal red blood cells start to express the D antigen, and mothers receive another dose at about 34 weeks, a few weeks before labor begins, during which the risk of feto-maternal hemorrhage is high. A final dose of anti-D IG is given after the baby has been delivered. Anti-D IG also may be given to cover other events that occur during the pregnancy that may lead to sensitization, such as antepartum bleeds and pre-eclampsia.[12]

### The Serious Role Hyperimmunes Play

Without hyperimmune globulins, many people who contract these serious diseases would otherwise die. But, while most people understand there is treatment, few fully understand the role played by these specialized plasma products — a serious role indeed. ❖

**RONALE TUCKER RHODES**, *MS, is the editor of* BioSupply Trends Quarterly.

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# Influenza can kill almost as many people a year as AIDS or breast cancer.[1,2]

## > Order FLUVIRIN® now and help protect your patients for the 2011-2012 flu season.

In 2010, more than 17,000 people are expected to die from AIDS[1] and nearly 40,000 women from breast cancer.[2] Though influenza may not seem like a serious disease, in any given flu season it may cause 3,000 to 49,000 flu-associated deaths.[3]

That's why the ACIP's new universal seasonal flu vaccination recommendations include all persons 4 years of age and older.[4] It's also why Novartis Vaccines is committed to providing seasonal flu vaccine doses on time.

In fact, in 2010 Novartis Vaccines completed the shipping of ~40 million seasonal flu vaccine doses ahead of schedule, allowing for early and convenient administration. FLUVIRIN is available to help protect people 4 years of age and older.

**> Make sure you have your supply of vaccine ready for the next flu season. Contact FFF Enterprises at (800) 843-7477 or visit www.MyFluVaccine.com**

### Indication

Fluvirin is an inactivated influenza virus vaccine indicated for active immunization of persons 4 years of age and older against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine.

Fluvirin vaccine is not indicated for children less than 4 years of age because there is evidence of diminished immune response in this age group.

Please see reverse for Important Safety Information.

NOVARTIS VACCINES

**Influenza Virus Vaccine Fluvirin®**

## Important Safety Information

Serious allergic reactions, including anaphylactic shock, have been observed in people receiving FLUVIRIN Influenza Virus Vaccine. FLUVIRIN vaccine should not be administered to individuals with a history of systemic hypersensitivity reaction to eggs or egg proteins or other components of FLUVIRIN vaccine, including thimerosal, or to anyone who has had a life-threatening reaction to previous influenza vaccination.

Pre-filled syringes of 2010/2011 FLUVIRIN influenza vaccine are tipped with caps which may contain natural rubber latex in trace amounts. Do not administer pre-filled syringe doses of FLUVIRIN vaccine to any patients with a demonstrated history of hypersensitivity to latex. Multi-dose vial presentations of FLUVIRIN are latex-free.

In clinical trials, the most common adverse events in adults were headache, fatigue, injection site reactions (pain, mass, redness, and induration), and malaise. These adverse events were generally mild/moderate and transient. Vaccination with FLUVIRIN vaccine may not protect all individuals who are susceptible to influenza.

Immunocompromised persons, including individuals receiving immunosuppressive therapy, may have a reduced immune response to FLUVIRIN vaccine. If Guillain-Barré syndrome has occurred within 6 weeks of receipt of prior influenza vaccine, the decision to use FLUVIRIN vaccine should be based on careful consideration of the potential benefits and risks. All people, including those who are pregnant, nursing, and/or taking other medications, should consult their healthcare providers before receiving FLUVIRIN vaccine.

Please see a Brief Summary of the FLUVIRIN Prescribing Information on the following pages.

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NOVARTIS VACCINES

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# FLUVIRIN® *(Influenza Virus Vaccine)*

**Suspension for Intramuscular Injection**
**2010-2011 Formula**
**Initial U.S. Approval: 1988**

**BRIEF SUMMARY: Please see package insert for full prescribing information.**

## 1 INDICATIONS AND USAGE

FLUVIRIN® is an inactivated influenza virus vaccine indicated for immunization of persons 4 years of age and older against influenza virus disease caused by influenza virus subtypes A and type B contained in the vaccine *[see DOSAGE FORMS AND STRENGTHS (3) in the full prescribing information]*.

FLUVIRIN® is not indicated for children less than 4 years of age because there is evidence of diminished immune response in this age group.

## 4 CONTRAINDICATIONS

### 4.1 Hypersensitivity

FLUVIRIN® should not be administered to anyone with known systemic hypersensitivity reactions to egg proteins (eggs or egg products), or to any component of FLUVIRIN®, or who has had a life-threatening reaction to previous influenza vaccinations.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Guillain-Barré Syndrome

If Guillain-Barré syndrome has occurred within 6 weeks of receipt of prior influenza vaccine, the decision to give FLUVIRIN® should be based on careful consideration of the potential benefits and risks.

### 5.2 Altered Immunocompetence

If FLUVIRIN® is administered to immunocompromised persons, including individuals receiving immunosuppressive therapy, the expected immune response may not be obtained.

### 5.3 Preventing and Managing Allergic Reactions

Prior to administration of any dose of FLUVIRIN®, the healthcare provider should review the patient's prior immunization history for possible adverse events, to determine the existence of any contraindication to immunization with FLUVIRIN® and to allow an assessment of benefits and risks. Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine.

The tip caps of the FLUVIRIN® prefilled syringes may contain natural rubber latex which may cause allergic reactions in latex sensitive individuals.

### 5.4 Limitations of Vaccine Effectiveness

Vaccination with FLUVIRIN® may not protect all individuals.

## 6 ADVERSE REACTIONS

### 6.1 Overall Adverse Reaction Profile

Serious allergic reactions, including anaphylactic shock, have been observed in individuals receiving FLUVIRIN® during postmarketing surveillance.

### 6.2 Clinical Trial Experience

Adverse event information from clinical trials provides a basis for identifying adverse events that appear to be related to vaccine use and for approximating the rates of these events.

However, because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine, and may not reflect rates observed in clinical practice.

**Adult and Geriatric Subjects**

Safety data were collected in a total of 2768 adult and geriatric subjects (18 years of age and older) who have received FLUVIRIN® in 29 clinical studies since 1982.

In 9 clinical studies since 1997, among 1261 recipients of FLUVIRIN®, 745 (59%) were women; 1211 (96%) were White, 23 (2%) Asian, 15 (1%) Black and 12 (1%) other; 370 (29%) of subjects were elderly (≥65 years of age). All studies have been conducted in the UK, apart from a study run in the US in 2005-2006 where FLUVIRIN® was used as a comparator for an unlicensed vaccine.

After vaccination, the subjects were observed for 30 minutes for hypersensitivity or other immediate reactions. Subjects were instructed to complete a diary card for three days following immunization (i.e. Day 1 to 4) to collect local and systemic reactions *(see Tables 1 and 2)*. All local and systemic adverse events were considered to be at least possibly related to the vaccine. Local and systemic reactions mostly began between day 1 and day 2. The overall adverse events reported in clinical trials since 1998 in at least 5% of the subjects are summarized in Table 3.

**TABLE 1**
**Solicited Adverse Events in the First 72-96 Hours After Administration of FLUVIRIN® in Adult (18-64 years of age) and Geriatric (≥65 years of age) Subjects**

| | 1998-1999*§ | | 1999-2000*§ | | 2000-2001*§ | |
|---|---|---|---|---|---|---|
| | 18-64 yrs N=66 | ≥65 yrs N=44 | 18-64 yrs N=76 | ≥65 yrs N=34 | 18-64 yrs N=75 | ≥65 yrs N=35 |
| **Local Adverse Events** | | | | | | |
| Pain | 16 (24%) | 4 (9%) | 16 (21%) | - | 9 (12%) | - |
| Mass | 7 (11%) | 1 (2%) | 4 (5%) | - | 8 (11%) | 1 (3%) |
| Inflammation | 5 (8%) | 2 (5%) | 6 (8%) | - | 7 (9%) | 1 (3%) |
| Ecchymosis | 4 (6%) | 1 (2%) | 3 (4%) | 1 (3%) | 4 (5%) | - |
| Edema | 2 (3%) | 1 (2%) | 1 (1%) | 2 (6%) | 3 (4%) | 1 (3%) |
| Reaction | 2 (3%) | - | 2 (3%) | - | 4 (5%) | 1 (3%) |
| Hemorrhage | - | - | 1 (1%) | - | - | - |
| **Systemic Adverse Events** | | | | | | |
| Headache | 7 (11%) | 1 (2%) | 17 (22%) | 3 (9%) | 4 (5%) | - |
| Fatigue | 3 (5%) | 2 (5%) | 4 (5%) | 1 (3%) | 3 (4%) | - |
| Malaise | 2 (3%) | 1 (2%) | 2 (3%) | 1 (3%) | 1 (1%) | - |
| Myalgia | 1 (2%) | - | 2 (3%) | - | - | - |
| Fever | 1 (2%) | - | 1 (1%) | - | - | - |
| Arthralgia | - | 1 (2%) | - | 1 (3%) | - | - |
| Sweating | - | - | 3 (4%) | - | 1 (1%) | 1 (3%) |

| | 2001-2002*^ | | 2002-2003*^ | | 2004-2005*^ | |
|---|---|---|---|---|---|---|
| | 18-64 yrs N=75 | ≥65 yrs N=35 | 18-64 yrs N=107 | ≥65 yrs N=88 | 18-64 yrs N=74 | ≥65 yrs N=61 |
| **Local Adverse Events** | | | | | | |
| Pain | 12 (16%) | 1 (3%) | 14 (13%) | 7 (8%) | 15 (20%) | 9 (15%) |
| Mass | 4 (5%) | 1 (3%) | - | - | - | - |
| Ecchymosis | 2 (3%) | - | 3 (3%) | 3 (3%) | 2 (3%) | 1 (2%) |
| Edema | 2 (3%) | 1 (3%) | 6 (6%) | 2 (2%) | - | - |
| Erythema | 5 (7%) | - | 11 (10%) | 5 (6%) | 16 (22%) | 5 (8%) |
| Swelling | - | - | - | - | 11 (15%) | 4 (7%) |
| Reaction | - | - | 2 (2%) | - | - | - |
| Induration | - | - | 14 (13%) | 3 (3%) | 11 (15%) | 1 (2%) |
| Pruritus | - | - | 1 (1%) | - | - | - |
| **Systemic Adverse Events** | | | | | | |
| Headache | 8 (11%) | 1 (3%) | 12 (11%) | 9 (10%) | 14 (19%) | 3 (5%) |
| Fatigue | 1 (1%) | 1 (3%) | - | - | 5 (7%) | 2 (3%) |
| Malaise | 3 (4%) | - | 3 (3%) | 4 (5%) | 1 (1%) | 1 (2%) |
| Myalgia | 3 (4%) | - | 5 (5%) | 3 (3%) | 8 (11%) | 1 (2%) |
| Fever | - | - | - | 1 (1%) | - | - |
| Arthralgia | - | - | 2 (2%) | - | 1 (1%) | - |
| Sweating | 3 (4%) | 1 (3%) | - | 2 (2%) | - | - |
| Shivering | - | - | - | 1 (1%) | - | - |

Results reported to the nearest whole percent; Fever defined as >38°C
- not reported
* Solicited adverse events in the first 72 hours after administration of FLUVIRIN®
§ Solicited adverse events reported by COSTART preferred term
^ Solicited adverse events reported by MedDRA preferred term

**TABLE 2**
**Solicited Adverse Events in the First 72 Hours After Administration of FLUVIRIN® in Adult Subjects (18-49 years of age)**

| | 2005-2006 US Trial FLUVIRIN® N=304 |
|---|---|
| **Local Adverse Events** | |
| Pain | 168 (55%) |
| Erythema | 48 (16%) |
| Ecchymosis | 22 (7%) |
| Induration | 19 (6%) |
| Swelling | 16 (5%) |

(continued)

**TABLE 2**
**Solicited Adverse Events in the First 72 Hours After Administration of FLUVIRIN® in Adult Subjects (18-49 years of age)**

| | 2005-2006 US Trial FLUVIRIN® N=304 |
|---|---|
| **Systemic Adverse Events** | |
| Headache | 91 (30%) |
| Myalgia | 64 (21%) |
| Malaise | 58 (19%) |
| Fatigue | 56 (18%) |
| Sore throat | 23 (8%) |
| Chills | 22 (7%) |
| Nausea | 21 (7%) |
| Arthralgia | 20 (7%) |
| Sweating | 17 (6%) |
| Cough | 18 (6%) |
| Wheezing | 4 (1%) |
| Chest tightness | 4 (1%) |
| Other difficulties breathing | 3 (1%) |
| Facial edema | - |

Results reported to the nearest whole percent
-not reported

**TABLE 3**
**Adverse Events Reported by at least 5% of Subjects in Clinical Trials since 1998**

| | 1998-1999§ | | 1999-2000§ | | 2000-2001§ | |
|---|---|---|---|---|---|---|
| | 18-64 yrs N=66 | ≥65 yrs N=44 | 18-64 yrs N=76 | ≥65 yrs N=34 | 18-64 yrs N=75 | ≥65 yrs N=35 |
| **Adverse Events** | | | | | | |
| Fatigue | 8 (12%) | 2 (5%) | 8 (11%) | 2 (6%) | 5 (7%) | - |
| Back pain | 4 (6%) | 3 (7%) | - | - | - | - |
| Cough increased | 2 (3%) | 2 (5%) | - | - | - | - |
| Ecchymosis | 4 (6%) | 1 (2%) | 4 (5%) | 1 (3%) | 5 (7%) | - |
| Fever | 3 (5%) | - | - | - | - | - |
| Headache | 12 (18%) | 5 (11%) | 22 (29%) | 5 (15%) | 14 (19%) | 2 (6%) |
| Infection | 3 (5%) | 2 (5%) | - | - | - | - |
| Malaise | 4 (6%) | 4 (9%) | 4 (5%) | 1 (3%) | - | - |
| Migraine | 4 (6%) | 1 (2%) | - | - | - | - |
| Myalgia | 4 (6%) | 1 (2%) | - | - | - | - |
| Sweating | 5 (8%) | 1 (2%) | - | - | - | - |
| Rhinitis | 3 (5%) | 1 (2%) | - | - | 5 (7%) | 2 (6%) |
| Pharyngitis | 6 (9%) | 1 (2%) | 10 (13%) | - | 6 (8%) | - |
| Arthralgia | - | - | - | 2 (6%) | - | - |
| Injection site pain | 16 (24%) | 4 (9%) | 16 (21%) | - | 9 (12%) | - |
| Injection site ecchymosis | 4 (6%) | 1 (2%) | - | - | 4 (5%) | - |
| Injection site mass | 7 (11%) | 1 (2%) | 4 (5%) | - | 8 (11%) | 1 (3%) |
| Injection site edema | - | - | 1 (1%) | 2 (6%) | - | - |
| Injection site inflammation | 5 (8%) | 2 (5%) | 6 (8%) | - | 7 (9%) | 1 (3%) |
| Injection site reaction | - | - | - | - | 4 (5%) | 1 (3%) |

| | 2001-2002^ | | 2002-2003^ | | 2004-2005^ | |
|---|---|---|---|---|---|---|
| | 18-64 yrs N=75 | ≥65 yrs N=35 | 18-64 yrs N=107 | ≥65 yrs N=88 | 18-64 yrs N=74 | ≥65 yrs N=61 |
| **Adverse Events** | | | | | | |
| Fatigue | 5 (7%) | 4 (11%) | 11 (10%) | 8 (9%) | 4 (5%) | 2 (3%) |
| Hypertension | - | - | 1 (1%) | 4 (5%) | - | - |
| Rhinorrhea | - | - | 2 (2%) | 5 (6%) | - | - |
| Headache | 20 (27%) | 2 (6%) | 35 (33%) | 18 (20%) | 12 (16%) | 1 (2%) |
| Malaise | 6 (8%) | 1 (3%) | 13 (12%) | 8 (9%) | - | - |

(continued)

**TABLE 3**
**Adverse Events Reported by at least 5% of Subjects in Clinical Trials since 1998**

| | 2001-2002^ | | 2002-2003^ | | 2004-2005^ | |
|---|---|---|---|---|---|---|
| | 18-64 yrs N=75 | ≥65 yrs N=35 | 18-64 yrs N=107 | ≥65 yrs N=88 | 18-64 yrs N=74 | ≥65 yrs N=61 |
| **Adverse Events** | | | | | | |
| Myalgia | 4 (5%) | 1 (3%) | 10 (9%) | 4 (5%) | - | - |
| Sweating | 3 (4%) | 3 (9%) | 2 (2%) | 5 (6%) | - | - |
| Rhinitis | 4 (5%) | - | - | - | - | - |
| Pharyngitis | - | - | - | - | 6 (8%) | - |
| Arthralgia | - | - | 5 (5%) | 4 (5%) | - | - |
| Sore throat | 4 (5%) | 1 (3%) | 5 (5%) | 4 (5%) | - | - |
| Injection site pain | 13 (17%) | 3 (9%) | 14 (13%) | 7 (8%) | 6 (8%) | 2 (3%) |
| Injection site ecchymosis | 4 (5%) | 1 (3%) | 4 (4%) | 4 (5%) | - | - |
| Injection site erythema | 5 (7%) | 2 (6%) | 11 (10%) | 5 (6%) | 4 (5%) | - |
| Injection site mass | 4 (5%) | 1 (3%) | - | - | - | - |
| Injection site edema | - | - | 6 (6%) | 2 (2%) | 4 (5%) | 1 (2%) |
| Injection site induration | - | - | 14 (13%) | 3 (3%) | 7 (9%) | - |

Results reported to the nearest whole percent; Fever defined as >38°C
- not reaching the cut-off of 5%
§ Solicited adverse events reported by COSTART preferred term
^ Solicited adverse events reported by MedDRA preferred term

**Adults (18 to 64 years of age)**
In adult subjects, solicited local adverse events occurred with similar frequency in all trials. The most common solicited adverse events occurring in the first 96 hours after administration (Tables 1 and 2) were associated with the injection site (such as pain, erythema, mass, induration and swelling) but were generally mild/moderate and transient. The most common solicited systemic adverse events were headache and myalgia.

The most common overall events in adult subjects (18-64 years of age) were headache, fatigue, injection site reactions (pain, mass, erythema, and induration) and malaise (Table 3).

**Geriatric Subjects (65 years of age and older)**
In geriatric subjects, solicited local and systemic adverse events occurred less frequently than in adult subjects. The most common solicited local and systemic adverse events were injection site pain, and headache (Tables 1 and 2). All were considered mild/moderate and were transient.

The most common overall events in elderly subjects (≥65 years of age) were headache and fatigue.

Only 11 serious adverse events in adult and geriatric subjects (18 years and older) have been reported to date from all the trials performed. These serious adverse events were a minor stroke experienced by a 67 year old subject 14 days after vaccination (1990), death of an 82 year old subject 35 days after vaccination (1990) in very early studies; death of a 72 year old subject 19 days after vaccination (1998-1999), a hospitalization for hemorrhoidectomy of a 38 year old male subject (1999-2000), a severe respiratory tract infection experienced by a 74 year old subject 12 days after vaccination (2002-2003), a planned transurethral resection of the prostate in a subject with prior history of prostatism (2004-2005), two cases of influenza (2005-2006), a drug overdose (2005-2006), cholelithiasis (2005-2006) and a nasal septal operation (2005-2006). None of these events were considered causally related to vaccination.

**Clinical Trial Experience in Pediatric Subjects**
In 1987 a clinical study was carried out in 38 'at risk' children aged between 4 and 12 years (17 females and 21 males). To record the safety of FLUVIRIN®, participants recorded their symptoms on a diary card during the three days after vaccination and noted any further symptoms they thought were attributable to the vaccine. The only reactions recorded were tenderness at the site of vaccination in 21% of the participants on day 1, which was still present in 16% on day 2 and 5% on day 3. In one child, the tenderness was also accompanied by redness at the site of injection for two days. The reactions were not age-dependent and there was no bias towards the younger children.

Three clinical studies were carried out between 1995 and 2004 in a total of 520 pediatric subjects (age range 6-47 months). Of these, 285 healthy subjects plus 41 'at risk' subjects received FLUVIRIN®. No serious adverse events were reported.

FLUVIRIN® should only be used for the immunization of persons aged 4 years and over.

**6.3 Postmarketing Experience**

The following additional adverse reactions have been reported during post-approval use of FLUVIRIN®. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure. Adverse events described here are included because: a) they represent reactions which are known to occur following immunizations generally or influenza immunizations specifically; b) they are potentially serious; or c) the frequency of reporting.

- *Body as a whole:* Local injection site reactions (including pain, pain limiting limb movement, redness, swelling, warmth, ecchymosis, induration), hot flashes/flushes; chills; fever; malaise; shivering; fatigue; asthenia; facial edema.
- *Immune system disorders:* Hypersensitivity reactions (including throat and/or mouth edema). In rare cases, hypersensitivity reactions have lead to anaphylactic shock and death.
- *Cardiovascular disorders:* Vasculitis (in rare cases with transient renal involvement), syncope shortly after vaccination.
- *Digestive disorders:* Diarrhea; nausea; vomiting; abdominal pain.
- *Blood and lymphatic disorders:* Local lymphadenopathy; transient thrombocytopenia.
- *Metabolic and nutritional disorders:* Loss of appetite.
- *Musculoskeletal:* Arthralgia; myalgia; myasthenia.
- *Nervous system disorders:* Headache; dizziness; neuralgia; paraesthesia; confusion; febrile convulsions; Guillain-Barré Syndrome; myelitis (including encephalomyelitis and transverse myelitis); neuropathy (including neuritis); paralysis (including Bell's Palsy).
- *Respiratory disorders:* Dyspnea; chest pain; cough; pharyngitis; rhinitis.
- *Skin and appendages:* Stevens-Johnson syndrome; sweating; pruritus; urticaria; rash (including non-specific, maculopapular, and vesiculobullous).

**6.4 Other Adverse Reactions Associated with Influenza Vaccination**

Anaphylaxis has been reported after administration of FLUVIRIN®. Although FLUVIRIN® contains only a limited quantity of egg protein, this protein can induce immediate hypersensitivity reactions among persons who have severe egg allergy. Allergic reactions include hives, angioedema, allergic asthma, and systemic anaphylaxis *[see CONTRAINDICATIONS (4)]*.

The 1976 swine influenza vaccine was associated with an increased frequency of Guillain-Barré syndrome (GBS). Evidence for a causal relation of GBS with subsequent vaccines prepared from other influenza viruses is unclear. If influenza vaccine does pose a risk, it is probably slightly more than 1 additional case/1 million persons vaccinated.

Neurological disorders temporally associated with influenza vaccination such as encephalopathy, optic neuritis/neuropathy, partial facial paralysis, and brachial plexus neuropathy have been reported.

Microscopic polyangiitis (vasculitis) has been reported temporally associated with influenza vaccination.

## 7 DRUG INTERACTIONS

**7.1 Concomitant Administration with Other Vaccines**

There are no data to assess the concomitant administration of FLUVIRIN® with other vaccines. If FLUVIRIN® is to be given at the same time as another injectable vaccine(s), the vaccines should always be administered at different injection sites.

FLUVIRIN® should not be mixed with any other vaccine in the same syringe or vial.

**7.2 Concurrent Use with Immunosuppressive Therapies**

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune response to FLUVIRIN®.

## 8 USE IN SPECIFIC POPULATIONS

**8.1 Pregnancy**

Pregnancy Category C: Animal reproduction studies have not been conducted with FLUVIRIN®. It is also not known whether FLUVIRIN® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. FLUVIRIN® should be given to a pregnant woman only if clearly needed.

**8.3 Nursing Mothers**

It is not known whether FLUVIRIN® is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when FLUVIRIN® is administered to a nursing woman.

**8.4 Pediatric Use**

The safety and immunogenicity of FLUVIRIN® have not been established in children under 4 years of age.

The safety and immunogenicity of FLUVIRIN® have been established in the age group 4 years to 16 years. The use of FLUVIRIN® in these age groups is supported by evidence from adequate and well controlled studies of FLUVIRIN® in adults that demonstrate the immunogenicity of FLUVIRIN® *[see ADVERSE REACTIONS (6) and CLINICAL STUDIES (14) in the full prescribing information]*.

**8.5 Geriatric Use**

Since 1997, of the total number of geriatric subjects (n=397) in clinical studies of FLUVIRIN®, 29% were 65 years and over, while 2.1% were 75 years and over.

Antibody responses were lower in the geriatric population than in younger subjects. Adverse events occurred less frequently in geriatric subjects (≥65 years) than in younger adults. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. *[See ADVERSE REACTIONS (6) and CLINICAL STUDIES (14) in the full prescribing information.]*



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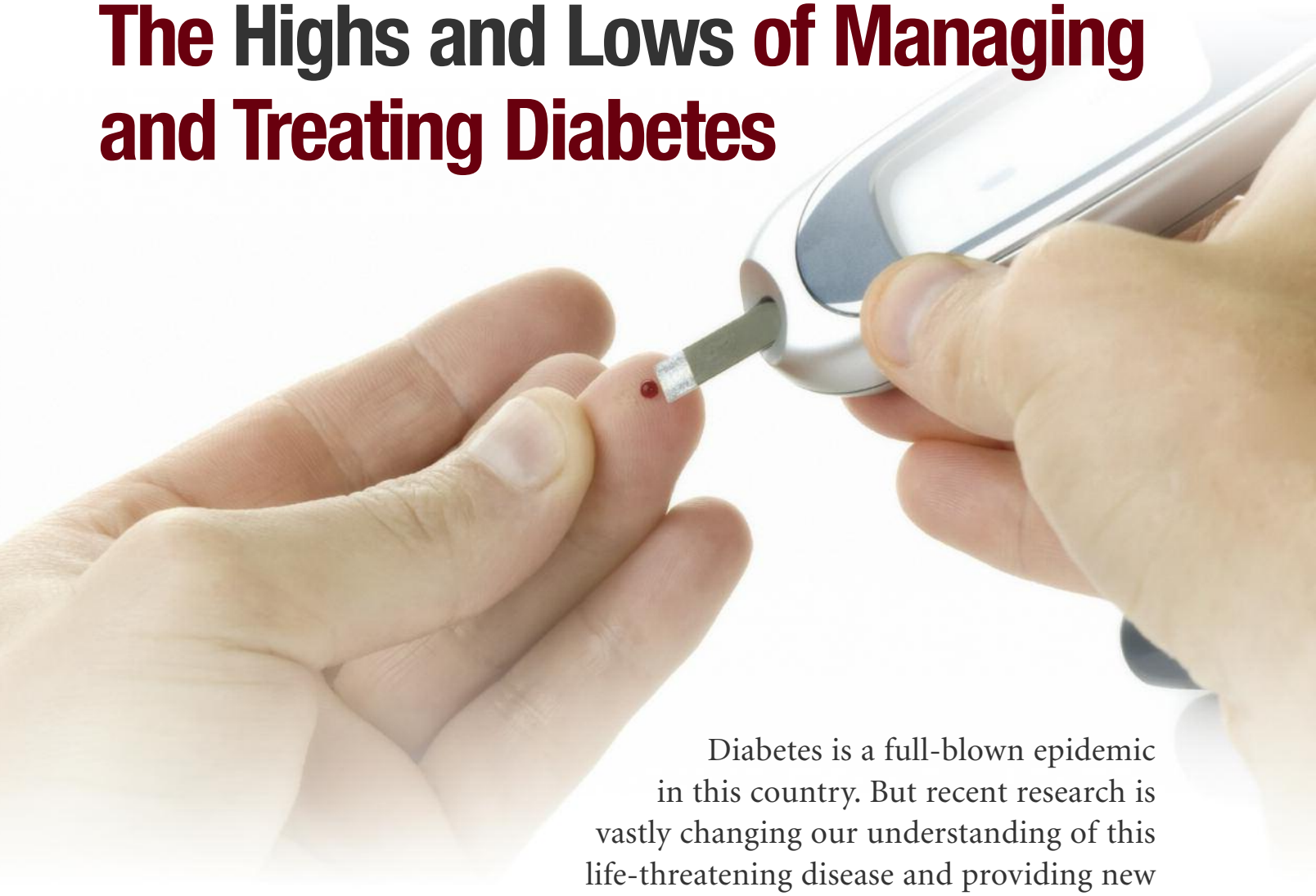
# The Highs and Lows of Managing and Treating Diabetes



Diabetes is a full-blown epidemic in this country. But recent research is vastly changing our understanding of this life-threatening disease and providing new clues about how to treat and, possibly, even cure it.

By Trudie Mitschang

According to the Centers for Disease Control and Prevention (CDC), one in every three Americans will develop diabetes in their lifetime; it is currently the sixth-leading cause of death in the U.S.[1] But America is not alone: In 2008, there were an estimated 246 million people with diabetes worldwide, and the World Health Organization (WHO) expects this figure to rise to 370 million by 2030.[2]

A stealthy and insidious illness, diabetes currently affects in excess of six million people who are asymptomatic and unaware they have it, making the disease that much harder to track and treat. Additionally, it is estimated that more than 40 million Americans can be classified as "pre-diabetic," meaning they have blood sugar levels higher than normal but still below the prevalent type 2 diagnosis level. As for direct healthcare costs, U.S. estimates have skyrocketed to nearly $116 billion annually.[3] Many public health authorities say diabetes cases have now reached epidemic numbers, demanding urgent and focused research aimed at prevention and treatment, and ultimately identifying a cure. For families impacted by this life-altering disease, the increased focus and attention could not come a moment too soon.

"Our son, Andy, was diagnosed with type 1 diabetes when he was 10," says Carol Johnson, an Indiana mother of three. "I recognized the symptoms right away — extreme fatigue and

excessive thirst — because Andy's uncle died from diabetes-related complications at the age of 24. When the doctor confirmed what we suspected, we were devastated."

Because the Johnson family has a history of diabetes, genetics and environmental factors are both suspected culprits in Andy's diagnosis. Now 18 and on an insulin pump, Andy faces an uphill battle in managing his health, and as a college-bound youth, is tasked with avoiding the insulin-spiking foods that are a ubiquitous part of dorm life, while also tracking his daily insulin levels without mom or dad around to remind him.

"I've been managing my treatment almost from the beginning, so I feel pretty confident about doing it while away at college," says Andy. "The hardest part has always been psychological; nobody, especially a kid, likes to be viewed as different."

## One Disease, Three Disease States

When we eat, food is turned into glucose, or sugar, which our bodies use for energy. In a healthy individual, the pancreas produces the hormone insulin, which transports glucose into the cells, where it can be used as fuel. In a person with diabetes, the body makes too little insulin or is unable to use the insulin it makes effectively. The result is excess sugar in the blood, which is sometimes referred to as "high blood sugar." The term diabetes is often used as an umbrella term to describe chronic high blood sugar, but there are actually three specific disease states:

• Type 1 diabetes, also called juvenile diabetes, is an autoimmune disease that is typically diagnosed in childhood. With this disease, the body makes little or no insulin and patients require daily insulin injections. The cause of type 1 diabetes is unknown, but genetic and environmental factors are suspected links.

• Type 2 diabetes makes up the majority of diabetes cases, typically striking in adulthood, although rates are increasing among children and adolescents. With type 2, the pancreas does not make enough insulin to keep blood glucose levels normal, often because the body does not respond well to insulin. Many people with type 2 diabetes do not know they have it. Type 2 diabetes is associated with obesity, poor diet and irregular exercise, and is potentially preventable and manageable with lifestyle changes.

• Gestational diabetes is high blood glucose that develops at any time during pregnancy in a woman who does not already have diabetes. Women who have gestational diabetes are at high risk of type 2 diabetes and cardiovascular disease later in life.

## Weighing In on the Obesity Link

The connection between excess weight and type 2 diabetes has been well-established. A 2009 Loyola University Health System study revealed that 62.4 percent of U.S. adults with type 2 diabetes are obese, and 20.7 percent are morbidly obese.[4] Among African-American adults with type 2 diabetes, one in three is morbidly obese. "The rate of morbid obesity among people with diabetes is increasing at a very alarming rate, and this has substantial public health implications," says Dr. Holly Kramer, a kidney specialist and lead author of the study published online in the *Journal of Diabetes and Its Complications*.

Researchers also suspect rising childhood obesity rates of being at the root of the epidemic number of children being diagnosed with type 2 diabetes. But, despite ample evidence regarding the link between obesity and diabetes, exactly why millions of overweight people develop the disease has remained somewhat of a medical mystery.

A 2001 study suggested the root cause was a hormone called resistin, which is produced by fat cells and incites tissues to resist insulin. However, in 2003, scientists debunked this theory in findings published in the *Journal of Clinical Endocrinology and Metabolism* that showed no correlation between resistin levels and body mass index, lipid profile or insulin resistance levels.[5]

Other studies connect the type of obesity (where fat is stored) with risk levels. Those who store it around the middle (the so-called apple shape) are at higher risk of developing diabetes than their pear-shaped counterparts. And, some nutritionists believe that high-carbohydrate, low-fiber diets are also part of the problem. Finally, because exercise makes your body's muscle cells more sensitive to insulin, a sedentary lifestyle is considered a diabetes risk factor.

## Lifestyle Changes Versus Surgery

Most physicians encourage lifestyle changes for patients with type 2 diabetes, including a healthier diet and regular exercise, but some are now saying that a last resort for morbidly obese diabetics may be bariatric weight-loss surgery. Scientists have discovered that diabetes all but disappears in some obese patients soon after the operation, and for many patients, weight-loss surgery can eliminate the need for diabetes-related medications.

In February of this year, the Harvard-affiliated Joslin Diabetes Center and Brigham and Women's Hospital announced plans for a clinical trial comparing weight-loss surgery and weight-management programs for the treatment of type 2 diabetes. The two-year study will examine whether patients test in the non-diabetic range for one year after either the surgical or medical and weight-management interventions. Previous observational studies estimate that 60 percent to 90 percent of bariatric surgery patients who were obese and had type 2 diabetes were later able to maintain normal blood glucose levels without medication.[6]

*In addition to its extremely high psychological and economical price tags, the consequences of undiagnosed or untreated diabetes are many.*

"Weight-loss surgery has become a go-to option for obese patients with type 2 diabetes because of the successes seen," says Dr. David Lautz, director of bariatric surgery at Brigham and Women's Hospital and instructor at Harvard Medical School. "We want to compare these popular procedures with particular lifestyle-modification and medical-management programs to determine more scientifically what the most effective option is, particularly for the less overweight patient."

The Cleveland Clinic's Bariatric and Metabolic Institute is hosting a similar study among 150 overweight and obese type 2 diabetics, some of whom will have surgery. Their progress will be compared with the progress of those who manage their diabetes with medicine. The goal is to see which group can achieve complete remission.

At this point, doctors are unsure how weight-loss surgery helps diabetics, but there is some evidence that it may not all be due to weight loss. Diabetes occurs when the body is unable to regulate blood sugar, and some researchers think that the rerouting of the digestive tract after the operation affects the gut hormones involved in blood sugar control. Currently, the American Diabetes Association states there is not enough evidence to generally recommend surgery for diabetics with a body mass index (BMI) lower than 35, outside of an experiment.

## Research Yields Promising Treatment Options

The main goal of diabetes treatment for both type 1 and type 2 patients is to keep blood sugar levels as close to normal as possible. Treatment options usually involve changes to the person's diet, weight-loss recommendations and an exercise regimen. Medication such as insulin shots, inhaled insulin, injected medicines that improve the release or use of insulin, or oral medication also may be prescribed. Additionally, diabetics need to get regular screening tests to rule out potential health complications.

Today, much of diabetes research is focused on the development of improved insulins that will better mimic natural insulin secretion. Other developing technology includes more efficient personal insulin pumps and monitoring systems; gene therapy; pancreas transplants; and even the use of an artificial pancreas. Each of these approaches still has drawbacks, but progress is being made. Speakers at a 2010 joint American Diabetes Association/Juvenile Diabetes Research Foundation (JDRF) symposium at the association's 70th Scientific Sessions said in a news release that the development of an artificial pancreas to effectively control blood glucose levels in children and adults with type 1 diabetes continues to make rapid advances. Those in the field predict that technology of this kind could become commercially available within the next few years.[7]

"We're all interested in people with diabetes achieving better glucose control," says Aaron Kowalski, PhD, research director of the Artificial Pancreas Project. "The community needs to hear what's happening and where we are headed."

The diabetes epidemic also has resulted in a push to create more efficient monitoring devices for patients. In the past, diabetics had to regularly test their urine to keep track of blood sugar levels; today, most diabetics use blood glucose meters to monitor them. With a typical glucose meter, the patient places a small sample of blood on a disposable test strip and then places that strip on the meter. The glucose in the blood adheres to chemicals on the test strip, and the meter measures how much glucose is present. After a blood glucose reading is done, the patient is responsible for administering insulin, if needed.

Insulin administration can be done through a syringe, an insulin pen, a jet injector, an insulin port or an insulin pump. From a lifestyle perspective, insulin pumps offer a tremendous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amount of freedom and improved patient compliance, since they can deliver insulin 24 hours a day through a catheter inserted under the skin. The patient wearing it can order the pump to deliver extra insulin at meals or other times when blood sugars may be higher than usual. New technology also links meters and pumps wirelessly, which means patients don't have to calculate and enter the correct amount of insulin into the pump. Carbohydrate counts and other data collected by the meter can be uploaded to a computer and printed out and given to a healthcare provider, improving accuracy of care recommendations.

## An Ounce of Prevention

Not all diabetes research is focused on the treatment of those who are already sick. Keeping people healthy through education and intervention is also an essential weapon when it comes to fighting diabetes. Statistics show that prevention or delay of type 2 diabetes is possible in some patients who are pre-diabetic. According to a diabetes fact sheet published by the CDC:[8]

• Progression to diabetes among those with pre-diabetes is not inevitable. Studies have shown that people with pre-diabetes who lose weight and increase their physical activity can prevent or delay diabetes and return their blood glucose levels to normal.

• The Diabetes Prevention Program, a large prevention study of people at high risk for diabetes, showed that lifestyle intervention reduced developing diabetes by 58 percent during a three-year period. The reduction was even greater (71 percent) among adults aged 60 years or older.

• The benefits of interventions to prevent or delay type 2 diabetes are both feasible and cost-effective, since lifestyle interventions are much more cost-effective than long-term use of prescription medications.

In addition to its extremely high psychological and economical price tags, the consequences of undiagnosed or untreated diabetes are many. Even with improved medications and treatment protocols, those with advanced diabetes are at risk of blindness, amputations, renal (kidney) failure, blood circulatory problems, heart disease and strokes. Diabetics also are at increased risk of developing serious complications from viral infections like influenza. In fact, the rate of complications from diabetes is high, according to a report released by the American Association of Clinical Endocrinologists titled *The State of Diabetes Complications in America*. The report showed that nearly 60 percent of people with diabetes have at least one of the complications caused by long-term failure to control the high blood-sugar levels tied to the disease.[9]

## No Quick Fix

The diabetes epidemic did not happen overnight, and it will not be a quick fix, despite increased education, intervention and prevention efforts. Controlling both type 1 and type 2 diabetes requires a high degree of patient involvement and compliance, coupled with behavior modification and lifestyle changes that often prove challenging to implement, especially among younger patients.

*The diabetes epidemic did not happen overnight, and it will not be a quick fix.*

For 18-year-old Andy Johnson, it comes down to accepting personal responsibility for tracking and treating the symptoms of diabetes on a daily basis. "I learned pretty early that this is my disease and I have to take responsibility for it," he says. "Becoming independent means that if I want to stay healthy, I can't look to my parents or the doctors to monitor my [insulin] levels or watch what I eat. It really is up to me." ❖

**TRUDIE MITSCHANG** *is a staff writer for* BioSupply Trends Quarterly *magazine.*

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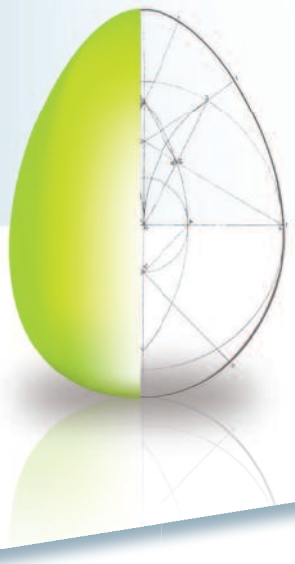

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**Important Safety Information**

Privigen is indicated for the treatment of patients with primary immunodeficiency (PI) associated with defects in humoral immunity, including but not limited to common variable immunodeficiency (CVID), X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.

**WARNING: Renal dysfunction, acute renal failure, osmotic nephrosis, and death may be associated with the administration of Immune Globulin Intravenous (Human) (IVIg) products in predisposed patients. Administer IVIg products at the minimum infusion rate possible. Renal dysfunction and acute renal failure occur more commonly in patients receiving IVIg products containing sucrose. Privigen does not contain sucrose. See full Prescribing Information for complete Boxed Warning.**

Privigen is contraindicated in patients who have had an anaphylactic or severe systemic reaction to the administration of human immune globulin, in patients with hyperprolinemia, and in IgA-deficient patients with antibodies to IgA and a history of hypersensitivity.

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In patients at risk for developing renal failure, monitor urine output and renal function, including blood urea nitrogen and serum creatinine. Thrombotic events have been reported with Privigen and other IVIg treatments. Monitor patients with risk factors for thrombotic events, including a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, hypercoagulable disorders, prolonged periods of immobilization, and/or known or suspected hyperviscosity.

Aseptic meningitis syndrome (AMS) may occur infrequently with Privigen and other IVIg treatments; AMS may occur more frequently with high doses and/or rapid infusion of IVIg. Hemolysis, hemolytic anemia, and pulmonary adverse events have also been reported. There have been reports of noncardiogenic pulmonary edema in patients administered IVIg. If transfusion-related acute lung injury is suspected, test product and patient for antineutrophil antibodies.

Privigen is derived from human plasma. The risk of transmission of infectious agents, including viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent, cannot be completely eliminated.

In clinical studies, the most common adverse reactions with Privigen were headache, pain, nausea, pyrexia/hyperthermia, fatigue, and chills.

**Please see brief summary of full Prescribing Information on adjacent pages.**

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**BRIEF SUMMARY OF PRESCRIBING INFORMATION**

# Privigen®, Immune Globulin Intravenous (Human), 10% Liquid

**Before prescribing, please consult full prescribing information, a brief summary of which follows. Some text and references refer to full prescribing information.**

**WARNING: ACUTE RENAL DYSFUNCTION/FAILURE**

- **Use of Immune Globulin Intravenous (IGIV) products, particularly those containing sucrose, have been reported to be associated with renal dysfunction, acute renal failure, osmotic nephropathy, and death.[1] Patients at risk of acute renal failure include those with any degree of pre-existing renal insufficiency, diabetes mellitus, advanced age (above 65 years of age), volume depletion, sepsis, paraproteinemia, or receiving known nephrotoxic drugs (*see Warnings and Precautions [5.2]*). Privigen does not contain sucrose.**
- **For patients at risk of renal dysfunction or failure, administer Privigen at the minimum infusion rate practicable (*see Dosage and Administration [2.3], Warnings and Precautions [5.2]*).**

## 1 INDICATIONS AND USAGE

Privigen is an Immune Globulin Intravenous (Human), 10% Liquid indicated for the treatment of the following conditions.

### 1.1 Primary Humoral Immunodeficiency

Privigen is indicated as replacement therapy for primary humoral immunodeficiency (PI). This includes, but is not limited to, the humoral immunodeficiency in common variable immunodeficiency (CVID), X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.

### 1.2 Chronic Immune Thrombocytopenic Purpura

Privigen is indicated for the treatment of patients with chronic immune thrombocytopenic purpura (ITP) to raise platelet counts.

## 3 DOSAGE FORMS AND STRENGTHS

Privigen is a liquid solution containing 10% IgG (0.1 g/mL) for intravenous infusion.

## 4 CONTRAINDICATIONS

- Privigen is contraindicated in patients who have had an anaphylactic or severe systemic reaction to the administration of human immune globulin.
- Because it contains the stabilizer L-proline, Privigen is contraindicated in patients with hyperprolinemia.
- Privigen is contraindicated in IgA-deficient patients with antibodies to IgA and a history of hypersensitivity.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Hypersensitivity

Severe hypersensitivity reactions may occur (*see Contraindications [4]*). In case of hypersensitivity, discontinue the Privigen infusion immediately and institute appropriate treatment. Medications such as epinephrine should be available for immediate treatment of acute hypersensitivity reactions.

Privigen contains trace amounts of IgA (≤25 mcg/mL) (*see Description [11]*). Patients with known antibodies to IgA may have a greater risk of developing potentially severe hypersensitivity and anaphylactic reactions. Privigen is contraindicated in patients with antibodies against IgA *and* a history of hypersensitivity reaction (*see Contraindications [4]*).

### 5.2 Renal Failure

Ensure that patients are not volume depleted before administering Privigen. Periodic monitoring of renal function and urine output is particularly important in patients judged to be at increased risk of developing acute renal failure. Assess renal function, including measurement of blood urea nitrogen (BUN) and serum creatinine, before the initial infusion of Privigen and at appropriate intervals thereafter. If renal function deteriorates, consider discontinuing Privigen. For patients judged to be at risk of developing renal dysfunction, administer Privigen at the minimum infusion rate practicable (*see Boxed Warning, Dosage and Administration [2.3]*).

### 5.3 Hyperproteinemia

Hyperproteinemia, increased serum viscosity, and hyponatremia may occur in patients receiving Privigen and other IGIV product treatments. It is critical to clinically distinguish true hyponatremia from a pseudohyponatremia that is associated with or causally related to hyperproteinemia with concomitant decreased calculated serum osmolality or elevated osmolar gap, because treatment aimed at decreasing serum free water in patients with pseudohyponatremia may lead to volume depletion, a further increase in serum viscosity, and a possible predisposition to thrombotic events.[2]

### 5.4 Thrombotic Events

Thrombotic events may occur following treatment with Privigen and other IGIV products.[3-5] Patients at risk include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, coagulation disorders, prolonged periods of immobilization, and/or known/suspected hyperviscosity.

Consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies. For patients judged to be at risk of developing thrombotic events, administer Privigen at the minimum rate of infusion practicable (*see Dosage and Administration [2.3]*). Weigh the potential risks and benefits of IGIV against those of alternative therapies in all patients for whom Privigen therapy is being considered.

### 5.5 Aseptic Meningitis Syndrome (AMS)

AMS may occur infrequently with Privigen (*see Adverse Reactions [6, 6.1]*) and other IGIV product treatments. Discontinuation of IGIV treatment has resulted in remission of AMS within several days without sequelae.[6] AMS usually begins within several hours to 2 days following IGIV treatment.

AMS is characterized by the following signs and symptoms: severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, nausea, and vomiting (*see Patient Counseling Information [17]*). Cerebrospinal fluid (CSF) studies are frequently positive with pleocytosis up to several thousand cells per cubic millimeter, predominantly from the granulocytic series, and with elevated protein levels up to several hundred mg/dL. Conduct a thorough neurological examination on patients exhibiting such signs and symptoms, including CSF studies, to rule out other causes of meningitis.

AMS may occur more frequently in association with high doses (2 g/kg) and/or rapid infusion of IGIV.

### 5.6 Hemolysis

Privigen may contain blood group antibodies that can act as hemolysins and induce *in vivo* coating of red blood cells (RBCs) with immunoglobulin, causing a positive direct antiglobulin reaction and, rarely, hemolysis.[7-9] Hemolytic anemia can develop subsequent to Privigen therapy due to enhanced RBC sequestration and/or intravascular RBC destruction.[10]

Hemolysis, possibly intravascular, occurred in two subjects treated with Privigen in the ITP study (*see Adverse Reactions [6, 6.1]*). These cases resolved uneventfully. Six other subjects experienced hemolysis in the ITP study as documented from clinical laboratory data. Monitor patients for clinical signs and symptoms of hemolysis (*see Patient Counseling Information [17]*). If these are present after Privigen infusion, perform appropriate confirmatory laboratory testing. If transfusion is indicated for patients who develop hemolysis with clinically compromising anemia after receiving IGIV, perform adequate cross-matching to avoid exacerbating on-going hemolysis.

### 5.7 Transfusion-Related Acute Lung Injury (TRALI)

Noncardiogenic pulmonary edema may occur in patients following IGIV treatment.[11] TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever. Symptoms typically appear within 1 to 6 hours following treatment.

Monitor patients for pulmonary adverse reactions (*see Patient Counseling Information [17]*). If TRALI is suspected, perform appropriate tests for the presence of anti-neutrophil antibodies in both the product and the patient's serum.

TRALI may be managed using oxygen therapy with adequate ventilatory support.

### 5.8 Volume Overload

The high-dose regimen (1 g/kg/day for 2 days) used to treat patients with chronic ITP is not recommended for individuals with expanded fluid volumes or where fluid volume may be of concern (*see Dosage and Administration [2.2]*).

### 5.9 Transmissible Infectious Agents

Privigen is made from human plasma. Based on effective donor screening and product manufacturing processes (*see Description [11]*), Privigen carries an extremely remote risk of transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) is also considered to be extremely remote. No cases of transmission of viral diseases or CJD have been associated with the use of Privigen. All infections suspected by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare professional to CSL Behring Pharmacovigilance at 1-866-915-6958. Before prescribing Privigen, the physician should discuss the risks and benefits of its use with the patient (*see Patient Counseling Information [17]*).

### 5.10 Monitoring: Laboratory Tests

- Periodic monitoring of renal function and urine output is particularly important in patients judged to be at increased risk of developing acute renal failure. Assess renal function, including measurement of blood urea nitrogen (BUN) and serum creatinine, before the initial infusion of Privigen and at appropriate intervals thereafter.
- Because of the potentially increased risk of thrombosis, consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies.
- If signs and/or symptoms of hemolysis are present after an infusion of Privigen, perform appropriate laboratory testing for confirmation.
- If TRALI is suspected, perform appropriate tests for the presence of anti-neutrophil antibodies in both the product and patient's serum.

### 5.11 Interference With Laboratory Tests

After infusion of IgG, the transitory rise of the various passively transferred antibodies in the patient's blood may yield positive serological testing results, with the potential for misleading interpretation. Passive transmission of antibodies to erythrocyte antigens (e.g., A, B, and D) may cause a positive direct or indirect antiglobulin (Coombs') test.

## 6 ADVERSE REACTIONS

The most serious adverse reaction observed in clinical study subjects receiving Privigen for PI was hypersensitivity in one subject. The most common adverse reactions observed in >10% of clinical study subjects with PI were headache, pain, nausea, fatigue, and chills.

The most serious adverse reactions observed in clinical study subjects receiving Privigen for chronic ITP were aseptic meningitis syndrome in one subject and hemolysis in two subjects. Six other subjects in the ITP study experienced hemolysis as documented from clinical laboratory data (*see Warnings and Precautions [5.5, 5.6]*). The most common adverse reactions observed in >10% of clinical study subjects with chronic ITP were headache, pyrexia/hyperthermia, and anemia.

### 6.1 Clinical Trials Experience

*Because different clinical studies are conducted under widely varying conditions, adverse reaction rates observed cannot be directly compared to rates in other clinical studies and may not reflect the rates observed in practice.*

Treatment of Primary Humoral Immunodeficiency

In a prospective, open-label, single-arm, multicenter clinical study, 80 subjects with PI (with a diagnosis of XLA or CVID) received Privigen intravenously every 3 or 4 weeks for up to 12 months (*see Clinical Studies [14.1]*). All subjects had been on regular IGIV replacement therapy for at least 6 months prior to participating in the study. Subjects ranged in age from 3 to 69; 57.5% were male and 42.5% were female.

The safety analysis included all 80 subjects, 16 on the 3-week schedule and 64 on the 4-week schedule. The median doses of Privigen administered intravenously ranged from 200 to 888 mg/kg every 3 weeks (median dose 428.3 mg/kg) or 4 weeks (median dose 440.6 mg/kg). A

total of 1038 infusions of Privigen were administered, 272 in the 3-week schedule and 766 in the 4-week schedule. Of the 1038 infusions, 435 were administered to females and 603 to males.
Routine premedication was not allowed. However, subjects who experienced two consecutive infusion-related adverse events (AEs) that were likely to be prevented by premedication were permitted to receive antipyretics, antihistamines, NSAIDs, or antiemetic agents. During the study, 8 (10%) subjects received premedication prior to 51 (4.9%) of the 1038 infusions administered.
Temporally associated AEs are those occurring during or within 72 hours after the end of an infusion, *irrespective of causality*. In this study, the upper bound of the 1-sided 97.5% confidence interval for the proportion of Privigen infusions temporally associated with one or more AEs was 23.8% (actual proportion: 20.8%). This is below the target of 40% for this safety endpoint. The total number of temporally associated AEs was 397 (a rate of 0.38 AEs per infusion), reflecting that some subjects experienced more than one AE during the observation period.
Table 2 lists the temporally associated AEs that occurred in more than 5% of subjects during a Privigen infusion or within 72 hours after the end of an infusion, *irrespective of causality*.

**Table 2: Adverse Events *Occurring in >5% of Subjects With PI During a Privigen Infusion or Within 72 Hours After the End of an infusion, *Irrespective of Causality***

| Adverse Event | Subjects (%) [n=80] | Infusions (%) [n=1038] |
|---|---|---|
| Headache | 35 (43.8) | 82 (7.9) |
| Pain | 20 (25.0) | 44 (4.2) |
| Fatigue | 13 (16.3) | 27 (2.6) |
| Nausea | 10 (12.5) | 19 (1.8) |
| Chills | 9 (11.3) | 15 (1.4) |
| Vomiting | 7 (8.8) | 13 (1.3) |
| Pyrexia | 6 (7.5) | 10 (1.0) |
| Cough | 5 (6.3) | 5 (0.5) |
| Diarrhea | 5 (6.3) | 5 (0.5) |
| Stomach discomfort | 5 (6.3) | 5 (0.5) |

*Excluding infections.

Of the 397 temporally associated AEs reported for the 80 subjects with PI, the investigators judged 192 to be related to the infusion of Privigen (including 5 serious, severe AEs described below). Of the 187 non-serious AEs related to the infusion of Privigen, 91 were mild, 81 were moderate, 14 were severe, and 1 was of unknown severity. The most common temporally associated AEs judged by the investigators to be "at least possibly" related to the infusion were headache (29% of subjects), pain (14% of subjects), nausea (11% of subjects), fatigue (11% of subjects), and chills (11% of subjects).
Sixteen subjects (20%) experienced 41 serious AEs. Five of these were related severe AEs (hypersensitivity, chills, fatigue, dizziness, and increased body temperature) that occurred in one subject and resulted in the subject's withdrawal from the study. Two other subjects withdrew from the study due to AEs related to Privigen treatment (chills and headache in one subject; vomiting in the other).
Seventy-seven of the 80 subjects enrolled in this study had a negative direct antiglobulin test (DAT) at baseline. Of these 77 subjects, 36 (46.8%) developed a positive DAT at some time during the study. However, no subjects showed evidence of hemolytic anemia.
During this study, no subjects tested positive for infection due to human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), or B19 virus (B19V).
Treatment of Chronic Immune Thrombocytopenic Purpura
In a prospective, open-label, single-arm, multicenter clinical study, 57 subjects with chronic ITP and a platelet count of 20 x $10^9$/L or less received a total of 2 g/kg dose of Privigen administered as 1 g/kg intravenous infusions daily for 2 consecutive days (*see Clinical Studies [14.2]*). Subjects ranged in age from 15 to 69; 59.6% were female and 40.4% were male.
Concomitant medications affecting platelets or other treatments for chronic ITP were not allowed. Thirty-two (56.1%) subjects received premedication with acetaminophen and/or an antihistamine.
Table 3 lists the temporally associated AEs that occurred in more than 5% of subjects with chronic ITP during a Privigen infusion or within 72 hours after the end of a treatment cycle (two consecutive infusions) with Privigen, *irrespective of causality*.

**Table 3: Adverse Events Occurring in >5% Subjects With Chronic ITP During a Privigen Infusion or Within 72 hours After the End of a Treatment Cycle*, *Irrespective of Causality***

| Adverse Event | Subjects (%) [n=57] | Infusions (%) [n=114] |
|---|---|---|
| Headache | 37 (64.9) | 41 (36.0) |
| Pyrexia/hyperthermia | 21 (36.8) | 22 (19.3) |
| Nausea | 6 (10.5) | 6 (5.3) |
| Epistaxis | 6 (10.5) | 6 (5.3) |
| Vomiting | 6 (10.5) | 6 (5.3) |
| Blood unconjugated bilirubin increased | 6 (10.5) | 6 (5.3) |
| Blood conjugated bilirubin increased | 5 (8.8) | 5 (4.4) |
| Blood total bilirubin increased | 4 (7.0) | 4 (3.5) |
| Hematocrit decreased | 3 (5.3) | 3 (2.6) |

* Two consecutive daily infusions.

Of the 183 temporally associated AEs reported for the 57 subjects with chronic ITP, the investigators judged 150 to be related to the infusion of Privigen (including the one serious AE described below). Of the 149 non-serious AEs related to the infusion of Privigen, 103 were mild, 37 were moderate, and 9 were severe. The most common temporally associated AEs judged by the investigators to be "at least possibly" related to the infusion were headache (65% of subjects) and pyrexia/hyperthermia (35% of subjects).
Three subjects experienced three serious AEs, one of which (aseptic meningitis) was related to the infusion of Privigen.
One subject withdrew from the study due to gingival bleeding, which was not related to Privigen.
Eight subjects, all of whom had a positive DAT, experienced transient drug-related hemolytic reactions, which were associated with elevated bilirubin, elevated lactate dehydrogenase, and a decrease in hemoglobin level within two days after the infusion of Privigen. Two of the eight subjects were clinically anemic but did not require clinical intervention.
Four other subjects with active bleeding were reported to have developed anemia without evidence of hemolysis.
In this study, there was a decrease in hemoglobin after the first Privigen infusion (median decrease of 1.2 g/dL by Day 8) followed by a return to near baseline by Day 29.
Fifty-six of the 57 subjects in this study had a negative DAT at baseline. Of these 56 subjects, 12 (21.4%) developed a positive DAT during the 29-day study period.

### 6.2 Postmarketing Experience

Because postmarketing reporting of adverse events is voluntary and from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to product exposure. Evaluation and interpretation of these postmarketing reactions is confounded by underlying diagnosis, concomitant medications, pre-existing conditions, and inherent limitations of passive surveillance.

**Privigen Postmarketing Experience**
Adverse reactions reported during worldwide postmarketing use of Privigen do not differ from what has been observed in clinical studies with Privigen and from what is known for IGIV products.

**General**
The following mild to moderate reactions may occur with the administration of IGIV products: headache, diarrhea, tachycardia, fever, fatigue, dizziness, malaise, chills, flushing, skin reactions, wheezing or chest tightness, nausea, vomiting, rigors, back pain, chest pain, myalgia, arthralgia, and changes in blood pressure. Immediate hypersensitivity and anaphylactic reactions are also a possibility.
The following adverse reactions have been identified and reported during the post-approval use of IGIV products.[12]

- *Renal*: Acute renal dysfunction/failure, osmotic nephropathy
- *Respiratory*: Apnea, Acute Respiratory Distress Syndrome (ARDS), TRALI, cyanosis, hypoxemia, pulmonary edema, dyspnea, bronchospasm
- *Cardiovascular:* Cardiac arrest, thromboembolism, vascular collapse, hypotension
- *Neurological:* Coma, loss of consciousness, seizures, tremor, aseptic meningitis syndrome
- *Integumentary:* Stevens-Johnson syndrome, epidermolysis, erythema multiforme, bullous dermatitis
- *Hematologic:* Pancytopenia, leukopenia, hemolysis, positive direct antiglobulin (Coombs') test
- *Musculoskeletal:* Back pain
- *Gastrointestinal:* Hepatic dysfunction, abdominal pain
- *General/Body as a Whole:* Pyrexia, rigors

## 7 DRUG INTERACTIONS

Passive transfer of antibodies may transiently interfere with the immune response to live virus vaccines such as measles, mumps, and rubella.[13] The immunizing physician should be informed of recent therapy with Privigen so that appropriate measures may be taken (*see Patient Counseling Information [17]*).

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Pregnancy Category C. Animal reproduction studies have not been conducted with Privigen. It is not known whether Privigen can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Privigen should be given to pregnant women only if clearly needed. Immunoglobulins cross the placenta from maternal circulation increasingly after 30 weeks of gestation.[14,15]

### 8.3 Nursing Mothers

Use of Privigen in nursing mothers has not been evaluated.

### 8.4 Pediatric Use

Treatment of Primary Humoral Immunodeficiency
Privigen was evaluated in 31 pediatric subjects (19 children and 12 adolescents) with PI. There were no apparent differences in the safety and efficacy profiles as compared to those in adult subjects. No pediatric-specific dose requirements were necessary to achieve the desired serum IgG levels. The safety and effectiveness of Privigen have not been established in pediatric patients with PI who are under the age of 3.
Treatment of Chronic Immune Thrombocytopenic Purpura
Safety and effectiveness of Privigen have not been established in pediatric patients with chronic ITP who are under the age of 15.

### 8.5 Geriatric Use

Clinical studies of Privigen did not include sufficient numbers of subjects age 65 and over to determine whether they respond differently from younger subjects.
Use caution when administering Privigen to patients age 65 and over who are judged to be at increased risk of developing renal insufficiency (*see Boxed Warning, Warnings and Precautions [5.2]*). Do not exceed recommended doses, and administer Privigen at the minimum infusion rate practicable.

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Bern, Switzerland

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# Specialty Drugs *on the Rise*

As specialty pharmaceuticals are prescribed more frequently to treat more common diseases, the number of them under development and expected to be approved by the FDA in the next several years is surpassing that of other categories of drugs.


By Ronale Tucker Rhodes, MS

Chronic illness has become a chronic problem in the U.S. It is estimated that 133 million Americans — almost one out of every two adults, or 45 percent of the population — have at least one chronic illness.[1,2] Almost 75 percent of individuals aged 65 and older have at least one chronic illness, and about 50 percent have at least two.[3] Chronic diseases are responsible for seven out of every 10 deaths in the U.S., killing more than 1.7 million Americans each year.[2] But, these diseases are often preventable and, now more than ever, manageable through early detection, improved diet and exercise, and treatment therapy.

In fact, one of the next great frontiers in healthcare for people, especially those who are approaching or are already in retirement, is specialty drugs. According to a recent article, these medicines are often produced biologically to treat specific complex and chronic diseases. "In recent years, scientists have begun to learn how the genes that regulate diseased cells work. And, now, usually by extracting and modifying substances from healthy cells, they are homing in on the molecular processes of these problem genes," says Peter Keating, the article's author.[4]

## Why So Special?

What are specialty pharmaceuticals? They include biologics and other injectable and high-cost pharmaceuticals that require special preparation, handling and monitoring, such as refrigeration or protection from light. And, while they can be administered either by a physician or patient, comprehensive education, training and compliance programs are needed to ensure proper use. According to the Centers for Medicare & Medicaid Services (CMS), specialty drugs are medications that cost more than $500 for a one-month supply. In actuality, these drugs usually cost annually in the range of $6,000 to $400,000.[5]

> One of the next great frontiers in healthcare for people, especially those who are approaching or are already in retirement, is specialty drugs.

Recently, the specialty drug category was expanded to incorporate oral medications that fit the CMS definition, which includes primarily oral oncologics and drugs with alternative and new delivery systems. According to Medco's *2009 Drug Trend Report*, specialty pharmaceuticals accounted for 12.8 percent of all pharmacy spending during 2008, an increase from 11.4 percent in 2007. And, by 2015, specialty drugs could account for 22 percent of all drug costs.[5,6]

## A Changing Drug Landscape

Yet, while specialty pharmaceuticals have traditionally been used to treat rare diseases, such as immune disease and hemophilia, that is changing. They are now being used for more common conditions, such as cancer, multiple sclerosis and rheumatoid arthritis. According to Medco, about one-third of new molecular entity approvals in recent years have been in the area of specialty drugs. And, the population of specialty drug users is expected to expand with new specialty treatments under development for a host of other diseases, including lupus, Alzheimer's disease, pain management, hereditary angioedema (HAE), hepatitis C, diabetes, osteoarthritis and osteoporosis.[5]

It is estimated that cancer treatments could soon be the top category for specialty drugs. Medco projected total annual spending increases on cancer drugs between 12 percent and 14 percent in 2009, a similar growth rate for 2010 and another increase of 11 percent to 13 percent in 2011, all fueled by newly diagnosed patients. As a whole, specialty drugs are growing due to expanded indications for existing treatments and more than 800 drugs in the pipeline as of mid-2009.[5]

What's interesting is that the route of administration for many new specialty drugs is oral versus injectable. According to Kevin O'Brien, RPh, president of Rumson Pharmacy in New Jersey, and cofounder and treasurer of the Community Specialty Pharmacy Network (CSPN), "approximately 30 percent of products in development for cancer are oral."[7]

## Drugs Pending and Approved

While numerous specialty drugs have been approved by the FDA in the past few years, there are also hundreds more in the pipeline that are expected to be approved.

**Cancer**. With the development of better-tolerated medicines, many types of cancer can now be managed more like a chronic disease. According to the American Cancer Society, the five-year survival rate for all cancers between 1996 and 2004 was 66 percent, an increase from the 50 percent rates seen between 1975 and 1977.[8] Rather than cytotoxic chemotherapy, medication such as rituximab, erlotinib, lenalidomide and pemetrexed are being used. In addition, some oral oncology drugs, such as imatinib, sunitinib, sorafenib, lapatinib and nilotinib provide patients more convenience and tolerability to treatment.[5]

Most recently, the FDA recommended fast-track approval of ipilimumab by Bristol-Myers Squibb. The drug was used in a study involving 676 patients in 125 cancer centers with stage III or IV metastatic melanoma who had been previously treated

For the treatment of hemophilia A

# Take a closer look at Koāte-DVI

## Proven efficacy

In clinical studies, just one dose of Koāte-DVI stopped over 90% of hemophilia A bleeding episodes.

## Commitment to safety

Koāte-DVI's patented Double Viral Inactivation (DVI) manufacturing process employs two independent steps to effectively inactivate viruses.

There have been no confirmed cases of virus transmission with Koāte-DVI.

Koāte-DVI is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses, and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent that can cause disease.

## Experience

Koāte-DVI has been used to treat hemophilia A for more than 10 years with 1.5 billion IUs infused worldwide.

Ask your doctor if Koāte-DVI is right for you.
For more information, visit Koāte-DVI.com.

## Important Safety Information

Koāte-DVI is indicated for the treatment of classical hemophilia (hemophilia A) in which there is a demonstrated deficiency of activity of the plasma clotting factor, factor VIII.

Allergic-type reactions may result from the administration of Antihemophilic Factor (Human) preparations. Reactions include tingling in the arm, ear, and face, blurred vision, headache, nausea, stomach ache, and jittery feeling.

Koāte-DVI is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses, and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent that can cause disease. There is also the possibility that unknown infectious agents may be present in such products.

Hepatitis B vaccination is essential for patients with hemophilia A; vaccination is recommended at birth or at the time of diagnosis. Hepatitis A vaccination is also recommended for hemophilia patients who are hepatitis A seronegative.

Please see brief summary of Koāte-DVI Full Prescribing Information on adjacent page.

**You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.**

Koāte®-DVI
Double Viral Inactivation
Antihemophilic Factor (Human)

Talecris BIOTHERAPEUTICS


Printed in USA November 2009 KD44-1109

# Koāte®-DVI

## Antihemophilic Factor (Human)

**Double Viral Inactivation**
**Solvent/Detergent Treated and Heated in Final Container at 80°C**

**BRIEF SUMMARY**
**CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION**
**FOR INTRAVENOUS USE ONLY**

### DESCRIPTION

Antihemophilic Factor (Human), Koāte®-DVI, is a sterile, stable, purified, dried concentrate of human Antihemophilic Factor (AHF, factor VIII, AHG) which has been treated with tri-n-butyl phosphate (TNBP) and polysorbate 80 and heated in lyophilized form in the final container at 80°C for 72 hours. Koāte-DVI is intended for use in therapy of classical hemophilia (hemophilia A).

Koāte-DVI is purified from the cold insoluble fraction of pooled fresh-frozen plasma by modification and refinements of the methods first described by Hershgold, Pool, and Pappenhagen. Koāte-DVI contains purified and concentrated factor VIII. The factor VIII is 300–1000 times purified over whole plasma. Part of the fractionation may be performed by another licensed manufacturer. When reconstituted as directed, Koāte-DVI contains approximately 50–150 times as much factor VIII as an equal volume of fresh plasma. The specific activity, after addition of Albumin (Human), is in the range of 9–22 IU/mg protein. **Koāte-DVI must be administered by the intravenous route**.

Each bottle of Koāte-DVI contains the labeled amount of antihemophilic factor activity in international units (IU). One IU, as defined by the World Health Organization standard for blood coagulation factor VIII, human, is approximately equal to the level of AHF found in 1.0 mL of fresh pooled human plasma. The final product when reconstituted as directed contains not more than (NMT) 1500 µg/mL polyethylene glycol (PEG), NMT 0.05 M glycine, NMT 25 µg/mL polysorbate 80, NMT 5 µg/g tri-n-butyl phosphate (TNBP), NMT 3 mM calcium, NMT 1 µg/mL aluminum, NMT 0.06 M histidine, and NMT 10 mg/mL Albumin (Human).

### CLINICAL PHARMACOLOGY

Hemophilia A is a hereditary bleeding disorder characterized by deficient coagulant activity of the specific plasma protein clotting factor, factor VIII. In afflicted individuals, hemorrhages may occur spontaneously or after only minor trauma. Surgery on such individuals is not feasible without first correcting the clotting abnormality. The administration of Koāte-DVI provides an increase in plasma levels of factor VIII and can temporarily correct the coagulation defect in these patients.

After infusion of Antihemophilic Factor (Human), there is usually an instantaneous rise in the coagulant level followed by an initial rapid decrease in activity, and then a subsequent much slower rate of decrease in activity. The early rapid phase may represent the time of equilibration with the extravascular compartment, and the second or slow phase of the survival curve presumably is the result of degradation and reflects the true biologic half-life of the infused Antihemophilic Factor (Human).

The removal and inactivation of spiked relevant and model enveloped and non-enveloped viruses during the manufacturing process for Koāte-DVI have been validated in laboratory studies at Talecris Biotherapeutics, Inc. Studies performed with the model enveloped viruses indicated that the greatest reduction was achieved by TNBP/polysorbate 80 treatment and 80°C heat. For this reason, VSV (Vesicular Stomatitis Virus, model for RNA enveloped viruses) and HIV-1 (Human Immunodeficiency Virus Type 1) were studied only at these two steps of the manufacturing process. The efficacy of the dry heat treatment was studied using all of the viruses, including BVDV (Bovine Viral Diarrheal Virus, model for hepatitis C virus) and Reo (Reovirus Type 3, model for viruses resistant to physical and chemical agents, such as hepatitis A), and the effect of moisture content on the inactivation of HAV (Hepatitis A Virus), PPV (Porcine Parvovirus, model for parvovirus B19), and PRV (Pseudorabies Virus, model for large enveloped DNA viruses) was investigated.

Table 1. Summary of In Vitro $Log_{10}$ Viral Reduction Studies

| | | Model for | Global Reduction Factor |
|---|---|---|---|
| Enveloped Model Viruses | HIV-1 | HIV-1/2 | ≥9.4 |
| | BVDV | HCV | ≥10.3 |
| | PRV | Large Enveloped DNA viruses | ≥9.3 |
| | VSV | RNA enveloped viruses | ≥10.9 |
| Non-enveloped Model Viruses | Reo | HAV and viruses resistant to chemical and physical agents | 9.4 |
| | HAV | HAV | ≥4.5 |
| | PPV | B19 | 3.7 |

Similar studies have shown that a terminal 80°C heat incubation for 72 hours inactivates non-lipid enveloped viruses such as hepatitis A and canine parvovirus in vitro, as well as lipid enveloped viruses such as hepatitis C.

Koāte-DVI is purified by a gel permeation chromatography step serving the dual purpose of reducing the amount of TNBP and polysorbate 80 as well as increasing the purity of the factor VIII.

A two-stage clinical study using Koāte-DVI was performed in individuals with hemophilia A who had been previously treated with other plasma-derived AHF concentrates. In Stage I of the pharmacokinetic study with 19 individuals, statistical comparisons demonstrated that Koāte-DVI is bioequivalent to the unheated product, Koāte®-HP. The incremental in vivo recovery ten minutes after infusion of Koāte-DVI was 1.90% IU/kg (Koāte-HP 1.82% IU/kg). Mean biologic half-life of Koāte-DVI was 16.12 hours (Koāte-HP 16.13 hours). In Stage II of the study, participants received Koāte-DVI treatments for six months on home therapy with a median of 54 days (range 24–93). No evidence of inhibitor formation was observed, either in the clinical study or in the preclinical investigations.

### INDICATIONS AND USAGE

Koāte-DVI is indicated for the treatment of classical hemophilia (hemophilia A) in which there is a demonstrated deficiency of activity of the plasma clotting factor, factor VIII. Koāte-DVI provides a means of temporarily replacing the missing clotting factor in order to control or prevent bleeding episodes, or in order to perform emergency and elective surgery on individuals with hemophilia.

Koāte-DVI contains naturally occurring von Willebrand's factor, which is co-purified as part of the manufacturing process.

Koāte-DVI has not been investigated for efficacy in the treatment of von Willebrand's disease, and hence is not approved for such usage.

### CONTRAINDICATIONS

None known.

### WARNINGS

**Koāte-DVI is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses, that can cause disease. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and/or removing certain viruses. Despite these measures, because this product is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically the Creutzfeldt-Jakob disease (CJD) agent. There is also the possibility that unknown infectious agents may be present in such products. ALL infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Talecris Biotherapeutics, Inc. [1-800-520-2807]. The physician should discuss the risks and benefits of this product with the patient, before prescribing or administering it to a patient.**

**Individuals who receive infusions of blood or plasma products may develop signs and/or symptoms of some viral infections, particularly hepatitis C. It is emphasized that hepatitis B vaccination is essential for patients with hemophilia and it is recommended that this be done at birth or diagnosis. Hepatitis A vaccination is also recommended for hemophilic patients who are hepatitis A seronegative.**

### PRECAUTIONS

**General**

1. Koāte-DVI is intended for treatment of bleeding disorders arising from a deficiency in factor VIII. This deficiency should be proven prior to administering Koāte-DVI.
2. Administer within 3 hours after reconstitution. Do not refrigerate after reconstitution.
3. **Administer only by the intravenous route.**
4. Filter needle should be used prior to administering.
5. Koāte-DVI contains levels of blood group isoagglutinins which are not clinically significant when controlling relatively minor bleeding episodes. When large or frequently repeated doses are required, patients of blood groups A, B, or AB should be monitored by means of hematocrit for signs of progressive anemia, as well as by direct Coombs' tests.
6. Product administration and handling of the infusion set and needles must be done with caution. Percutaneous puncture with a needle contaminated with blood can transmit infectious viruses including HIV (AIDS) and hepatitis. Obtain immediate medical attention if injury occurs.

   Place needles in sharps container after single use. Discard all equipment including any reconstituted Koāte-DVI product in accordance with biohazard procedures.

**Pregnancy Category C**

Animal reproduction studies have not been conducted with Koāte-DVI. It is also not known whether Koāte-DVI can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Koāte-DVI should be given to a pregnant woman only if clearly needed.

**Pediatric Use**

Koāte-DVI has not been studied in pediatric patients. Koāte-HP, solvent/detergent treated Antihemophilic Factor (Human), has been used extensively in pediatric patients.

Spontaneous adverse event reports with Koāte-HP for pediatric use were within the experience of those reports for adult use.

**Information for Patient**

Some viruses, such as parvovirus B19 or hepatitis A, are particularly difficult to remove or inactivate at this time. Parvovirus B19 most seriously affects pregnant women, or immune-compromised individuals.

Symptoms of parvovirus B19 infection include fever, drowsiness, chills and runny nose followed about 2 weeks later by a rash and joint pain. Evidence of hepatitis A may include several days to weeks of poor appetite, tiredness, and low-grade fever followed by nausea, vomiting, and pain in the belly. Dark urine and a yellowed complexion are also common symptoms. Patients should be encouraged to consult their physician if such symptoms appear.

### ADVERSE REACTIONS

Allergic-type reactions may result from the administration of Antihemophilic Factor (Human) preparations.

Ten adverse reactions related to 7 infusions were observed during a total of 1053 infusions performed during the clinical study of Koāte-DVI, for a frequency of 0.7% infusions associated with adverse reactions. All reactions were mild and included tingling in the arm, ear, and face, blurred vision, headache, nausea, stomach ache, and jittery feeling.

### CAUTION

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unsuccessfully with other cancer drugs.[9] Several other cancer drugs are up for review by the FDA. Phenoxodiol (Marshall Edwards) in oral dosage form for the treatment of late-stage, hormone-refractory prostate cancer has been given fast-track review. Telatinib (ACT Biotech), an oral kinase inhibitor to treat gastric cancer, GVAX CML vaccine (BioSante) to treat chronic myeloid leukemia, sapacitabine or CYC682 (Cyclacel) to treat both acute myeloid leukemia and myelodysplastic syndromes, and biovaxID (Biovest International) to treat mantle cell lymphoma have been given orphan drug designations. In addition, dasatinib (Sprycel, Otsuka) to treat adult patients with newly diagnosed chronic myeloid leukemia has been given priority review.[10]

**Multiple sclerosis (MS).** The new drugs for MS are oral treatments, a big change from the market that has long been dominated by injectables. In January, the FDA approved dalfampridine, formerly known as fampridine SR (Ampyra, Acorda Therapeutics), the first oral medication shown to enhance some neurological functions in people with the disease.[11] Then, in September, the FDA approved fingolimod (Gilenya, Novartis), the first of the long-anticipated oral treatments to reduce relapses and delay disability progression in patients with relapsing forms of MS.[12] Prior to this approval, the first line of treatment was injections of interferon beta-1, an immune modulator.

Several other promising oral therapies are being developed to treat MS. One is cladribine (Movectro; Merck Serono),

## Understanding the FDA Drug Approval Designations

On average, it takes 12 years and more than $500 million to get a new drug from the laboratory onto the pharmacy shelf in the United States. For more than 90 years, the entity responsible for protecting the public health, by ensuring that these new drugs and all prescription and nonprescription medications are "safe and effective," is the Food and Drug Administration (FDA).

Opinion varies about whether the FDA approval process for new drugs is too hasty, which places the public at risk, or too lengthy, which delays the arrival of superior drugs and raises the costs of bringing new drugs to market, resulting in many new drug developments being halted. In response to these criticisms, the FDA has instituted several designations during the past 20 years to accelerate the availability of new drugs, while still ensuring that manufacturers demonstrate that the drugs' benefits outweigh their risks for a specific population and a specific use, and that the drugs meet standards for safety and effectiveness. In addition, the FDA has implemented a separate designation to encourage the development of less-profitable drugs to treat rare conditions.

***Fast Track.*** The fast-track process was designed to expedite the review of drugs to treat serious diseases and fill an unmet medical need. Drugs are generally determined to be serious if they will have an impact on patient survival and/or day-to-day functioning or, if not used, will cause the disease to progress to a more serious condition. Obviously, providing a therapy where none exists fills an unmet medical need. However, even if there is an existing therapy, an unmet medical need can still be shown through a variety of factors, such as superior effectiveness, lack of serious side effects, etc.

Drug companies must apply for fast-track designation, which they can do at any time during the drug development process. If granted, early and frequent communication between the FDA and a drug company can occur throughout the drug development review process to ensure questions and issues are resolved quickly, which can often lead to earlier drug approval and access by patients. Drugs with fast-track designation are likely to also be considered appropriate to receive a priority review.

***Accelerated Approval.*** The accelerated approval regulation was instituted in 1992. A drug can be granted accelerated approval to treat serious diseases that fill an unmet medical need based on a surrogate endpoint. A surrogate endpoint is a laboratory measurement or physical sign that is used in clinical trials as a substitute measurement that represents a clinically meaningful outcome, such as survival or symptom improvement. Once accelerated approval has been granted, the drug can be used to treat patients, but it must go through Phase IV confirmatory trials to prove that the clinical benefit was met. If it is, the FDA grants traditional approval for the drug.

***Priority Review.*** Under the Prescription Drug User Fee Act (PDUFA) enacted in 1992, the FDA created a two-tiered review system. The first, standard review, applies to new drug applications for drugs that offer only minor improvement over existing marketed therapies. The goal for approving a standard review is 10 months. A priority review designation is given to new drug applications for drugs that offer major advances in treatment or provide a treatment where no adequate therapy exists for both

which the FDA granted priority review for in August 2010. The drug was approved in September by the Australian Therapeutic Goods Administration for the treatment of relapsing-remitting multiple sclerosis (MS) for a maximum period of two years.[13] BG-12 (dimethyl fumarate, Biogen Idec) is an investigational oral therapy in Phase III clinical development for the treatment of relapsing-remitting MS, which has received fast-track designation in MS from the FDA. PEGylated interferon beta-1a (CinnoVex, Biogen Idec) is under investigation for the treatment of relapsing MS and is currently enrolling a Phase III clinical trial. And, daclizumab (Zenapax, Biogen Idec) is an investigational agent in clinical development for the treatment of MS in collaboration between Abbott and Biogen Idec.[14]

serious and less serious diseases. The goal for reviewing a drug with priority review is six months. The drug company must request a priority review designation when filing the new drug application. Neither review system affects the length of the clinical trial period.

***Orphan Drug Status.*** The Office of Orphan Product Development (OOPD) was established by the FDA to exercise the rights given to them under the Orphan Drug Act of January 1983 to develop cures for rare diseases. Because drugs for rare diseases (which often treat fewer than 200,000 people) are much less profitable than those developed to treat common diseases, companies granted orphan drug status for the development of drugs that treat rare diseases are provided tax reductions, as well as exclusive patent rights for a period of seven years. A company must request an orphan designation by submitting an application to the OOPD. If approved, the designation does not alter the standard regulatory requirements and process for obtaining marketing approval.

For a more detailed explanation of these designations, visit the FDA websites listed in the sources below.

**Sources:**


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- U.S. Food and Drug Administration. Fast Track, Accelerated Approval and Priority Review. Accessed at www.fda.gov/forconsumers/byaudience/forpatientadvocates/speedingaccesstoimportantnewtherapies/ucm128291.htm.


**Rheumatoid arthritis (RA).** Tumor necrosis factor (TNF) inhibitors, which are a category of specialty drugs, have been used for a decade in the treatment of RA. Those currently approved by the FDA include etanercept, adalimumab, infliximab, certolizumab and golimumab. Other types of biologics also have gained FDA approval for patients who are unresponsive to TNF inhibitor therapy, including rituximab and abatacept.[5] Most recently, the FDA approved tocilizumab (Actemra, Hoffman La-Roche), a treatment that targets interleukin 6, for the treatment of moderately to severely active RA in adults whose disease has inadequately responded to therapy with one or more TNF antagonists.[15] BG-12 (dimethyl fumarate, Biogen Idec), mentioned above, is also an investigational oral therapy in Phase II clinical trials for RA.[14]

**Diabetes.** A number of new drug developments are being investigated to treat diabetes, many of which will hinge upon the new FDA guidelines evaluating cardiovascular risk. Two that are being closely watched are liraglutide (Victoza, Novo Nordisk) and exenatide long-acting (Byetta LAR, Bydureon, Amylin/Lilly/Alkermes). Victoza, Bydureon and Byetta are all part of a new class of drugs called GLP-1 analogs. Liraglutide is a once-daily injectable GLP-1 analog and is approved for use in foreign markets.[7] Bydureon is a once-weekly formulation of exenatide, the active ingredient in Byetta, which has been available in the U.S. since June 2005 and is used in approximately 60 countries worldwide to improve glycemic control in adults with type 2 diabetes.[16]

Several other drugs also are in the pipeline. Inhaled insulin (Afresa, MannKind) is an ultra-rapid-acting insulin that mimics meal-related early insulin release. Teplizumab (Lilly/Macrogenics) is a humanized anti-CD3 monoclonal antibody to treat type 1 diabetes and is in Phase III clinical trials. Dapagliflozin (Bristol-Myers Squibb/AstraZeneca) is an inhibitor that lowers insulin-dependent glucose by increasing urinary glucose excretion and is also in Phase III clinical trials.[7] And, Tolera Therapeutics was granted orphan drug status by the FDA for TOL101 (anti-TCR murine monoclonal antibody, type IgM) for the treatment of recent onset immune-mediated type 1 diabetes mellitus in patients 16 years of age and younger with preserved pancreatic B-cell function.[10]

**Hepatitis C.** One of the most promising classes of new specialty drugs is protease inhibitors for combating hepatitis C. A number of companies are hoping to be the first to market a hepatitis C drug that outperforms the current standard of care, which is interferon combined with ribavirin. The most promising is Vertex Pharmaceuticals' telaprevir. To date, more than 2,500 people with hepatitis C have received telaprevir-based regimens as part of Phase II studies and the Phase III Advance, Illuminate and Realize studies. Vertex was expected to submit a new drug application to the FDA in the fourth quarter of 2010.[17]

Merck and Bristol-Myers Squibb also are developing protease inhibitors for hepatitis C. Merck recently announced results from its Phase III study of boceprevir, which is used in combination with Pegintron (peginterferon alfa-2b) and Rebetol (ribavirin, USP) (Peg/riba) for the treatment of patients with HCV genotype 1 infection who were previously treated and in patients who are new to treatment. Merck had plans to submit a new drug application to the FDA on a rolling basis, and had expected to complete regulatory submissions in the U.S. and EU in 2010.[18] Bristol-Myers Squibb recently acquired ZymoGenetics' pegylated-interferon lambda, a novel interferon drug candidate. It also announced interim results from Phase IIa of its Emerge clinical trial of the drug administered with ribavirin in treatment-naive hepatitis C virus patients.[19]

Recently, however, development was stopped on another promising hepatitis C drug candidate from Novartis and Human Genome Sciences, Zalbin/Joulferon (albinterferon alfa-2b), in response to a letter from the FDA together with prior feedback from the European Medicines Agency, as well as results from a new Phase II trial.[20]

**Lupus.** Patients with lupus may have their first new treatment in 50 years if the FDA approves belimumab (Benlysta, HGS/GlaxoSmithKline) for the treatment of antibody-positive patients with systemic lupus erythematosus (SLE). After two successful Phase III clinical trials, the FDA has granted the drug priority review status.[21] Clinical trials of another drug to treat lupus, ocrelizumab (RG1594, Roche/Biogen Idec), was halted due to safety concerns.[22]

**Alzheimer's**. A front-runner for treating Alzheimer's disease is intravenous immunoglobulin (Gammagard, Baxter), which has shown significant clinical benefits and is now in Phase III clinical trials. Other drugs in Phase III trials include bapineuzumab (Wyeth), solanezumab (Lilly), dimebon (Pfizer) and LY450139 (Lilly).[7]

**Osteoarthritis/pain management**. After filing a new drug application with Phase III clinical results, NicOx received a complete response letter from the FDA recommending one or more long-term controlled studies to assess the cardiovascular and gastrointestinal safety of naproxcinod for the relief of the signs and symptoms of osteoarthritis.[10] In addition, Phase II studies of the drug tanezumab (Pfizer) that showed it was highly effective in relieving the pain of osteoarthritis and lower back pain were halted last September when some patients experienced worsening of the disease. However, the FDA is reviewing the safety of that drug, and it could still emerge as an effective treatment.[23]

**Hereditary angioedema (HAE)**. In late 2008, the FDA approved Cinryze (Viropharma), the first and only FDA-approved C1 inhibitor therapy for routine prophylaxis against HAE attacks in the U.S.[24] Then, in December 2009, the FDA approved ecallantide (Kalbitor, Dyax) for the treatment of HAE in patients 16 and older.[25] One other C1 inhibitor that is in development is icatibant (Firazyr; Jerini), a drug that has been approved for treating HAE in Europe.[5]

It is estimated that cancer treatments could soon be the top category for specialty drugs.

**Osteoporosis**. In June, the FDA approved denosumab (Prolia, Amgen), a fully human monoclonal antibody, for treatment of postmenopausal women who have a high risk for osteoporotic fractures, including those with a history of fracture or multiple risk factors for fracture, or those who have failed or are intolerant to other osteoporosis therapy. Denosumab is the first RANK ligand inhibitor to receive FDA approval.[26]

## A Hefty Price Tag

All of these specialty drugs come at a price, however. Biologics are expensive, as mentioned previously, costing in the range of $6,000 to $400,000 annually. Rather than charge patients a copay, insurers often charge a portion of the cost of

When thrombotic risk is high in hereditary antithrombin deficiency

# Proceed Safely


## Thrombate III—treating hereditary antithrombin deficiency for more than 16 years

- A proven therapy to prevent thromboembolic events in high-risk situations, such as[1]:
  - Surgery
  - Obstetrical procedures (including childbirth)
  - Acute thromboembolism
- Pasteurized to inactivate viruses, with no confirmed cases of virus transmission
  - Thrombate III is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses, and, theoretically, the Creutzfeldt-Jakob disease agent that can cause disease
- An antithrombin concentrate purified from human plasma


To order, call Talecris USA Customer Service at **1-800-243-4153** or visit **www.thrombate.com**.

For technical questions, call Talecris Clinical Communications at **1-800-520-2807** or visit **www.thrombate.com**.

**References: 1.** Thrombate III [prescribing information]. Research Triangle Park, NC: Talecris Biotherapeutics, Inc.; 2008. **2.** Data on file, Talecris Biotherapeutics, Inc., 1988. **3.** Scott GR, Robinson MJ, Wilczek J, Berson MR. *FDA Drug and Device Product Approvals*. Springfield, VA: Division of Drug Information Resources, OM, CDER, US Dept of Health and Human Services, Public Health Service; 1991;14(2):333.

**Important Safety Information**

Thrombate III is indicated for the treatment of patients with hereditary antithrombin deficiency in connection with surgical or obstetrical procedures or when they suffer from thromboembolism.

In clinical studies with Thrombate III, the most common side effects were dizziness, chest tightness, nausea and foul taste in mouth.

The anticoagulant effect of heparin is enhanced by concurrent treatment with Thrombate III in patients with hereditary AT-III deficiency. Thus, in order to avoid bleeding, reduced dosage of heparin is recommended during treatment with Thrombate III.

Thrombate III is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses, and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent that can cause disease. There is also the possibility that unknown infectious agents may be present in such products.

Individuals who receive infusions of blood or blood plasma may develop signs and/or symptoms of some viral infections, particularly hepatitis C.

**Please see brief summary of Thrombate III full Prescribing Information on adjacent page.**

Talecris BIOTHERAPEUTICS

Thrombate III® antithrombin III (human)



Printed in USA November 2009 TH86-1109

# THROMBATE III®
## Antithrombin III (Human)

**BRIEF SUMMARY**
**CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION**

**FOR INTRAVENOUS USE ONLY**

### DESCRIPTION

Antithrombin III (Human), THROMBATE III® is a sterile, nonpyrogenic, stable, lyophilized preparation of purified human antithrombin III.

THROMBATE III is prepared from pooled units of human plasma from normal donors by modifications and refinements of the cold ethanol method of Cohn. When reconstituted with Sterile Water for Injection, USP, THROMBATE III has a pH of 6.0–7.5, a sodium content of 110–210 mEq/L, a chloride content of 110–210 mEq/L, an alanine content of 0.075–0.125 M, and a heparin content of not more than 0.1 IU heparin/IU AT-III. THROMBATE III contains no preservative and must be administered by the intravenous route. In addition, THROMBATE III has been heat-treated in solution at 60°C ± 0.5°C for not less than 10 hours.

Each vial of THROMBATE III contains the labeled amount of antithrombin III in international units (IU) per vial. The potency assignment has been determined with a standard calibrated against a World Health Organization (WHO) antithrombin III reference preparation.

The manufacturing process was investigated for its capacity to decrease the infectivity of an experimental agent of transmissible spongiform encephalopathy (TSE), considered as a model for the vCJD and CJD agents.

An individual production step in the THROMBATE III manufacturing process has been shown to decrease TSE infectivity of that experimental model agent. The TSE reduction step is the Effluent I to Effluent II + III fractionation step (6.0 logs). These studies provide reasonable assurance that low levels of CJD/vCJD agent infectivity, if present in the starting material, would be removed.

### CLINICAL PHARMACOLOGY

Antithrombin III (AT-III), an $alpha_2$-glycoprotein of molecular weight 58,000, is normally present in human plasma at a concentration of approximately 12.5 mg/dL and is the major plasma inhibitor of thrombin. Inactivation of thrombin by AT-III occurs by formation of a covalent bond resulting in an inactive 1:1 stoichiometric complex between the two, involving an interaction of the active serine of thrombin and an arginine reactive site on AT-III. AT-III is also capable of inactivating other components of the coagulation cascade including factors IXa, Xa, XIa, and XIIa, as well as plasmin.

The neutralization rate of serine proteases by AT-III proceeds slowly in the absence of heparin, but is greatly accelerated in the presence of heparin. As the therapeutic antithrombotic effect in vivo of heparin is mediated by AT-III, heparin is ineffective in the absence or near absence of AT-III.

The prevalence of the hereditary deficiency of AT-III is estimated to be one per 2000 to 5000 in the general population. The pattern of inheritance is autosomal dominant. In affected individuals, spontaneous episodes of thrombosis and pulmonary embolism may be associated with AT-III levels of 40%–60% of normal. These episodes usually appear after the age of 20, the risk increasing with age and in association with surgery, pregnancy and delivery. The frequency of thromboembolic events in hereditary antithrombin III (AT-III) deficiency during pregnancy has been reported to be 70%, and several studies of the beneficial use of Antithrombin III (Human) concentrates during pregnancy in women with hereditary deficiency have been reported. In many cases, however, no precipitating factor can be identified for venous thrombosis or pulmonary embolism. Greater than 85% of individuals with hereditary AT-III deficiency have had at least one thrombotic episode by the age of 50 years. In about 60% of patients thrombosis is recurrent. Clinical signs of pulmonary embolism occur in 40% of affected individuals. In some individuals, treatment with oral anticoagulants leads to an increase of the endogenous levels of AT-III, and treatment with oral anticoagulants may be effective in the prevention of thrombosis in such individuals.

In clinical studies of THROMBATE III conducted in 10 asymptomatic subjects with hereditary deficiency of AT-III, the mean in vivo recovery of AT-III was 1.6% per unit per kg administered based on immunologic AT-III assays, and 1.4% per unit per kg administered based on functional AT-III assays. The mean 50% disappearance time (the time to fall to 50% of the peak plasma level following an initial administration) was approximately 22 hours and the biologic half-life was 2.5 days based on immunologic assays and 3.8 days based on functional assays of AT-III. These values are similar to the half-life for radiolabeled Antithrombin III (Human) reported in the literature of 2.8–4.8 days.

In clinical studies of THROMBATE III, none of the 13 patients with hereditary AT-III deficiency and histories of thromboembolism treated prophylactically on 16 separate occasions with THROMBATE III for high thrombotic risk situations (11 surgical procedures, 5 deliveries) developed a thrombotic complication. Heparin was also administered in 3 of the 11 surgical procedures and all 5 deliveries. Eight patients with hereditary AT-III deficiency were treated therapeutically with THROMBATE III as well as heparin for major thrombotic or thromboembolic complications, with seven patients recovering. Treatment with THROMBATE III reversed heparin resistance in two patients with hereditary AT-III deficiency being treated for thrombosis or thromboembolism.

During clinical investigation of THROMBATE III, none of 12 subjects monitored for a median of 8 months (range 2–19 months) after receiving THROMBATE III, became antibody positive to human immunodeficiency virus (HIV-1). None of 14 subjects monitored for ≥ 3 months demonstrated any evidence of hepatitis, either non-A, non-B hepatitis or hepatitis B.

### INDICATIONS AND USAGE

THROMBATE III is indicated for the treatment of patients with hereditary antithrombin III deficiency in connection with surgical or obstetrical procedures or when they suffer from thromboembolism.

Subjects with AT-III deficiency should be informed about the risk of thrombosis in connection with pregnancy and surgery and about the inheritance of the disease.

The diagnosis of hereditary antithrombin III (AT-III) deficiency should be based on a clear family history of venous thrombosis as well as decreased plasma AT-III levels, and the exclusion of acquired deficiency.

AT-III in plasma may be measured by amidolytic assays using synthetic chromogenic substrates, by clotting assays, or by immunoassays. The latter does not detect all hereditary AT-III deficiencies.

The AT-III level in neonates of parents with hereditary AT-III deficiency should be measured immediately after birth. (Fatal neonatal thromboembolism, such as aortic thrombi in children of women with hereditary antithrombin III deficiency, has been reported.)

Plasma levels of AT-III are lower in neonates than adults, averaging approximately 60% in normal term infants. AT-III levels in premature infants may be much lower. Low plasma AT-III levels, especially in a premature infant, therefore, do not necessarily indicate hereditary deficiency. It is recommended that testing and treatment with THROMBATE III of neonates be discussed with an expert on coagulation.

### CONTRAINDICATIONS

None known.

### WARNINGS

**THROMBATE III is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses and theoretically, the Creutzfeldt-Jakob (CJD) agent that can cause disease. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and/or removing certain viruses. Despite these measures, such products can still potentially transmit disease. There is also the possibility that unknown infectious agents may be present in such products. Individuals who receive infusions of blood or plasma products may develop signs and/or symptoms of some viral infections, particularly hepatitis C. ALL infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Talecris Biotherapeutics, Inc. [1-800-520-2807].**

**The physician should discuss the risks and benefits of this product with the patient, before prescribing or administering it to a patient.**

The anticoagulant effect of heparin is enhanced by concurrent treatment with THROMBATE III in patients with hereditary AT-III deficiency. Thus, in order to avoid bleeding, reduced dosage of heparin is recommended during treatment with THROMBATE III.

### PRECAUTIONS

**General**

1. Administer within 3 hours after reconstitution. Do not refrigerate after reconstitution.
2. Administer only by the intravenous route.
3. THROMBATE III, once reconstituted, should be given alone, without mixing with other agents or diluting solutions.
4. Product administration and handling of the needles must be done with caution. Percutaneous puncture with a needle contaminated with blood can transmit infectious virus including HIV (AIDS) and hepatitis. Obtain immediate medical attention if injury occurs.

   Place needles in sharps container after single use. Discard all equipment including any reconstituted THROMBATE III product in accordance with biohazard procedures.

The diagnosis of hereditary antithrombin III (AT-III) deficiency should be based on a clear family history of venous thrombosis as well as decreased plasma AT-III levels, and the exclusion of acquired deficiency.

**Laboratory Tests**

It is recommended that AT-III plasma levels be monitored during the treatment period. Functional levels of AT-III in plasma may be measured by amidolytic assays using chromogenic substrates or by clotting assays.

**Drug Interactions**

The anticoagulant effect of heparin is enhanced by concurrent treatment with THROMBATE III in patients with hereditary AT-III deficiency. Thus, in order to avoid bleeding, reduced dosage of heparin is recommended during treatment with THROMBATE III.

**Pregnancy Category B**

Reproduction studies have been performed in rats and rabbits at doses up to four times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to THROMBATE III. It is not known whether THROMBATE III can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

**Pediatric Use**

Safety and effectiveness in the pediatric population have not been established. The AT-III level in neonates of parents with hereditary AT-III deficiency should be measured immediately after birth. (Fatal neonatal thromboembolism, such as aortic thrombi in children of women with hereditary antithrombin III deficiency, has been reported.)

Plasma levels of AT-III are lower in neonates than adults, averaging approximately 60% in normal term infants. AT-III levels in premature infants may be much lower. Low plasma AT-III levels, especially in a premature infant, therefore, do not necessarily indicate hereditary deficiency. It is recommended that testing and treatment with THROMBATE III of neonates be discussed with an expert on coagulation.

### ADVERSE REACTIONS

In clinical studies involving THROMBATE III, adverse reactions were reported in association with 17 of the 340 infusions during the clinical studies. Included were dizziness (7), chest tightness (3), nausea (3), foul taste in mouth (3), chills (2), cramps (2), shortness of breath (1), chest pain (1), film over eye (1), light-headedness (1), bowel fullness (1), hives (1), fever (1), and oozing and hematoma formation (1). If adverse reactions are experienced, the infusion rate should be decreased, or if indicated, the infusion should be interrupted until symptoms abate.

### CAUTION

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the drug, typically 25 percent to 35 percent of the overall cost. According to Avelere Health, a Washington, D.C., consulting firm, "86 percent of Medicare Part D plans and 10 percent of private insurance plans now force patients to share costs rather than make copayments."[4]

While numerous specialty drugs have been approved by the FDA in the past few years, there are also hundreds more in the pipeline that are expected to be approved.

Does this mean that patients will opt to forgo treatment with these specialty drugs? Not so, says a 2006 study by Rand Corp., which reports that rising copayments can reduce the use of prescription drugs by 30 percent to 50 percent, but expensive tiers for specialty drugs lower their use by only 1 percent to 21 percent. This is not only because these drugs are effective, but there are few alternatives.[4]

## New Therapies, More Treatment Options

Despite the high cost, as the number of chronic illnesses in need of treatment with specialty drugs continues to rise, researchers in the pharmaceutical industry are making great strides. Today, the industry is not only helping Americans who have long suffered from chronic disease to live a quality of health and life they never thought they would, but it is also providing more and improved options to individuals with more common chronic conditions. ❖

**RONALE TUCKER RHODES**, *MS, is the editor of* BioSupply Trends Quarterly.

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# Myths and Facts

## Measles and Mumps

Measles and mumps are rare diseases in the U.S. today due to greater immunity from a preventive vaccine, but these diseases still pose a real threat.

By Ronale Tucker Rhodes, MS

No one thinks much about measles and mumps anymore. This is because it is believed that these diseases have been all but eradicated. Unfortunately, that couldn't be further from the truth. Measles is very rare in regions of the world and in countries, such as the U.S., that are able to keep vaccination coverage high. But, worldwide, there are estimated to be 10 million cases of measles and more than 197,000 deaths from the disease each year, more than half of which occur in India.[1] And, while most people in the U.S. have now been vaccinated against mumps, making it a rare disease, mumps has started to reappear; a mumps outbreak occurred in 2006 in the U.S., which marked a 20-fold increase in the number of cases.[2,3]

Measles and mumps were most prevalent in the 18th and 19th centuries. While the first known report of measles was from an Arab physician writing in his medical notes in the 9th

century about the differences between measles and smallpox, it wasn't until 1757 that Francis Home, a Scottish physician, first demonstrated that measles was caused by an infectious agent present in the blood of patients. In 1954, the virus that causes measles was isolated in Boston by John F. Enders and Thomas C. Peebles. Before the first measles vaccine was developed in 1963, each year in the U.S. about 450 people died, 48,000 were hospitalized, 7,000 had seizures and about 1,000 suffered permanent brain damage or deafness from the disease. Today, there are about 50 reported cases each year, most of which originate out of the country.[1]

Mumps was first described by a Greek physician and philosopher named Hippocrates in the 5th century. But, it became a plague in the 18th and 19th centuries when an epidemic broke out all around the world, including in military barracks, prisons, boarding schools and ships at sea. Drs. Claude D. Johnson and Ernest William Goodpasture were the first to prove that a virus caused mumps in 1934. Prior to the introduction of the first mumps vaccine in 1967, the disease became nationally reportable in the U.S., with an estimated 212,000 cases in 1964. Since 2001, there have been, on average, 200 to 300 cases per year reported in the U.S.[4]

Comparing the prevalence back then to now can lead many to believe that these diseases are no longer a threat, particularly in the U.S. But, the seriousness of them, especially measles, makes that belief a myth. Indeed, the only way to continue a decreased incidence is to separate the myths from the facts.

## Separating Myth from Fact

Myth: Measles and mumps are no longer common diseases.

Fact: Measles remains a common disease in many parts of the world, and outbreaks are common. While rare in the U.S., the risk for exposure to measles can be high for many U.S. travelers and citizens living in other countries. Unvaccinated U.S. travelers returning to the U.S. and visitors to the U.S. can unknowingly bring measles into the country, causing outbreaks or epidemics among unvaccinated people and undervaccinated communities.[5]

The most recent mumps outbreak that occurred in 2006 in the Midwest sickened 6,600 individuals, a jump from the 314 cases reported in the U.S. in 2005. This outbreak prompted a study by researchers at the Centers for Disease Control and Prevention (CDC) to gauge the prevalence of mumps antibodies among Americans of different age groups in the years before the 2006 outbreak. Using data from a U.S. national health study conducted between 1999 and 2004, they found that 90 percent of 6- to 49-year-olds had antibodies to mumps in their blood, a level that is at the low end of what is needed to prevent significant outbreaks of the infection. The hardest hit population during the 2006 outbreak was non-Hispanic whites born between 1977 and 1986; only 87 percent of them had mumps antibodies, compared to 90 percent of other racial groups. The CDC estimates that between 90 percent and 92 percent of the population must be immunized against mumps to provide so-called "herd immunity."[3]

Myth: Measles and mumps are not life-threatening diseases.

Fact: While serious problems resulting from measles and mumps are rare, they do occur. Measles begins with a fever that lasts for a couple of days, followed by a cough, runny nose and conjunctivitis (pink eye). A rash also occurs, starting on the face and upper neck, spreading down the back and trunk, and then extending to the arms and hands, as well as the legs and feet. The rash lasts about five days and fades in the same order it appeared. Between 6 percent and 20 percent of people who get measles will get an ear infection, diarrhea or even pneumonia. One out of 1,000 will develop inflammation of the brain (encephalitis/meningitis), and about one out of 1,000 will die.[6]

Mumps begins with a fever, headache, muscle aches, tiredness and loss of appetite, followed by parotitis (swelling of the salivary glands near the jaw line below the ears), which gives the appearance of "chipmunk cheeks."[7] The most common complication is inflammation of the testicles (orchitis) in males who have reached puberty. Other rare complications include encephalitis/meningitis, inflammation of the ovaries (oophoritis) and/or breasts (mastitis) in females who have reached puberty, and spontaneous abortion, particularly in early pregnancy.[2]

*Measles and mumps are so contagious that any individual who is not immune will probably get the disease if exposed to one of the viruses.*

Myth: Measles and mumps are not that contagious.

Fact: Both measles and mumps are respiratory diseases caused by a virus that normally grows in cells that line the back of the throat and lungs. The viruses, spread through droplets sprayed in the air by breathing, coughing or sneezing, remain active and contagious on infected surfaces for up to two hours. Both are so contagious that any individual who is not immune will probably get the disease if exposed to one of the viruses. Measles is contagious from about four days before the rash

starts to about four days after. Mumps is contagious approximately seven days before the onset of parotitis until eight days after. The CDC recommends isolation of measles patients for four days after the onset of the rash, and isolation of mumps patients for five days after the onset of parotitis.[1,2,6]

**Myth**: A vaccine is not needed to prevent measles and mumps, since these diseases can be easily treated.

**Fact**: Both measles and mumps are vaccine-preventable diseases. The measles-mumps-rubella (MMR) vaccine was invented in 1971 and came into public use in 1977. American schools made the MMR vaccine compulsory in 1990.[4] However, there is no treatment for either disease once it is contracted. The only "treatment" is supportive care, which involves providing relief of symptoms as the body fights the virus. Supportive care can include intravenous (IV) fluids, medications to control fever or pain, antibiotics to treat secondary infections from bacteria, and good nursing care. Clearly, the best option is to prevent the disease with the MMR vaccine.[2,8]

## *All children and most adults need to receive the MMR vaccine.*

Four vaccines are FDA-approved in the U.S., all of which are manufactured by Merck & Co. Inc. The most commonly administered vaccine is the M-M-R II vaccine, a combined measles-mumps-rubella vaccine. Another vaccine, ProQuad, is a combined measles-mumps-rubella-varicella vaccine. (Rubella is a milder form of measles, and varicella is another term for chickenpox.) Over the years, more and more vaccines have been combined to reduce the number of vaccinations administered to a child in one visit. The M-M-R II and ProQuad vaccinations are examples of this. Merck & Co. also markets two other vaccines, Attenuvax to prevent only measles and Mumpsvax to treat only mumps. But, in October 2009, the company announced that, based on input from the Advisory Committee on Immunization Practices (ACIP), professional societies, scientific leaders and customers, it is not going to resume production of these vaccines.[9]

**Myth**: Only children need to be vaccinated against measles and mumps.

**Fact**: All children and most adults need to receive the MMR vaccine. The ACIP recommends routine vaccination for all children, beginning at age 12 to 15 months, with a second dose given between ages 4 and 6. Further, the ACIP recommends that adults born in 1957 or later receive the second dose (the booster) if they lack documentation of vaccination, are a healthcare worker, plan to travel internationally, are exposed to measles in an outbreak setting, were previously vaccinated with a killed measles or mumps vaccine (introduced in the 1960s), or were vaccinated with an unknown type of measles vaccine during the years 1963 through 1967.[10] Complete prescribing information for both the MMR and MMRV vaccines can be found on the packaging instructions at www.fda.gov/ BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm093830.htm.

**Myth**: The MMR vaccine is not effective in preventing the disease.

**Fact**: More than 95 percent of individuals who receive a single dose of MMR vaccine will develop immunity to all three viruses. A second vaccine dose gives immunity to almost all of those who did not respond to the first dose.[6]

**Myth**: The vaccine to prevent measles and mumps causes autism.

**Fact**: The link between autism and the MMR vaccine has been studied extensively. Concerns were first raised just more than a decade ago by British physician Andrew Wakefield, who, based on a study of 12 children, proposed that there was a link between the vaccine and bowel disease and autism. That research, published in an article in *The Lancet* in 1998, has since been widely discredited, and in 2004, *The Lancet* published a retraction submitted by 10 of the 13 original authors of the article, which stated that there was no connection between the MMR vaccine and the bowel disease/autism syndrome. Numerous other national and international studies also have failed to find a connection between MMR vaccination and autism. In 2004, the independent Institute of Medicine (IOM) issued a report that concluded there is no evidence to support an association between the MMR vaccine or thimerosal-containing vaccines and the development of autism. In 2008, there were more than 20 peer-reviewed medical journal articles that refute the connection, and only three that suggest a connection.[10, 11]

*More than 95 percent of individuals who receive a single dose of MMR vaccine will develop immunity to all three viruses.*

The most recent study concerning the MMR vaccine and the increased risk of autism included 96 Polish children ages 2 to 15 who had been diagnosed with autism. Researchers compared each child with two healthy children the same age and sex who had been treated by the same doctor. Some of the children had received the MMR vaccine, while others had not been vaccinated at all or had received a vaccine against measles only. Overall, the study found, children who had received the MMR vaccine actually had a lower risk of autism than their unvaccinated peers. Nor was there any evidence of an increased autism risk with the measles-only vaccine.[12]

**Myth**: The MMR vaccine is too risky because it is associated with increased risk of febrile seizures in children.

**Fact**: The risk of a febrile seizure (a brief, fever-related convulsion that does not lead to epilepsy or seizure disorders) after any measles-containing vaccine is low: less than one febrile seizure per 1,000 injections. However, a recent CDC-funded study that analyzed 459,000 children aged 12 to 23 months from health systems across the U.S. has shown that there is double the risk of a febrile seizure for 1- to 2-year-old children when receiving the four-in-one measles-mumps-rubella-varicella (MMRV) vaccine compared with same-day administration of the separate MMR and varicella (chickenpox) vaccines. The CDC recommends that either vaccine be used for the first dose in 1- to 2-year-olds; however, families with a strong preference should receive separate MMR and varicella vaccines.[13]

## Dispelling the Myths Now

Preventive vaccines that substantially reduce the incidence of contagious diseases such as measles and mumps have been introduced with great success over the past several decades. But, even in countries where vaccination coverage is high, the risk of contracting these diseases is still present. The only way to eradicate them is to have a complete understanding of their seriousness and press for universal vaccination. ❖

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Introducing

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Immune Globulin Intravenous (Human)

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- Seven validated pathogen elimination steps including:
  - 20 nm nanofiltration
  - Dual specific inactivation: pasteurization and solvent detergent
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  - 15.0 log reduction of PPV (PVB19 model)
  - ≥ 13.3 log reduction of EMCV (HAV model)
  - ≥ 6.2 log reduction through 4% PEG precipitation and ≥ 5.5 log reduction through 20 nm nanofiltration of an experimental agent considered a model for the vCJD and CJD agents [3]


**Please see reverse for Important Safety Information and Black Box Warning.**

(1) Data on file, Instituto Grifols, S. A.
(2) Berger M. et al. Efficacy, Pharmacokinetics, Safety and Tolerability of Flebogamma® 10% DIF, a high purity human intravenous immunoglobulin in primary immunodeficiency. J Clin Immunol 2010; 30 (2): 321-9.
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## Important Safety Information

Flebogamma® 10% DIF is a human immune globulin intravenous (IGIV) that is indicated for the treatment of primary immune deficiency (PI), including the humoral immune defect in common variable immunodeficiency, x-linked agammaglobulinemia, severe combined immunodeficiency, and Wiskott - Aldrich syndrome.

**WARNING: ACUTE RENAL DYSFUNCTION AND ACUTE RENAL FAILURE**

- **Use of immune globulin intravenous (IGIV) products, particularly those containing sucrose, has been reported to be associated with renal dysfunction, acute renal failure, osmotic nephropathy, and death (1). Patients at risk of acute renal failure include those with any degree of pre-existing renal insufficiency, diabetes mellitus, advanced age (above 65 years of age), volume depletion, sepsis, paraproteinemia, or those receiving known nephrotoxic drugs** (*see Warnings and Precautions [5.2]*). **Flebogamma® 10% DIF does not contain sucrose.**
- **For patients at risk of renal dysfunction or failure, administer Flebogamma® 10% DIF at the minimum infusion rate practicable** (*see Dosage and Administration [2.3], Warnings and Precautions [5.2]*).

Flebogamma® 10% DIF is contraindicated in patients who have had a history of anaphylactic or severe systemic reactions to the administration of human immune globulin and in IgA deficient patients with antibodies to IgA and a history of hypersensitivity. In case of hypersensitivity, discontinue Flebogamma® 10% DIF infusion immediately and institute appropriate treatment. Medications such as epinephrine should be available for immediate treatment of acute hypersensitivity reactions.

In patients at risk for developing acute renal failure, monitor renal function, including blood urea nitrogen, serum creatinine, and urine output.

Hyperproteinemia, increased serum viscosity, and hyponatremia may occur in patients receiving Flebogamma® 10% DIF therapy.

Thrombotic events may occur during or following treatment with Flebogamma® 10% DIF. Monitor patients at risk for thrombotic events, including those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, coagulation disorders, prolonged periods of immobilization, and known or suspected hyperviscosity.

Aseptic meningitis syndrome (AMS) may occur infrequently with Flebogamma® 10% DIF treatment. AMS may occur more frequently following high doses and/or rapid infusion of IGIV.

Flebogamma® 10% DIF may contain blood group antibodies that can act as hemolysins and induce *in vivo* coating of red blood cells (RBCs) with immunoglobulin, causing a positive direct antiglobulin reaction and hemolysis.

Non-cardiogenic pulmonary edema [Transfusion-Related Acute Lung Injury (TRALI)] may occur in patients following Flebogamma® 10% DIF treatment. If TRALI is suspected, perform appropriate tests for the presence of antineutrophil antibodies and anti-HLA antibodies in both the product and patient serum.

All patients, but especially individuals receiving Flebogamma® 10% DIF for the first time or being restarted on the product after a treatment hiatus of more than 8 weeks, may be at a higher risk for the development of fever, chills, nausea, and vomiting. Careful monitoring of recipients and adherence to recommendations regarding dosage and administration may reduce the risk of these types of events.

Because Flebogamma® 10% DIF is made from human plasma, it may carry a risk of transmitting infectious agents, e.g. viruses, and theoretically, the Creutzfeldt-Jakob (CJD) agent. No cases of transmission of viral diseases or CJD have ever been identified for Flebogamma® 10% DIF.

The most common adverse reactions (reported in ≥ 5% of clinical trial subjects) occurring during or within 72 hours of the end of an infusion were headache, chills, fever, shaking, fatigue, malaise, anxiety, back pain, muscle cramps, abdominal cramps, blood pressure changes, chest tightness, palpitations, tachycardia, nausea, vomiting, cutaneous reactions, wheezing, rash, arthralgia, and edema. The most serious adverse reactions observed with Flebogamma® 10% DIF were back pain, chest discomfort, and headache (2 patients); and chest pain, maculopathy, rigors, tachycardia, bacterial pneumonia, and vasovagal syncope (1 patient).

**Please refer to enclosed Flebogamma® 10% DIF full prescribing information for full prescribing details, including comprehensive adverse event profile and black box warning.**

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GRIFOLS

# Immune Globulin Intravenous (Human)
# Flebogamma® 10% DIF
## For intravenous use only
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## BRIEF SUMMARY
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### INDICATIONS AND USAGE
Flebogamma® 10% DIF is a human immune globulin intravenous (IGIV) that is indicated for the treatment of primary immune deficiency (PI), including the humoral immune defect in common variable immunodeficiency, x-linked agammaglobulinemia, severe combined immunodeficiency, and Wiskott - Aldrich syndrome.

### DOSAGE AND ADMINISTRATION
The recommended dose of Flebogamma® 10% DIF for patients with PI is 300 to 600 mg/kg body weight (3.0 to 6.0 mL/kg), administered every 3 to 4 weeks.

The infusion of Flebogamma® 10% DIF should be initiated at a rate of 0.01 mL/kg body weight/minute (1.0 mg/kg/minute). If there are no adverse drug reactions, the infusion rate for subsequent infusions can be slowly increased to the maximum rate of 0.08 mL/kg/minute (8 mg/kg/minute).

Ensure that patients with pre-existing renal insufficiency are not volume depleted. For patients judged to be at risk for renal dysfunction or thrombotic events, administer Flebogamma® 10% DIF at the minimum infusion rate practicable, and consider discontinuation of administration if renal function deteriorates.

### CONTRAINDICATIONS
Flebogamma® 10% DIF is contraindicated in patients who have had a history of anaphylactic or severe systemic reactions to the administration of human immune globulin and in IgA deficient patients with antibodies to IgA and a history of hypersensitivity.

### WARNINGS AND PRECAUTIONS

**WARNING: ACUTE RENAL DYSFUNCTION AND ACUTE RENAL FAILURE**

- **Use of immune globulin intravenous (IGIV) products, particularly those containing sucrose, has been reported to be associated with renal dysfunction, acute renal failure, osmotic nephropathy, and death (1). Patients at risk of acute renal failure include those with any degree of pre-existing renal insufficiency, diabetes mellitus, advanced age (above 65 years of age), volume depletion, sepsis, paraproteinemia, or those receiving known nephrotoxic drugs** *(see Warnings and Precautions [5.2])*. **Flebogamma® 10% DIF does not contain sucrose.**
- **For patients at risk of renal dysfunction or failure, administer Flebogamma® 10% DIF at the minimum infusion rate practicable** *(see Dosage and Administration [2.3], Warnings and Precautions [5.2])*.

- Weigh the potential risks and benefits of Flebogamma® 10% DIF against those of alternative therapies in all patients for whom Flebogamma® 10% DIF is being considered.
- Before prescribing Flebogamma® 10% DIF, the physician should discuss risks and benefits of its use with patients.

#### Hypersensitivity
Severe hypersensitivity reactions may occur. In case of hypersensitivity, discontinue Flebogamma® 10% DIF infusion immediately and institute appropriate treatment. Medications such as epinephrine should be available for immediate treatment of acute hypersensitivity reactions.

#### Renal Dysfunction/Failure
Periodic monitoring of renal function and urine output is particularly important in patients judged to be at increased risk of developing acute renal failure. Assess renal function, including measurement of blood urea nitrogen (BUN) and serum creatinine, before the initial infusion of Flebogamma® 10% DIF and at appropriate intervals thereafter. If renal function deteriorates, consider discontinue use of Flebogamma® 10% DIF.

In patients who are at risk of developing renal dysfunction because of pre-existing renal insufficiency or predisposition to acute renal failure, administer Flebogamma® 10% DIF at the minimum rate of infusion practicable.

#### Hyperproteinemia
Hyperproteinemia, increased serum viscosity, and hyponatremia may occur in patients receiving Flebogamma® 10% DIF therapy. It is clinically critical to distinguish true hyponatremia from a pseudo-hyponatremia that is temporally or causally related to hyperproteinemia with concomitant decreased calculated serum osmolarity or elevated osmolar gap, because treatment aimed at decreasing serum free water in patients with pseudohyponatremia may lead to volume depletion, a further increase in serum viscosity and a higher risk of thrombotic events.

Thrombotic events may occur during or following treatment with Flebogamma® 10% DIF. Monitor patients at risk for thrombotic events, including those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, coagulation disorders, prolonged periods of immobilization, and known or suspected hyperviscosity.

Consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies. For patients judged to be at risk of developing thrombotic events, administer Flebogamma® 10% DIF at the minimum rate of infusion practicable *(see Dosage and Administration [2.3])*.

#### Aseptic Meningitis Syndrome (AMS)
AMS may occur infrequently with Flebogamma® 10% DIF treatment. Discontinuation of IGIV treatment has resulted in remission of AMS within several days without sequelae (3-4).

AMS is characterized by the following signs and symptoms: severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, nausea, and vomiting (*see Patient Counseling Information* [17]). Cerebrospinal fluid (CSF) studies frequently reveal pleocytosis up to several thousand cells per cubic millimeter, predominantly from the granulocytic series and elevated protein levels up to several hundred mg/dL, but negative culture results. Conduct a thorough neurological examination to patients exhibiting such signs and symptoms, including CSF studies, to rule out other causes of meningitis.
AMS may occur more frequently following high doses (2 g/kg) and/or rapid infusion of IGIV.

#### Hemolysis
Flebogamma® 10% DIF may contain blood group antibodies that can act as hemolysins and induce *in vivo* coating of red blood cells (RBCs) with immunoglobulin, causing a positive direct antiglobulin reaction and hemolysis (5-6). Delayed hemolytic anemia may develop subsequent to Flebogamma® 10% DIF therapy due to enhanced RBC sequestration (7), and acute hemolysis, consistent with intravascular hemolysis, has been reported.

Monitor patients for clinical signs and symptoms of hemolysis. If signs and/or symptoms of hemolysis are present after Flebogamma® 10% DIF infusion, perform appropriate confirmatory laboratory testing (*see Patient Counseling Information* [17]).

#### Transfusion-Related Acute Lung Injury (TRALI)
Non-cardiogenic pulmonary edema may occur in patients following Flebogamma® 10% DIF treatment (11). TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever. Symptoms typically appear within 1 to 6 hours following treatment.

Monitor patients for pulmonary adverse reactions (*see Patient Counseling Information* [17]). If TRALI is suspected, perform appropriate tests for the presence of anti-neutrophil antibodies and anti-HLA antibodies in both the product and patient serum. TRALI may be managed using oxygen therapy with adequate ventilatory support.

#### Infusion Reactions
All patients, but especially individuals receiving Flebogamma® 10% DIF for the first time or being restarted on the product after a treatment hiatus of more than 8 weeks, may be at a higher risk for the development of fever, chills, nausea, and vomiting. Careful monitoring of recipients and adherence to recommendations regarding dosage and administration may reduce the risk of these types of events (*see Dosage and Administration [2.3]*).

#### Transmissible Infectious Agents
Because Flebogamma® 10% DIF is made from human plasma, it may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically, the Creutzfeldt-Jakob (CJD) agent. No cases of transmission of viral diseases or CJD have ever been identified for Flebogamma 10% DIF. All infections suspected by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Grifols Biologicals at 1-888-474-3657. Before prescribing or administering Flebogamma® 10% DIF, the physician should discuss the risks and benefits of its use with the patient (*see Patient Counseling Information* [17]).

#### Monitoring: Laboratory Tests
- Periodic monitoring of renal function and urine output is particularly important in patients judged to be at increased risk of developing acute renal failure. Assess renal function, including measurement of BUN and serum creatinine, before the initial infusion of Flebogamma® 10% DIF and at appropriate intervals thereafter.
- Consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies, because of the potentially increased risk of thrombosis.
- If signs and/or symptoms of hemolysis are present after an infusion of Flebogamma® 10% DIF, perform appropriate laboratory testing for confirmation.
- If TRALI is suspected, perform appropriate tests for the presence of anti-neutrophil antibodies and anti-HLA antibodies in both the product and patient's serum.

#### Interference with Laboratory Tests
After infusion of IgG, the transitory rise of the various passively transferred antibodies in the patient's blood may yield positive serological testing results, with the potential for misleading interpretation. Passive transmission of antibodies to erythrocyte antigens (e.g., A, B, and D) may cause a positive direct or indirect antiglobulin (Coombs') test.

#### Adverse Reactions
The most common adverse reactions (reported in ≥ 5% of clinical trial subjects) occurring during or within 72 hours of the end of an infusion were headache, chills, fever, shaking, fatigue, malaise, anxiety, back pain, muscle cramps, abdominal cramps, blood pressure changes, chest tightness, palpitations, tachycardia, nausea, vomiting, cutaneous reactions, wheezing, rash, arthralgia, and edema. The most serious adverse reactions observed with Flebogamma® 10% DIF were back pain, chest discomfort, and headache (2 patients); and chest pain, maculopathy, rigors, tachycardia, bacterial pneumonia, and vasovagal syncope (1 patient).

#### 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.*

In a multicenter, open-label, non-randomized, historically controlled clinical study, 46 individuals with primary humoral immunodeficiency received infusion doses of Flebogamma 10% DIF at 300 to 600 mg/kg body weight every 3 weeks (mean dose 469 mg/kg) or 4 weeks (mean dose 457 mg/kg) for up to 12 months (*see Clinical Studies [14.1]*). Routine pre-medication was not allowed. Of the 601 infusions administered, 130 infusions (22%) in 21 (47%) subjects were given pre-medications (antipyretic, antihistamine, or antiemetic agent) because of experience with consecutive infusion-related adverse reactions.

One subject experienced four serious adverse events (AEs, bacterial pneumonia, subcutaneous abscess and two episodes of cellulitis) and withdrew from the study. Two other subjects who participated in the study discontinued prematurely due to AEs (back pain/chest pain/headache; and chills/tachycardia). Three subjects experienced four serious non-related AEs (drug abuse/depression; hernia; and sinusitis).

Forty-five (98%) subjects experienced at least 1 AE irrespective of the relationship with the product, and these subjects reported a total of 723 AEs. Thirty-eight subjects (83%) had an adverse reaction at some time during the study that was considered product-related. Of the 21 subjects receiving pre-medications, 12 (57%) subjects reported adverse reactions during or within 72 hours after the infusion in 48 of the 130 pre-medicated infusions (37%).

**Table 2. Treatment-related Adverse Events Occurring in ≥ 5% of Subjects with PI during a Flebogamma® 10% DIF Infusion or within 72 Hours after the End of an infusion**

| Adverse Event | Subjects (%) [N=46] | Infusions (%) [N=601] |
|---|---|---|
| Headache | 24 (52%) | 67 (11%) |
| Rigors | 17 (37%) | 37 (6%) |
| Pyrexia | 15 (33%) | 27 (5%) |
| Tachycardia | 10 (22%) | 18 (3%) |
| Hypotension | 9 (20%) | 11 (2%) |

| Adverse Event | Subjects (%) [N=46] | Infusions (%) [N=601] |
|---|---|---|
| Back pain | 8 (17%) | 27 (5%) |
| Myalgia | 8 (17%) | 17 (3%) |
| Body temperature increased | 4 (9%) | 6 (1%) |
| Nausea | 4 (9%) | 6 (1%) |
| Pain | 4 (9%) | 8 (1%) |
| Chest discomfort | 3 (7%) | 4 (1%) |
| Chest pain | 3 (7%) | 5 (1%) |
| Infusion site reaction | 3 (7%) | 4 (1%) |
| Pain in extremity | 3 (7%) | 3 (0.5%) |

The total number of adverse events occurring during or within 72 hours after the end of an infusion, *irrespective of causality*, was 359, excluding non-serious infections.

Table 3 lists the AEs that occurred in greater than 5% of subjects during a Flebogamma® 10% DIF infusion or within 72 hours after the end of an infusion, *irrespective of causality.*

**Table 3. Adverse Events Occurring in ≥ 5% of Subjects with PI during a Flebogamma® 10% DIF Infusion or within 72 Hours after the End of an infusion, *Irrespective of Causality***

| Adverse Event | Subjects (%) [N=46] | Infusions (%) [N=601] |
|---|---|---|
| Headache | 28 (61%) | 71 (12%) |
| Pyrexia | 17 (37%) | 27 (5%) |
| Rigors | 17 (37%) | 37 (6%) |
| Back pain | 13 (28%) | 29 (5%) |
| Cough or Productive cough | 12 (26%) | 5 (1%) |
| Nausea | 12 (26%) | 8 (1%) |
| Hypotension | 10 (22%) | 13 (2%) |
| Tachycardia | 10 (22%) | 19 (3%) |
| Myalgia | 9 (20%) | 17 (3%) |
| Diarrhea | 8 (17%) | 2 (0.3%) |
| Infusion site reaction | 8 (17%) | 8 (1%) |
| Pharyngolaryngeal pain | 7 (15%) | 3 (1%) |
| Nasal congestion | 7 (15%) | 2 (0.3%) |
| Postnasal drip | 7 (15%) | 4 (1%) |
| Arthralgia | 6 (13%) | 2 (0.3%) |
| Conjunctivitis | 6 (13%) | 2 (0.3%) |
| Pain | 6 (13%) | 10 (2%) |
| Vomiting | 6 (13%) | 0 (0%) |
| Dizziness | 5 (11%) | 3 (1%) |
| Fatigue | 5 (11%) | 1 (0.2%) |
| Urinary tract infection | 5 (11%) | 4 (1%) |
| Chest pain | 5 (11%) | 4 (1%) |
| Ear pain | 5 (11%) | 1 (0.2%) |
| Pain in extremity | 5 (11%) | 2 (0.3%) |
| Dyspnea | 5 (11%) | 0 (0%) |
| Rhinorrhea | 4 (9%) | 1 (0.2%) |
| Wheezing | 4 (9%) | 4 (1%) |
| Body temperature increased | 4 (9%) | 6 (1%) |
| Neck pain | 4 (9%) | 2 (0.3%) |
| Sinus pain | 4 (9%) | 1 (0.2%) |
| Chest discomfort | 4 (9%) | 4 (1%) |
| Crackles lung | 4 (9%) | 2 (0.3%) |
| Abdominal pain | 3 (7%) | 2 (0.3%) |
| Dyspepsia | 3 (7%) | 1 (0.2%) |
| Toothache | 3 (7%) | 0 (0%) |
| Gastroesophageal reflux disease | 3 (7%) | 0 (0%) |
| Lymphadenopathy | 3 (7%) | 3 (1%) |
| Respiratory tract congestion | 3 (7%) | 0 (0%) |
| Fall | 3 (7%) | 1 (0.2%) |
| Hypertension | 3 (7%) | 4 (1%) |

In this study, the upper bound of the 1-sided 95% confidence interval for the proportion of Flebogamma® 10% DIF infusions associated with one or more AEs was 37.8% (total infusions: 208; actual proportions: 34.6%). The average percent of infusions with AEs during or within 72 hours after the end of an infusion for each individual subject was 36.7% and the upper bound of the 1-sided 95% confidence interval was 43.9%.

AE reporting was based upon a clinical protocol precluding pre-medication against AEs. Pre-medication could be utilized only after the first 2 infusions only in those patients that exhibited adverse events.

Forty-three of the 46 subjects enrolled in this study had a negative Coombs test at baseline. Of these 43 subjects, 10 (23.3%) developed a positive Coombs test at some time during the study. However, no subjects showed evidence of hemolytic anemia.

### Post-marketing Experience

*Because adverse reactions are reported voluntarily post-approval from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to product exposure. The following adverse reactions have been identified during post approval use of intravenous immune globulins, including Flebogamma 5% (see References [15]).*

| | |
|---|---|
| **Infusion reactions** | Hypersensitivity (e.g., anaphylaxis), headache, diarrhea, tachycardia, fever, fatigue, dizziness, malaise, chills, flushing, urticaria or other skin reactions, wheezing or other chest discomfort, nausea, vomiting, rigors, back pain, myalgia, arthralgia, and changes in blood pressure |
| **Renal** | Acute renal dysfunction/failure, osmotic nephropathy |
| **Respiratory** | Apnea, Acute Respiratory Distress Syndrome (ARDS), Transfusion-Related Acute Lung Injury (TRALI), cyanosis, hypoxemia, pulmonary edema, dyspnea, bronchospasm |
| **Cardiovascular** | Cardiac arrest, thromboembolism, vascular collapse, hypotension |
| **Neurological** | Coma, loss of consciousness, seizures, tremor, aseptic meningitis syndrome |
| **Integumentary** | Stevens-Johnson Syndrome, epidermolysis, erythema multiformae, dermatitis (e.g., bullous dermatitis) |
| **Hematologic** | Pancytopenia, leukopenia, hemolysis, positive direct antiglobulin (Coombs) test |
| **Musculoskeletal** | Back pain |
| **Gastrointestinal** | Hepatic dysfunction, abdominal pain |
| **General/Body as a Whole** | Pyrexia, rigors |

## DRUG INTERACTIONS

Passive transfer of antibodies may transiently impair the immune response to live attenuated virus vaccines such as measles, mumps, and rubella. Inform the immunizing physician of recent therapy with Flebogama® 10% DIF so that appropriate measures may be taken (*see Patient Counseling Information* [17]).

## USE IN SPECIFIC POPULATIONS

### Pregnancy

Pregnancy Category C. Animal reproduction studies have not been performed with Flebogamma® 10% DIF. It is also not known whether Flebogamma® 10% DIF can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Flebogamma® 10% DIF should be given to a pregnant woman only if clearly needed. Immunoglobulins cross the placenta from maternal circulation increasingly after 30 weeks of gestation.

### Nursing Mothers

Use of Flebogamma® 10% DIF has not been evaluated in nursing mothers.

### Pediatric Use

Three (3) pediatric patients with primary humoral immunodeficiency (two between the ages of 6 and 10, and one 16 year old) were included in the clinical evaluation of Flebogamma® 10% DIF. This number of subjects is too small to establish safety and efficacy in the pediatric population (*see Clinical Studies [14]*).

### Geriatric Use

Use caution when administering Flebogamma® 10% DIF to patients over 65 years of age who are judged to be at increased risk for developing certain adverse reactions such as thromboembolic events and acute renal failure (*see Boxed Warning, Warnings and Precautions [5.2]*). Do not exceed the recommended dose, and infuse Flebogamma® 10% DIF at the minimum infusion rate practicable.

One (1) patient with primary humoral immunodeficiency at or over the age of 65 was included within the clinical evaluation of Flebogamma® 10% DIF. This number of geriatric patients was too small for separate evaluation from the younger patients for safety or efficacy (*see Clinical Studies [14]*).

## HOW SUPPLIED/STORAGE AND HANDLING

Flebogamma® 10% DIF is supplied in single-use, individually laser etched vials containing the labeled amount of functionally active IgG.

The following presentations of Flebogamma® 10% DIF are available:

| NDC Number | Fill Size | Grams Protein |
|---|---|---|
| 61953-0005-1 | 50 mL | 5g |
| 61953-0005-2 | 100 mL | 10g |
| 61953-0005-3 | 200 mL | 20g |

Each vial has an integral suspension band and a label with two peel-off strips showing the product name and lot number.

**DO NOT FREEZE.**

When stored at room temperature (up to 25 ºC [77 ºF]), Flebogamma® 10% DIF is stable for up to 24 months, as indicated by the expiration date printed on the outer carton and container label.

Keep Flebogamma® 10% DIF in its original carton to protect it from light.

**Manufactured by INSTITUTO GRIFOLS, S.A.**
**Barcelona - Spain**
**U.S. License No. 1181**
**Distributed by GRIFOLS BIOLOGICALS Inc.**
**Los Angeles - CA 90032**
**Phone: 888-GRIFOLS (888-474-3657)**

# A Heritage of Visionary Leadership

"My father and what he stood for should be a lesson to us. He died an old man but always lived as a young one. He demanded of himself before demanding of others. He made sacrifices himself before asking them of others. He believed that the right to live in the world entailed the duty to make the greatest effort to work for the world and for humanity."

— Dr. Victor Grifols Lucas' words at his father's funeral, Dr. Jose Antonio Grifols Roig, co-founder of Grifols.

BY TRUDIE MITSCHANG

**AS A GLOBAL** corporation, Grifols has firmly established itself as a standard bearer within the plasma therapies industry. In fact, the name Grifols has become synonymous with safety and efficacy; the company has established patented manufacturing methods and protocols that exceed safety requirements in almost every area of the supply chain. At the helm of this inspirational organization, Victor Grifols is keenly aware of his personal and corporate responsibility as a standard bearer; the company was founded by his grandfather and three generations of the family have since led the company. Most notably, every vial of product produced displays not just his company's name, but also his family's legacy.

"My grandfather started this company in 1940 at the end of the Spanish Civil War and the beginning of World War II; these were difficult times, but it did not stop him from succeeding," says Victor Grifols. "Because of his vision and leadership, I am able to sit here today and oversee a global organization with over 6,000 employees. The spirit my grandfather and later my uncle and my father put into the company is still being transmitted to our employees today."

At Grifols, the company's mission statement is both simple and profound: What matters most: people. And people include, in order of importance to the company: donors, patients, employees and shareholders. It is a philosophy that is interwoven throughout the company culture, impacting everything from the way products are manufactured, to the daily interactions between management and employees.

## Promoting Relationship Leadership

Passionate about leading by example, Victor Grifols is as comfortable discussing day-to-day operations in the company lunch room as he is addressing a room full of shareholders. "I spend about 80 percent of my time with employees — many have been with the company for 30 years or more," he says. "In our company, we know each other for many years, and our people are very loyal and knowledgeable. As a leader, I believe you should never ask your people to do something you won't do yourself. For example, when addressing operating expenses, if you ask employees to fly coach, you fly coach as well. That's part of leading by example."

With headquarters in Barcelona, Spain, and a newly constructed twin manufacturing plant in Los Angeles, Calif., the Grifols group of companies sustains a full and active research and development program that has obtained more than 300 patents in over 30 countries for plasma derivatives alone, and some 200 official product registrations in more than 50 countries. Grifols serves healthcare professionals and patients in over 90 countries around the world.

A desire for excellence led Grifols to found its own engineering company that has custom-designed machines and facilities for both Grifols and other biopharmaceutical companies around the world. Additionally, Grifols' plasma screening processes were one of the first approved by the Food and Drug Administration (FDA) to use nucleic acid testing (NAT) methods — a process that not only detects a whole virus, but will also detect non-infectious virus fragments. "Our FDA-approved manufacturing facilities are among the most modern in existence," says Victor Grifols.

## A History of Innovation

Grifols' contributions to the plasma therapies industry are numerous, dating back to 1943 with the production of the first freeze-dried plasma in continental Europe, and to 1951 when Victor Grifols' uncle, Dr. Jose A. Grifols Lucas, presented a landmark study that described a method for returning red blood cells to the donor, leading to the development of plasmapheresis, a technique now used worldwide. This process permits people to donate plasma more frequently, thereby making more plasma medicines available to patients who need them. Plasma medicines are used to treat a variety of rare and often life-threatening diseases. But scientific discoveries aside, it has been the consistent emphasis on product efficacy and safety that has made Grifols an industry leader.

"My grandfather and father were always obsessed with the safety of the products. You can make a beautiful, chemically perfect plasma derivative with all the right formulations, but because we are dealing with a biological material, that same derivative can be infectious," says Victor Grifols. "Quality is extremely important and it goes hand-in-hand with safety. Our company has always been devoted to both quality and safety."

"My father believed it was his duty to humanity to make the greatest possible contribution to the field for which society had prepared him. Anything else would have been dishonest."

— Dr. J.A. Grifols Roig, founder, Grifols

When it comes to research and development, Grifols is constantly leading initiatives that will have a positive impact on the customers it serves. Currently, the company has embarked on a multi-national medical study to analyze the effects of plasmapheresis, albumin and gamma globulin on the advancement of Alzheimer's disease. Early results are promising. "We hope to prove these products, used in combination, can be an efficacious and affordable treatment to help delay the advancement of Alzheimer's, a disease that is growing at epidemic rates," says Victor Grifols.

## Spreading the Message of "Good Blood"

The plasma therapies industry came under fire three decades ago when a new and deadly virus contaminated the blood supply, infecting thousands of patients. At the time, acquired immunodeficiency syndrome (AIDS) was an unknown disease, and therefore HIV antibodies were not yet a part of the blood supply screening process. Unfortunately, that incident still has negative ramifications today, with some still questioning whether the industry has done enough to ensure the safety and purity within the plasma supply chain.

"Even 30 years later, we are still paying the price for the AIDS outbreak in the 1980s," says Victor Grifols. "It is something we still have to address, and as a company, we address it by establishing and maintaining the most stringent safety and testing standards in the industry. We can say with certainty that the blood and plasma supply chain is much safer today than it was 50 years ago. But, this is an evolving field. We can also say with certainty that the field will be safer 50 years from today. Safety is a never-ending pursuit."

Part of promoting safety within the company and the industry, according to Grifols, is prioritizing education and training for employees. Grifols formed the Academy of Plasmapheresis in Glendale, Ariz., as part of its long history of continuous improvement and commitment to education. The Grifols Academy offers company employees a program of standardized education in plasma sciences, with an emphasis on the fundamentals of quality and ethics. It also provides life-long learning to participants, develops competencies and instills the sense of Grifols' identity and values in its teammates.

"Our campus in Arizona encompasses a mock plasma center for training, a real plasma center for donating and a teaching academy," explains Victor Grifols. By understanding the stringent guidelines and steps involved in bringing a blood plasma product to market, everyone involved can take greater ownership of the critical role they play. All of this results in a safer product for the patient." ❖

**TRUDIE MITSCHANG** *is a staff writer for* BioSupply Trends Quarterly *magazine.*

# A New Kind of Normal

For patients like Curtis Pease who depend on immune globulin infusions, finding the right infusion setting can help streamline treatment and improve quality of life.

by TRUDIE MITSCHANG

**IMAGINE TAKING YOUR** infant to the pediatrician for a routine mumps vaccine, only to have him contract the very disease you were attempting to avoid. What if your next child inexplicably stopped walking and standing following a polio vaccine? It sounds surreal, but that's exactly what happened to Joanne Pease when her son Curtis and his younger brother Jeff were just babies. What Joanne didn't know at the time is that both boys had an undiagnosed immune disorder that made them vulnerable to infection from normally safe live vaccines. Joanne later testified at Senate hearings to have live vaccines discontinued, although legislative changes did little to ease the blow for the Pease family, whose third son, Mitchell, was born with the same immune disorder. Thankfully, Mitchell was diagnosed early and able to avoid any additional health complications. Still, for this resilient clan, learning to live with chronic illness and its subsequent treatments has become a way of life — a new kind of normal.

## Transitioning from Hospital to Homecare

The Pease siblings suffer from X-linked agammaglobulinemia (XLA), a congenital immunodeficiency that occurs in about one in 250,000 males and is inherited in an X-linked recessive pattern. Females carrying the mutation pass it to their children. But, thanks to advances in medicine, many primary immune deficiency diseases like this one

can be successfully treated. The mainstay of therapy is intravenous immunoglobulin (IVIG). "When I was young, I was sick all the time and nobody knew why," recalls Curtis. "Finally, when I was $2^1/_2$, I was sent to Children's Hospital and accurately diagnosed. Once I started IVIG, my health improved dramatically within a matter of weeks."

People with primary immune deficiencies like the Pease brothers suffer from chronic infections because their bodies lack certain kinds of antibodies. These important cells, also called immunoglobulins, help the body destroy germs that cause infections. IVIG temporarily replaces the immunoglobulins, or antibodies, that many immune-deficient patients are missing.

Curtis and his brothers depend on IVIG to maintain their health and quality of life. But where, when and how often they infuse has evolved over the years, based on their ages and preferences. Obviously, living with a chronic illness is never easy, and figuring out which treatment protocols are most effective is influenced by many factors, including insurance coverage, access to care and lifestyle of the patients involved. As young children, Curtis and his brothers received one shot of intramuscular IG every 10 days, but as they grew older, they began IVIG treatments that were administered in a hospital setting every three weeks.

The hospital infusions were effective but tiresome for active young boys, and Curtis' father, Dan, decided to learn how to perform the infusions himself so that they could begin administering the treatments at home. Home infusions, whether performed by a nurse or family member, offer the patient privacy and comfort not available in a hospital setting, as well as the ability to plan infusion times around their own schedule. With three chronically ill boys to care for, the convenience of infusing at home was obviously appealing to the Pease family.

"When Dad first learned to do infusions, the nurse taught him at the hospital and then came out to the house for a week and let him practice on fake arms," says Curtis. "The nurse supervised him for a while, but he got the hang of it very quickly; today, he's better at finding a vein than most nurses at the hospital!"

## From IVIG to Self-Administered Care

As the oldest of the Pease siblings, Curtis felt the pull of independence first. While he appreciated having his father administer the weekly infusions, he began desiring a greater level of freedom and control over his own healthcare. That's when he made the decision to try subcutaneous immune globulin (SCIG) infusions.

The SCIG infusion, which is readily self-administered once a patient has been trained, offers an alternative infusion method to IVIG. It is also administered more frequently than IVIG. As a result, trough levels for SCIG patients often stay more even than those of IVIG patients. Curtis' brothers complete their IVIG infusions in about 45 minutes every two weeks, whereas an SCIG infusion for Curtis takes up to two hours weekly. Curtis feels the autonomy and increased feeling of wellness he gets from this method outweigh the time differential. "The bottom line for me is that I hate needles, and while subcutaneous takes a bit longer, you can't miss and there are no veins involved. For me, it is the best treatment option," Curtis says.

Curtis and his two brothers suffer from X-linked agammaglobulinemia (XLA), a congenital immunodeficiency.

part of homecare for family members, or, as in Curtis' case, they can administer their own infusions.

Paying for immune globulin treatments can be prohibitive, and the Pease family has been fortunate that a series of job changes has kept them continually insured for the infusions they depend upon, while helping them avoid the insurance cap chronically ill patients dread. "I made it my business to learn as much as possible about insurance and to fight for our rights," says Joanne.

*"The bottom line for me is that I hate needles, and while subcutaneous takes a bit longer, you can't miss and there are no veins involved. For me, it is the best treatment option," Curtis says.*

Proponents of SCIG say the infusion method is relatively inexpensive to administer and can be performed by people without formal medical training (no need to worry about small air bubbles in a syringe, for example). People can perform SCIG infusions at home as "When we wanted my husband to administer the boys' infusions at home, for example, we had to request a case manager and convince our insurance company that they would save a lot of money by allowing us to make that change. In the end, everyone benefited."

## Thankful for Every Day

At age 27, Curtis has been living with chronic illness for more than 25 years. Because it's all he's known, he says he feels pretty "normal" most of the time. He makes his living as a cabinet refinisher and shares a house with his younger brother Jeff. And like a lot of young men, when he's not working he enjoys sports and riding ATVs. "The only time I really notice that I'm sick is at the end of a workday when I get very tired," Curtis says. "I've accomplished most of the things I've wanted to do because I refuse to let the disease limit me. I just wish I had more energy and stamina. Maybe future treatments will be able to address that issue."

Although many patients like Curtis find encouragement through various support groups, Curtis says he's had no need for one; his immediate family provides all the empathy, understanding and support he needs. "I've had this disease my whole life and so have my brothers. Jeff has polio on top of XLA, but he's in remission and doing just fine. We are all fighters, and we don't let this diagnosis get us down. At the same time, we've learned not to take anything for granted. We have a lot to be thankful for." ❖

**TRUDIE MITSCHANG** *is a staff writer for* BioSupply Trends Quarterly.

# The Mysterious Tale of von Willebrand Disease

Finally, there are more options for a unique bleeding disorder.

by KEITH BERMAN, MPH, MBA

**THE INTRIGUE BEGAN** in 1924, when a physician named Erik von Willebrand described curious bleeding problems in 23 of 66 family members living on a remote island in the gulf between Sweden and the doctor's home country of Finland. The symptoms he observed most commonly included bleeding from the gums, severe nosebleeds and excessive bleeding following tooth extraction, trivial wounds and menstruation.

But unlike hemophilia, which is sex-linked and thus affects males almost exclusively, these unusual bleeding episodes equally affected both males and females in that large Finnish family. When Dr. von Willebrand measured their whole blood coagulation time, it was normal. So, too, were their platelet counts. Yet, strangely, those who were affected had clearly prolonged bleeding times. He decided to call it "hereditary pseudohemophilia." Soon afterward, others started to report patients with similar intermittent bleeding symptoms.

It would take nearly 50 years for scientists to finally identify the defective protein that accounts for the mysterious disorder that was renamed von Willebrand disease (VWD). This unusual protein, once called "factor VIII-related antigen" because it complexes with and stabilizes the critical factor VIII clotting protein, was formally named von Willebrand factor (VWF) in the 1970s.

## Von Willebrand Factor: The Elephant in the Plasma

Remarkably, the elusive VWF also turns out to be the largest protein found in human plasma. But VWF is unique for yet another reason: It's actually made up of a series of repeating subunits called "multimers." Depending on the number of subunits, these multimers circulate in blood in sizes ranging from around 500 to 20,000 kilodaltons. The largest subgroup of these VWF proteins is appropriately called "high molecular weight multimers," or HMWMs.[1]

Today, we appreciate that VWF not only protects factor VIII (FVIII) against inactivation and clearance, but HMWMs in particular are essential for platelet plug formation by adhering to and then diverting circulating platelets to sites of vascular injury.[1]

By the 1980s, specialized assays that measure the *amount* of VWF present in plasma (VWF:Ag) and its *function* (ristocetin cofactor activity, or VWF:RCo) helped hematologists definitively diagnose the cause of many cases of abnormal bleeding that couldn't otherwise be explained.

What this testing also revealed came as another surprise: VWD is by far the most frequent inherited bleeding disorder, with an estimated prevalence of roughly 1 percent in the general population. The vast majority of these individuals remain undiagnosed either because they're generally asymptomatic or because their bleeding symptoms are too minor to prompt them to seek medical attention.

Only about one in 10,000 persons with VWD experiences significant recurring bleeding problems that lead to a diagnosis. Around 70 percent to 80 percent of these patients with "Type 1" disease have decreased levels of structurally normal VWF; most respond to intranasal or intravenous treatment with desmopressin, a synthetic hormone that promotes the release of FVIII and VWF from tissue storage sites.

An estimated one person per million in the U.S. population has the rare, severe "Type 3" form of the disease.[2] These individuals have virtually undetectable amounts of VWF. Without the VWF that serves as its natural stabilizer, very low levels of FVIII — a few percent of normal — may be present. The result is frequent serious bleeding problems that may involve the joints and soft tissues, as well as classical mucosal bleeding.

Most of the remaining 20 percent to 30 percent of persons diagnosed with VWD fall into one of several "Type 2" categories, resulting from a host of gene mutations that cause functional deficiencies in their circulating VWF. Simply boosting the level of their dysfunctional VWF with desmopressin usually won't adequately control bleeds in most of these individuals. Their own VWF isn't up to the task of protecting FVIII from proteolysis or attracting and binding platelets at the site of injury.

These Type 2 and 3 patients, as well as Type 1 patients who fail to adequately respond to desmopressin, need replacement therapy with fully functional VWF.

*Only about one in 10,000 persons with VWD experiences significant recurring bleeding problems that lead to a diagnosis.*

## Treating VWD: The Early Days

For many years, physicians had to rely on plasma transfusions to deliver a therapeutic amount of VWF. But, with only about one international unit (IU) of FVIII:C and one IU of VWF:RCo activity per milliliter, large volumes and repeated transfusions often were required to elevate circulating VWF to protective levels.

In the 1960s, multiple units of cryoprecipitate — with 80 IU to 120 IU of FVIII:C and VWF:RCo in each 15 milliliter bag — could be safely administered with much less risk of complications caused by fluid volume overload. Unfortunately, each unit of cryoprecipitate comes with a small but finite risk of infection and serious transfusion reactions. The VWF content also varies with each bag prepared from individual blood donors, creating the risk of inappropriate dosing.

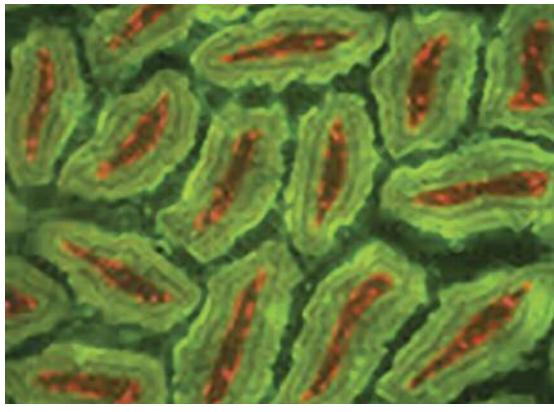
What was really needed was a VWF-containing product that could be dosed with very small volumes, with a better safety profile and consistent VWF content.

## Humate-P: The First Product Labeled for VWD

Originally approved by the Food and Drug Administration (FDA) as a FVIII replacement therapy for hemophilia A, CSL Behring's Humate-P (Antihemophilic Factor/von Willebrand Factor Complex [Human]) was additionally approved in 1999 for the treatment of spontaneous and trauma-induced bleeding in severe VWD and mild and moderate VWD where desmopressin is known or suspected to be inadequate.

For the first time, patients could be dosed with a standardized product labeled with its VWF:RCo potency, with monitoring and additional infusions as needed to maintain a therapeutic level. In contrast with most other available plasma-based FVIII concentrates, the process used to manufacture Humate-P retains VWF and preserves the HMWM subfraction that is so important for platelet adhesion and hemostatic efficacy.

In pivotal U.S. and European studies evaluating VWD patients undergoing a range of major and minor surgeries, Humate-P provided excellent or good hemostatic efficacy in well over 90 percent of subjects. More than 25 percent of patients enrolled in both trials had severe Type 3 disease.



Interestingly, while the physiologic ratio of VWF:RCo to FVIII:C is 1:1, Humate-P contains 2.4 IU of VWF:RCo for every IU of FVIII:C. But, regardless of this ratio, recommended dosing of all products is based on VWF activity expressed as VWF:RCo.

## Alphanate: A Second VWF Option

Grifols' Alphanate (Antihemophilic Factor/von Willebrand Factor Complex [Human]) is another product originally indicated for use in hemophilia A. The particular type of affinity column chromatography used to purify Alphanate retains the entire VWF:FVIII complex, in contrast to other affinity-purified products that capture only the FVIII protein.

In 2007, Alphanate was FDA-approved for surgical and/or invasive procedures in patients with VWD in whom desmopressin is ineffective or contraindicated. Like Humate-P, Alphanate was shown in pivotal trials to be effective in preventing excessive bleeding in well over 90 percent of subjects undergoing a variety of

surgical procedures.

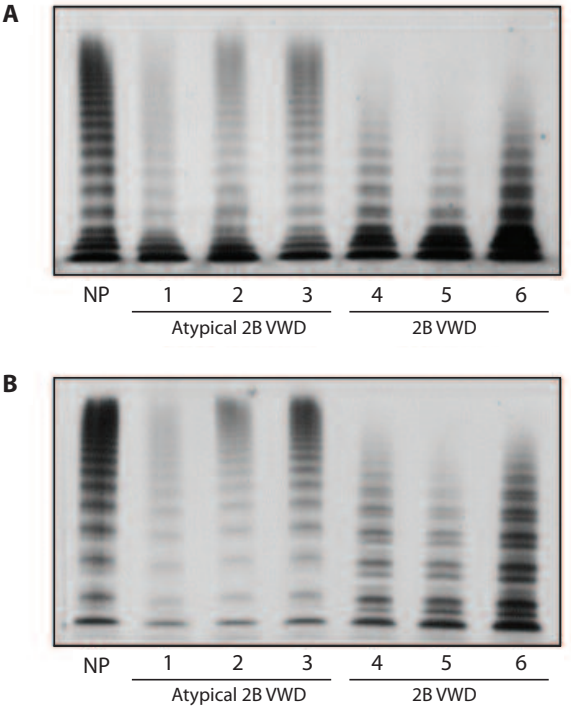
Alphanate is not indicated for treatment of spontaneous bleeding in VWD or for use in patients with severe (Type 3) VWD undergoing major surgery. But this shortcoming in the product labeling may soon be rectified if Alphanate is shown to effectively prevent excessive surgical bleeding in a U.S. trial involving 15 subjects with Type 3 VWD. That trial was scheduled to complete enrollment in December 2010.

While the labeling for Alphanate guarantees that it contains not less than 0.4 IU of VWF:RCo per IU of FVIII:C, the VWF:RCo potency is actually similar to or modestly higher than FVIII:C in most production lots. Like Humate-P, both VWF:RCo and FVIII:C potency values for Alphanate are indicated on the vial label.

## Wilate: Designed Specifically for VWD

Protein chemists at Octapharma have gone to great lengths to develop a purification process that preserves the structural integrity of VWF and to create a physiologic balance in the content of VWF:RCo. The result is Wilate (Antihemophilic Factor/von Willebrand Factor Complex [Human]), which received FDA approval in December 2009 for the treatment of spontaneous and trauma-induced bleeding episodes in patients with severe VWD, as well as patients with mild or moderate VWD in whom the use of desmopressin is known or suspected to be ineffective or contraindicated. Wilate is not indicated for prevention of excessive bleeding during and after surgery in VWD patients, but Octapharma is currently organizing a clinical trial designed to address this label limitation.

The Wilate process applies gentle size exclusion chromatography to try to minimize degradation of VWF proteins, including the fragile HMWMs. While specific purification steps vary between the three preparations, there are currently no available data to clearly document important differences in HMWM content or integrity. But, if measurable differences actually did exist, would they translate into hemostasis efficacy differences? Answering this hypothetical question would require large, carefully designed crossover or head-to-head trials.




*Plasma VWF multimer pattern observed in atypical type 2B and 2B VWD patients compared with normal plasma (NP). Electrophoresis was performed using 1.2% **(A)** and 2.2% **(B)** agarose gel containing 0.1% SDS. Multimers were detected using a $^{125}$I-labeled anti-VWF antibodies. Large VWF multimers are at the top, small multimers at the bottom. *Source: Casonato, A.* ***Reduced survival of type 2B von Willebrand factor, irrespective of large multimer representation or thrombocytopenia.*** Haematologica. *2010 Aug;95(8):1366-72. Epub 2010 Mar 19.*

*Nearly nine decades after Dr. von Willebrand first alerted the world about a strange disease he discovered on a small archipelago, physicians now have a set of easy diagnostic tools to identify those who have it.*

With whatever VWF:FVIII concentrate that is chosen, the physician needs to vigilantly monitor circulating levels of both VWF and FVIII. The goal is to elevate and maintain the patient's plasma VWF:RCo activity to protective levels during the bleeding risk period, while avoiding raising the FVIII level too high above its normal range. Repeated administration of VWF:FVIII without adequate monitoring can result in "supranormal" FVIII levels. A FVIII level of 200 percent of normal or higher may be associated with a risk of venous thromboembolism (VTE).[3]

## Promising Advances for VWD on the Horizon

Aside from some Type 3 patients with recurrent joint or gastrointestinal (GI) tract hemorrhages, it is uncommon to prescribe a VWF:FVIII prophylaxis regimen to prevent spontaneous bleeds

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In VWF/FVIII replacement therapy...

# An Evidence-Based Perspective

**Humate-P delivers results, patient after patient, treatment after treatment, decade after decade**

## Preferred

Most prescribed VWF/FVIII concentrate treatment[1,2]

- Extensive clinical experience[1,2]
- Long record of success[1,2]

## Proven

Reliable hemostatic control for all VWD types across many clinical applications[3-6]

- Episodic/on-demand therapy[3,4]
- Perioperative and postoperative therapy[5,6]

## Purified

Integrated Safety System[1]

- Designed to maximize virus removal/inactivation while maintaining biological integrity[1]

Built on data **HUMATE-P®**
Antihemophilic Factor/von Willebrand Factor Complex (Human)

### Important Safety Information

Humate-P is indicated for treatment and prevention of bleeding in adult patients with hemophilia A (classical hemophilia). Humate-P is also indicated in adult and pediatric patients with von Willebrand disease (VWD) for (1) treatment of spontaneous and trauma-induced bleeding episodes, and (2) prevention of excessive bleeding during and after surgery. This applies to patients with severe VWD, and patients with mild and moderate VWD for whom use of desmopressin is known or suspected to be inadequate. Humate-P is not indicated for the prophylaxis of spontaneous bleeding episodes.

Humate-P is contraindicated in individuals with a history of anaphylactic or severe systemic response to antihemophilic factor or von Willebrand factor preparations.

Monitor for intravascular hemolysis and decreasing hematocrit values in patients with A, B, and AB blood groups who are receiving large or frequent doses. Also monitor VWF:RCo and FVIII levels in VWD patients, especially those undergoing surgery.

Thromboembolic events have been reported in VWD patients receiving coagulation factor replacement. Caution should be exercised and antithrombotic measures considered, particularly in patients with known risk factors for thrombosis.

Humate-P is derived from human plasma. The risk of transmission of infectious agents, including viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent, cannot be completely eliminated.

In patients receiving Humate-P in clinical studies for treatment of VWD, the most commonly reported adverse reactions observed by >5% of subjects are allergic-anaphylactic reactions, including urticaria, chest tightness, rash, pruritus, and edema. For patients undergoing surgery, the most common adverse reactions are postoperative wound and injection-site bleeding, and epistaxis.

**Please see brief summary of full Prescribing Information on reverse.**

**References: 1.** Data on file. CSL Behring LLC. **2.** Berntorp E, Archey W, Auerswald G, et al. A systematic overview of the first pasteurised VWF/FVIII medicinal product, Haemate P/Humate-P: history and clinical performance. *Eur J Haematol.* 2008;80(Suppl 70):3-35. **3.** Gill JC, Ewenstein BM, Thompson AR, Mueller-Velten G, Schwartz BA, for the Humate-P Study Group. Successful treatment of urgent bleeding in von Willebrand disease with factor VIII/VWF concentrate (Humate-P): use of the ristocetin cofactor assay (VWF:RCo) to measure potency and to guide therapy. *Haemophilia.* 2003;9(6):688-695. **4.** Lillicrap D, Poon M-C, Walker I, Xie F, Schwartz BA, and members of the Association of Hemophilia Clinic Directors of Canada. Efficacy and safety of the factor VIII/von Willebrand factor concentrate, Haemate-P/Humate-P: ristocetin cofactor unit dosing in patients with von Willebrand disease. *Thromb Haemost.* 2002;87(2):224-230. **5.** Lethagen S, Kyrle PA, Castaman G, Haertel S, Mannucci PM, for the Haemate P Surgical Study Group. von Willebrand factor/factor VIII concentrate (Haemate P) dosing based on pharmacokinetics: a prospective multicenter trial in elective surgery. *J Thromb Haemost.* 2007;5(7):1420-1430. **6.** Thompson AR, Gill JC, Ewenstein BM, Mueller-Velten G, Schwartz BA, for the Humate-P Study Group. Successful treatment for patients with von Willebrand disease undergoing urgent surgery using factor VIII/VWF concentrate (Humate-P). *Haemophilia.* 2004;10(1):42-51.


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**BRIEF SUMMARY OF PRESCRIBING INFORMATION**

# Humate-P®
# Antihemophilic Factor/von Willebrand Factor Complex (Human)

**Before prescribing, please consult full prescribing information, a brief summary of which follows. Some text and references refer to full prescribing information.**

## 1 INDICATIONS AND USAGE

### 1.1 Hemophilia A

Humate-P, Antihemophilic Factor/von Willebrand Factor Complex (Human), is indicated for treatment and prevention of bleeding in adults with hemophilia A (classical hemophilia).

### 1.2 Von Willebrand Disease (VWD)

Humate-P is also indicated in adult and pediatric patients with von Willebrand disease (VWD) for:

(1) treatment of spontaneous and trauma-induced bleeding episodes, and

(2) prevention of excessive bleeding during and after surgery. This applies to patients with severe VWD as well as patients with mild to moderate VWD where use of desmopressin (DDAVP) is known or suspected to be inadequate.

Controlled clinical trials to evaluate the safety and efficacy of prophylactic dosing with Humate-P to prevent spontaneous bleeding have not been conducted in VWD subjects *(see Clinical Studies [14])*.

## 3 DOSAGE FORMS AND STRENGTHS

Humate-P is a sterile, lyophilized powder for intravenous administration. Each vial of Humate-P contains the labeled amount of VWF:RCo and FVIII activity expressed in International Units (IU). The average ratio of VWF:RCo to FVIII is 2.4:1.

Approximate potencies are shown below; check each carton/vial for the actual potency prior to reconstitution:

| VWF:RCo/vial | FVIII/vial | Diluent |
|---|---|---|
| 600 IU | 250 IU | 5 mL |
| 1200 IU | 500 IU | 10 mL |
| 2400 IU | 1000 IU | 15 mL |

IU = International Units.

## 4 CONTRAINDICATIONS

Humate-P is contraindicated in individuals who have had an anaphylactic or severe systemic reaction to antihemophilic factor or von Willebrand factor preparations.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Thromboembolic Events (VWD Patients)

Thromboembolic events have been reported in VWD patients receiving Antihemophilic Factor/von Willebrand Factor Complex replacement therapy, especially in the setting of known risk factors for thrombosis.[3,4] Early reports indicate a higher incidence may occur in females. Endogenous high levels of FVIII have also been associated with thrombosis, but no causal relationship has been established. Exercise caution and consider antithrombotic measures in all at-risk VWD patients who are receiving coagulation factor replacement therapy.

### 5.2 Monitoring for Intravascular Hemolysis

Humate-P contains blood group isoagglutinins (anti-A and anti-B). When doses are very large or need to be repeated frequently (for example, when inhibitors are present or when pre- and post-surgical care is involved), monitor patients of blood groups A, B, and AB for signs of intravascular hemolysis and decreasing hematocrit values and treat appropriately.

### 5.3 Monitoring VWF:RCo and FVIII Levels

Monitor the VWF:RCo and FVIII levels of VWD patients receiving Humate-P using standard coagulation tests, especially in cases of surgery. It is advisable to monitor trough VWF:RCo and FVIII:C levels at least once a day in order to adjust the dosage of Humate-P as needed to avoid excessive accumulation of coagulation factors (*see Dosage and Administration [2.2, 2.3]*).

### 5.4 Transmission of Infectious Agents

Humate-P is made from human plasma. Products made from human plasma may contain infectious agents (e.g., viruses and theoretically, the Creutzfeldt-Jakob disease [CJD] agent) that can cause disease (*see Description [11] and Patient Counseling Information [17.1]*). The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and/or removing certain viruses during manufacturing (*see Description [11.1] for virus reduction measures*).

Despite these measures, such products can still potentially transmit disease. There is also the possibility that unknown infectious agents may be present in such products. Thus the risk of transmission of infectious agents cannot be eliminated completely. **Report all infections thought by a physician possibly to have been transmitted by this product to CSL Behring Pharmacovigilance at 1-866-915-6958 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.**

Some viruses, such as Parvovirus B19 virus (B19V) or hepatitis A (HAV), are particularly difficult to remove or inactivate. B19V may most seriously affect pregnant women and immune-compromised individuals.

Although the overwhelming number of B19V and HAV cases are community acquired, reports of these infections have been associated with the use of some plasma-derived products. Therefore, physicians should be alert to the potential symptoms of B19V and HAV infections (*see Patient Counseling Information [17.1]*).

Symptoms of B19V may include low-grade fever, rash, arthralgias, and transient symmetric, nondestructive arthritis. Diagnosis is often established by measuring B19V-specific IgM and IgG antibodies. Symptoms of HAV include low-grade fever, anorexia, nausea, vomiting, fatigue, and jaundice. A diagnosis may be established by measuring specific IgM antibodies.

Physicians should strongly consider administration of hepatitis A and hepatitis B vaccines to individuals receiving plasma derivatives. Potential risks and benefits of vaccination should be weighed by the physician and discussed with the patient.

## 6 ADVERSE REACTIONS

The most serious adverse reaction observed in patients receiving Humate-P is anaphylaxis. Thromboembolic events have also been observed in patients receiving Humate-P for the treatment of VWD (*see Warnings and Precautions [5.1]*). Reports of thromboembolic events in VWD patients with other thrombotic risk factors receiving coagulation factor replacement therapy have been obtained from spontaneous reports, published literature, and a European clinical study. In some cases, inhibitors to coagulation factors may occur. However, no inhibitor formation was observed in any of the clinical studies.

In patients receiving Humate-P in clinical studies for treatment of VWD, the most commonly reported adverse reactions observed by >5% of subjects are allergic-anaphylactic reactions (including urticaria, chest tightness, rash, pruritus, and edema. For patients undergoing surgery, the most common adverse reactions are postoperative wound and injection-site bleeding, and epistaxis.

### 6.1 Clinical Studies Experience

*Because clinical studies are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared to rates in other clinical trials and may not reflect the rates observed in practice.*

Treatment of Bleeding Episodes in VWD

Allergic symptoms, including allergic reaction, urticaria, chest tightness, rash, pruritus, and edema, were reported in 6 of 97 (6%) subjects in a Canadian retrospective study (*see Clinical Studies [14.1]*). Four of 97 (4%) subjects experienced seven adverse events that were considered to have a possible or probable relationship to Humate-P. These included chills, phlebitis, vasodilation, paresthesia, pruritus, rash, and urticaria. All were mild in intensity with the exception of a moderate case of pruritus.

In a prospective, open-label safety and efficacy study of Humate-P in VWD subjects with serious life- or limb-threatening bleeding or undergoing emergency surgery, seven of 71 (10%) subjects experienced nine adverse reactions. These were one occurrence each of mild vasodilation and mild pruritis; two occurrences of mild paresthesia; and one occurrence each of moderate peripheral edema and extremity pain and severe pseudothrombocytopenia (platelet clumping with a false low reading). Humate-P was discontinued in the subject who experienced the peripheral edema and extremity pain.

Prevention of Excessive Bleeding During and After Surgery in VWD

Among the 63 VWD subjects who received Humate-P for prevention of excessive bleeding during and after surgery, including one subject who underwent colonoscopy without the planned polypectomy, the most common adverse events were postoperative hemorrhage (35 events in 19 subjects with five subjects experiencing bleeding at up to three different sites), postoperative nausea (15 subjects), and postoperative pain (11 subjects). Table 5 presents the postoperative hemorrhagic adverse events.

**Table 5: Hemorrhagic Adverse Events in 63 Surgical Subjects**

| Adverse Event | Surgical Procedure Category | Number of Subjects/ Events | Onset* (Number of Events) | | Severity (Number of Events) | | |
|---|---|---|---|---|---|---|---|
| | | | On | Post | Mild | Mod | Severe |
| Wound/injection site bleeding | Major | 8/11 | 7 | 4 | 9 | – | 2 |
| | Minor | 2/2 | 2 | – | 1 | 1 | – |
| | Oral | 2/6 | – | 6 | 3 | 3 | – |
| Epistaxis | Major | 4/4 | 2 | 2 | 3 | 1 | – |
| | Minor | 1/1 | 1 | – | 1 | – | – |
| Cerebral hemorrhage/ subdural hematoma | Major | 1/2 | 2† | – | – | 2 | – |
| Gastrointestinal bleeding | Major | 1/3 | 3‡ | – | – | 2 | 1 |
| Menorrhagia | Major | 1/1 | 1§ | – | – | 1 | – |
| Groin bleed | Oral | 1/1 | – | 1 | 1 | – | – |

| Adverse Event | Surgical Procedure Category | Number of Subjects/ Events | Onset* (Number of Events) | | Severity (Number of Events) | | |
|---|---|---|---|---|---|---|---|
| Ear bleed | Major | 1/1 | 1 | – | 1 | – | – |
| Hemoptysis | Major | 1/1 | 1 | – | 1 | – | – |
| Hematuria | Major | 1/1 | 1 | – | 1 | – | – |
| Shoulder bleed | Major | 1/1 | 1 | – | 1 | – | – |

* On = on-therapy; onset while receiving Humate-P or within 1 day of completing Humate-P administration. Post = post-therapy; onset at least one day after completing Humate-P administration.
† Reported as serious adverse events following intracranial surgery.
‡ Two of these events were reported as serious adverse events following gastrojejunal bypass.
§ Reported as a serious adverse event requiring hysterectomy following hysteroscopy and dilation and curettage.

Table 6 lists the non-hemorrhagic adverse events reported in at least two subjects, regardless of causality, and the adverse events that were possibly related to Humate-P. Pulmonary embolus considered possibly related to Humate-P occurred in one elderly subject who underwent bilateral knee replacement.

**Table 6: Non-Hemorrhagic and Possibly Related Adverse Events in 63 Surgical Subjects**

| Body System | Adverse Event (AE) | Number of Subjects With an AE Possibly Related to Humate-P | Number of Subjects With an AE Regardless of Causality* |
|---|---|---|---|
| Body as a whole | Pain | – | 11 |
| | Fever | – | 4 |
| | Abdominal pain | – | 3 |
| | Infection | – | 3 |
| | Surgery | – | 3 |
| | Back pain | – | 2 |
| | Facial edema | – | 2 |
| Cardiovascular | Chest pain | – | 3 |
| | Pulmonary embolus† | 1 | 1 |
| | Thrombophlebitis† | 1 | 1 |
| Digestive | Nausea | 1 | 15 |
| | Constipation | – | 7 |
| | Vomiting | 1 | 3 |
| | Sore throat | – | 2 |
| Hemic and lymphatic system | Anemia / decreased hemoglobin | – | 2 |
| Metabolic/ nutritional | Increased SGPT | 1 | 1 |
| Nervous | Dizziness | 1 | 5 |
| | Headache | 1 | 4 |
| | Increased sweating | – | 3 |
| | Insomnia | – | 2 |
| Skin and appendages | Pruritus | – | 3 |
| | Rash | 1 | 1 |
| Urogenital | Urinary retention | – | 4 |
| | Urinary tract infection | – | 2 |

* Events occurring in two or more subjects.
† Events occurring in separate subjects.

Eight subjects experienced 10 postoperative serious adverse events: one with subdural hematoma and intracerebral bleeding following intracranial surgery related to an underlying cerebrovascular abnormality; one with two occurrences of gastrointestinal bleeding following gastrojejunal bypass; and one each with sepsis, facial edema, infection, menorrhagia requiring hysterectomy following hysteroscopy and dilation and curettage, pyelonephritis, and pulmonary embolus.

### 6.2 Postmarketing Experience

*The following adverse reactions have been identified during postapproval use of Humate-P. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to Humate-P exposure.*

Adverse reactions reported in patients receiving Humate-P for treatment of VWD or hemophilia A are allergic-anaphylactic reactions (including urticaria, chest tightness, rash, pruritus, edema, and shock), development of inhibitors to FVIII, and hemolysis. Additional adverse reactions reported for VWD are thromboembolic complications, chills and fever, and hypervolemia.

## 7 DRUG INTERACTIONS

None reported.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Pregnancy Category C. Animal reproduction studies have not been conducted with Humate-P. It is also not known whether Humate-P can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Humate-P should be given to a pregnant woman only if clearly needed.

### 8.2 Labor and Delivery

It is not known whether Humate-P can cause harm to the mother or the fetus when administered during labor and delivery. Humate-P should be given during labor and delivery only if clearly needed.

### 8.3 Nursing Mothers

It is not know whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Humate-P is administered to a nursing woman.

### 8.4 Pediatric Use

Hemophilia A

Adequate and well-controlled studies with long-term evaluation of joint damage have not been done in pediatric subjects. Joint damage may result from suboptimal treatment of hemarthroses.

VWD

The safety and effectiveness of Humate-P for the treatment of VWD was demonstrated in 26 pediatric subjects, including infants, children, and adolescents, but have not been evaluated in neonates. The safety of Humate-P for the prevention of excessive bleeding during and after surgery was demonstrated in eight pediatric subjects (ages 3 to 15) with VWD. Of the 34 pediatric subjects studied for either treatment of bleeding episodes in VWD or prevention of excessive bleeding during and after surgery, four were infants (1 month to under 2 years of age), 23 were children (2 through 12 years), and seven were adolescents (13 through 15 years).

As in adults, pediatric patients should be dosed based on body weight (kg) (*see Dosage and Administration [2.2, 2.3]*).

### 8.5 Geriatric Use

Clinical studies of Humate-P did not include sufficient numbers of subjects 65 years of age and older to determine whether they respond differently from younger subjects. As for all patients, dosing for geriatric patients should be appropriate to their overall situation.

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New Photo or violet hue

in persons with VWD. Administration of VWF:FVIII concentrates is generally limited to surgical coverage or treatment of spontaneous bleeding episodes. But, as we've learned with hemophilia patients suffering from recurrent joint or soft tissue hemorrhage, it's far from ideal to simply allow persons with VWD to experience repeated GI, joint, menstrual or other potentially serious bleeds.

Recognizing the proven efficacy of prophylactic care in many hemophilia patients, in 2007 Swedish and U.S. investigators initiated the von Willebrand Disease International Prophylaxis Study (VIP). This ambitious clinical trial is currently recruiting subjects to evaluate escalating dosages of VWF:FVIII products — including Humate-P, Alphanate and Wilate — with the goal of reducing bleeding episodes in patients who meet certain eligibility criteria. If results from this largest-ever 200-subject VWD treatment trial prove compelling, individualized prophylaxis with VWF:FVIII products could become the new standard of care for thousands of people living with VWD.


A little farther out on the horizon, the first fully recombinant VWF:FVIII product is now being tested by Baxter Healthcare in a Phase I safety and tolerability trial. This extraordinary feat of genetic engineering comes to clinic 25 years after the VWF gene was cloned and the protein was successfully sequenced.

If shown to be safe and effective, Baxter's novel rVWF:rFVIII could set a new theoretical safety standard relating to risk of viral transmission. Of course, it's difficult to take issue with the viral safety record for plasma-based VWF:FVIII and FVIII-only concentrates; there have been no reports of viral transmission involving any licensed product since 1986.

Nearly nine decades after Dr. von Willebrand first alerted the world about a strange disease he discovered on a small archipelago, physicians now have a set of easy diagnostic tools to identify those who have it. Just as important, they also now have several very effective treatment options for people affected with VWD — with the promise of still better ones to come. ❖

*Recognizing the proven efficacy of prophylactic care in many hemophilia patients, in 2007 Swedish and U.S. investigators initiated the von Willebrand Disease International Prophylaxis Study (VIP).*

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1. Furlan, M. Von Willebrand factor: molecular size and functional activity. *Annals of Hematology*, 1996;72:341-8.
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**KEITH BERMAN**, *MPH, MBA, is the founder of Health Research Associates, providing reimbursement consulting, business development and market research services to biopharmaceutical, blood product and medical device manufacturers and suppliers. Berman previously worked in product development, reimbursement development and market research roles at Baxter Healthcare, Siemens Medical and MiniMed Technologies (now a Medtronic division). Since 1989, he has also served as editor of* International Blood/Plasma News, *a blood products industry newsletter.*

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GRIFOLS

# BioResearch

Summaries of up-to-date clinical research published in medical journals internationally.

## Intradermal Flu Vaccine at Reduced Dose Elicits Similar Response as Full-Dose IM Injection in Older Adults

U.S. investigators randomized 257 healthy community-dwelling adults ages 65 and older to receive one of four different trivalent inactivated influenza vaccine regimens:

- standard dose (15 mcg of each of three hemagglutinin vaccine antigens in 0.5 mL) by intramuscular (IM) injection;
- reduced-dose vaccine (9 mcg in 0.3 mL) by IM injection;
- reduced-dose vaccine (9 mcg in 0.3 mL) by intradermal (ID) injection; or
- two split reduced-dose ID injections (4.5 mcg in 0.15 mL each).

The respective seroprotection rates were 65.6 percent, 57.8 percent, 68.9 percent and 67.2 percent against the A/H1N1 strain; 76.6 percent, 75.0 percent, 75.4 percent and 75.0 percent against the A/H3N2 strain; and 26.6 percent, 17.2 percent, 16.4 percent and 25.0 percent against the B strain. Subsequent full-dose IM vaccination of participants randomized to reduced-dose vaccine by either the IM or ID routes failed to improve seroprotection rates. Local reactions, including redness, swelling and itching, were significantly more frequent among recipients of ID injections.

The authors concluded that delivery of influenza vaccine at 60 percent of the standard dose by either IM or ID route elicited antibody responses generally similar to full-dose IM vaccination among healthy elderly persons.

*Chi, RC, Rock, MT, Neuzil, KM. Immunogenicity and safety of intradermal influenza vaccination in healthy older adults.* Clinical Infectious Diseases, *2010 May 15; 50(10):1331-8.*

## In Vitro IVIG Anti-Complement Activity Points to Potential Mechanism of Action in MMN

While the pathogenesis of multifocal motor neuropathy (MMN) has yet to be established, anti-GM1 IgM antibodies are often identified in these patients, suggesting an autoimmune process involving complement. Intravenous immunoglobulin (IVIG) is a first-line treatment for MMN, but its mechanism of action is unknown.

Japanese investigators designed in vitro experiments to test 1) whether anti-GM1 IgM antibodies found in sera of MMN patients mediate complement activation that may trigger nerve cell damage, and 2) whether IVIG inhibits this complement activation.

Sera with reactive IgM antibodies against GM1 were obtained from 13 patients with MMN. Anti-GM1 IgM antibodies mediated deposition of four key complement proteins — C1q, C4b, C3b and C5b-9 — in GM1-coated microtiter plate wells. The deposition of complement was highly correlated with anti-GM1 IgM antibody titer. Introduction of IVIG into the wells dose-dependently reduced the deposition of these complement components.

These results, together with earlier data, suggest that IgM-induced, complement-mediated nodal injury of peripheral motor nerves generates conduction block and accounts for muscle weakness, according to the authors. The ability of IVIG to inhibit this type of complement activation *in vitro* suggests that *in vivo* it may act to reduce membrane attack complex-mediated damage, leading to improved muscle strength.

*Yuki, N, Watanabe, H, Nakajima, T, et al. IVIG blocks complement deposition mediated by anti-GM1 antibodies in multifocal motor neuropathy.* Journal of Neurology, Neurosurgery & Psychiatry, *2010 Jul 28 [Epub ahead of print].*

## A Higher IgG Trough Level May Reduce Risk of Pneumonia in PIDD Patients on IVIG Therapy

The pre-infusion trough levels of IgG required to minimize infection risk in IVIG-treated patients with primary immunodeficiency disease (PIDD) remains uncertain. To address this question, U.S. investigators identified and quantitatively combined all available studies evaluating IgG trough levels and pneumonia incidence in PIDD patients receiving IVIG replacement therapy for hypogammaglobulinemia.

Seventeen studies published between 1982 and 2009, totaling 676 patients and 2,127 patient-years of follow-up, were included in this meta-analysis. Pneumonia incidence declined by 27 percent with each 100 mg/dL increment in trough IgG (incidence rate ratio, 0.726; 95 percent confidence interval, 0.658-0.801). The incidence of pneumonia with maintenance of a 500 mg/dL IgG trough level (0.113 cases per patient-year) was fivefold higher than a trough level of 1,000 mg/dL (0.023 cases per patient-year).

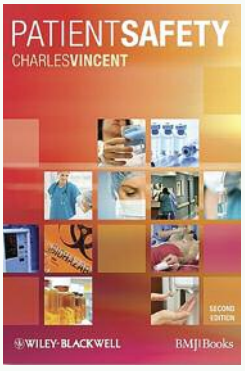
While a 500 mg/dL emerged from early studies as an appropriate initial minimum IgG trough target, subsequent clinical evidence has prompted recommendations for higher targets, generally to levels near or above the lower limit of IgG concentration (about 700 mg/dL) in normal healthy adults. The authors concluded that their findings offer evidence that pneumonia risk can be progressively reduced by higher trough IgG levels up to at least 1,000 mg/dL.

*Orange, JS, Grossman, WJ, Navickis, RJ, et al. Impact of trough IgG on pneumonia incidence in primary immunodeficiency: A meta-analysis of clinical studies.* Clinical Immunology, *2010 Oct;137(1):21-30.*

**KEITH BERMAN**, *MPH, MBA, is the founder of Health Research Associates and editor of* International Blood Plasma News.

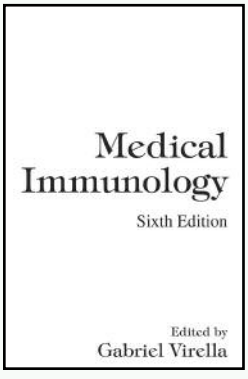
# BioResources

Recently released resources for the biopharmaceuticals marketplace.




**Patient Safety (2nd ed.)**
*Author: Charles Vincent*

Published in July, this second edition of *Patient Safety* places a stronger practical emphasis on what can be done to improve the safety of healthcare by describing how patient safety evolved, the research that underpins the issue, key conceptual issues that have to be addressed, and the practical action needed to reduce error and harm. Chapters include the evolution of patient safety; the hazards of healthcare; human error and systems thinking; design, technology and standardization; clinical interventions and process improvement; and the journey to safety. It is intended for all healthcare professionals.
www.wileyblackwell.com

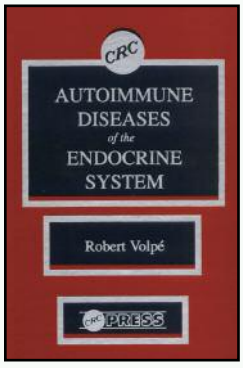



**Medical Immunology (6th ed.)**
*Author: Gabriel Virella*

This sixth edition of *Medical Immunology* has an abundance of illustrations, diagrams and algorithms for a reader-friendly review of critical material. It is fully updated and revised to update and explore current diagnostic and clinical applications of immunology, as well as strategies for the modulation of immune response and the treatment of hypersensitivity, autoimmune response and immune deficiency conditions. Organized into four sections that review clinical applications, methodological advances, immunological diseases and cutting-edge interventions, this book leads readers through state-of-the-sciences technologies and demonstrates their implementation in day-to-day clinical practice.
informahealthcare.com

**Statins: The World Market 2010-2025**
**Stem Cells: The Hype and the Hope 2010-2025**
**Breast Cancer Drugs: World Market Prospects 2010-2025**
**World Generic Drug Market Outlook 2010-2025**
*Author: VisionGain*

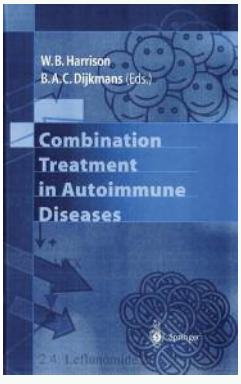
These reports are comprehensive analyses of the prospects for diseases and drugs from 2010 to 2025, including unique sales forecasts, market share analyses, discussions of research and development pipeline developments, and analyses of commercial drivers and restraints, including SWOT analyses. There are comprehensive tables and figures, as well as interviews with experts.
www.visiongain.com




**Autoimmune Diseases of the Endocrine System**

*Author: Robert Volpe*

*Autoimmune Diseases of the Endocrine System* is a comprehensive, easy-to-read discussion of the organ-specific autoimmune endocrine diseases, emphasizing new contributions and trends for research and management. It begins with a brief chapter introducing the general principles of immunology, followed by discussions covering topics such as immunogenetics and animal models and how they can be applied toward interpreting human autoimmune endocrine diseases, autoimmune thyroid diseases, insulin-dependent diabetes mellitus hypophysitis, and Addison's disease. The book also discusses future trends toward gaining an understanding of these disorders and possible therapeutic principles.
www.crcpress.com




**Combination Treatment in Autoimmune Diseases**
*Editors: W.B. Harrison and B.A.C. Dijkmans*

*Combination Treatment in Autoimmune Diseases* consists of contributions from the most prominent experts in this field. In the first section, the general principles of combination treatment are discussed, from rationale and methodology to benefits of risks in daily practice. The second section concerns specific diseases. And, the last section is devoted to the future. The editors hope to come back with an issue that will look back and determine whether the experts' predictions have come true.
www.springerpub.com

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# BioProducts

## Noninvasive Hemoglobin Test

Masimo's portable, palm-sized Pronto-7 is a 2.5 transcutaneous anemia monitoring system that offers noninvasive, quick and accurate spot-check testing of hemoglobin (SpHb), SpO2, pulse rate and perfusion index. It is designed to screen populations for insufficient levels of hemoglobin in the blood and to carry out diagnosis of severe anemia. The device helps clinicians by facilitating timely diagnosis and treatment decisions and reduces the need to wait for lab results. It is easy to use, decreases the risk of accidental needle sticks and exposure to blood-borne pathogens, and requires no lab consumables or waste disposal.
Masimo, (949) 297-7000, www.masimo.com/pronto-7/index.htm

## Automated Prescription System

PROmanager-Rx is a fully automated system for storing and dispensing manufacturer-packaged unit-dose oral solids. Barcode-driven robotics scan every dose twice, providing the greatest possible safety and accuracy, as well as simplifying tasks such as managing returns, expired meds and overall inventory. The system works by receiving patient orders electronically from the Connect-Rx system, which reads the patient barcode label, associates the patient's information with the Connect-Rx order, rotates the storage carousel to the position where the medication is stored, scans and selects the medication, and then delivers it either to a cassette on the bin conveyor or to a front chute, where the dispense is verified by barcode ID scanning. The system also automatically restocks itself using barcoded restocking trays. The operator fills the restocking trays with unit-dose medications, loads the trays into the restock drawer and notifies the system that the medications are ready for restocking. It scans each tray to determine the inventory expiration date; scans each medication to verify medication identification and to assign a storage location; and picks up and places the medication into its assigned location.


McKesson Corp., (800) 594-9145, www.promanager-rx.com

## Anti-Counterfeiting Technology

TruTags are edible spectral microtags that can be used to authenticate and identify a wide range of goods. In medicine, the tags can be mixed into the coating of a tablet or capsule and tracked at the dosage level. They are made of the highest purity silica, rendering them biologically inert and edible. TruTags can be made either in irregular, random shapes within a specified size range, or in regular shapes, such as discs or squares, via an optional photolithographic process. And while their visual clarity and small size challenge the limits of human vision, each tag contains a custom-manufactured spectral signature chosen from over one trillion possibilities. The product's unique "spectral barcodes" can be measured via a portable spectrometer-based optical reader, then quickly verified against other cryptographic information printed on the package so that the item and packaging are authenticated together; tampering with either the package or the contents would flag a security violation. Additionally, each tag can reference a label in a secure database, where additional information about the item can be stored as desired, such as a link to a another e-pedigree track and trace system.

Tru Tag Technologies, (808) 949-2208, www.trutags.com

## Medical News Online Portal

MediConnect Global's myMediConnect personal health record and consumer health portal now offers its users access to selected Harvard Medical School consumer health content within the portal. Users will have complimentary access to the monthly *Harvard Health Letter* newsletter, as well as access to more than 200 Harvard Reviews of Health News postings per year, which feature key insights from school physicians who cover trending healthcare news headlines and provide trenchant analysis, together with advice on how consumers should react to current issues being discussed in the popular media.
MediConnect Global Inc., (800) 489-8710, www.mediconnect.net

# BioDashboard

CALCULATOR

## IVIG Reimbursement Calculator

**Medicare Reimbursement Rates**
Rates are effective January 1 through March 31, 2011.

| Product | Manufacturer | HCPCS | Hospital Outpatient ASP+5% (per gram) | Physician Office ASP+6% (per gram) |
|---|---|---|---|---|
| CARIMUNE NF | CSL Behring | J1566 | $61.970 | $62.560 |
| FLEBOGAMMA 5% & 10% DIF | Grifols | J1572 | $70.808 | $71.482 |
| GAMMAGARD LIQUID | Baxter BioScience | J1569 | $76.410 | $77.138 |
| GAMMAGARD S/D | Baxter BioScience | J1566 | $61.970 | $62.560 |
| GAMMAPLEX | Bio Products Laboratory Limited | J3590* | $74.586** | $74.586 |
| GAMUNEX-C | Talecris Biotherapeutics | J1561 | $74.562 | $75.272 |
| OCTAGAM | Octapharma | J1568 | $71.390 | $72.070 |
| PRIVIGEN | CSL Behring | J1459 | $69.506 | $70.168 |

*J3490, Unclassified drugs; J3590, Unclassified biologics
**ASP + 6% (Medicare pass-through drug)

Calculate your reimbursement online at www.FFFenterprises.com.

REFERENCE TABLES

## IG Reference Table

| Product | Size | Manufacturer | Indications |
|---|---|---|---|
| CARIMUNE NF (Lyophilized) | 3 g, 6 g, 12 g | CSL Behring | PIDD, ITP |
| FLEBOGAMMA 5% & 10% DIF (Liquid) | 0.5 g, 2.5 g, 5 g, 10 g, 20 g | Grifols | PIDD |
| GAMMAGARD LIQUID (10%) | 1 g, 2.5 g, 5 g, 10 g, 20 g | Baxter BioScience | PIDD |
| GAMMAGARD S/D (Lyophilized, 5% or 10%) | 2.5 g, 5 g, 10 g | Baxter BioScience | PIDD, ITP, CLL, KD |
| GAMMAPLEX (Liquid, 5%) | 5 g, 10 g | Bio Products Laboratory Limited | PIDD |
| GAMUNEX-C (Liquid, 10%) | 1 g, 2.5 g, 5 g, 10 g, 20 g | Talecris Biotherapeutics | PIDD, ITP, CIDP |
| GAMUNEX-C (Liquid, 10%, SCIG) | 1 g, 2.5 g, 5 g, 10 g, 20 g | Talecris Biotherapeutics | PIDD |
| HIZENTRA (Liquid, 20%, SCIG) | 5 mL, 10 mL, 20 mL | CSL Behring | PIDD |
| OCTAGAM (Liquid, 5%) | 1 g, 2.5 g, 5 g, 10 g, 25 g | Octapharma | PIDD |
| PRIVIGEN (Liquid, 10%) | 5 g, 10 g, 20 g | CSL Behring | PIDD, ITP |
| VIVAGLOBIN (Liquid, 16%, SCIG) | 3 mL, 10 mL, 20 mL | CSL Behring | PIDD |

**CIDP** Chronic inflammatory demyelinating polyneuropathy
**CLL** Chronic lymphocytic leukemia
**ITP** Immune thrombocytopenic purpura
**KD** Kawasaki disease
**PIDD** Primary immune deficiency disease

## 2011-2012 Influenza Vaccine

**Administration Codes:** G0008 (Medicare plans) 90471 (non-Medicare plans)
**Diagnosis Code:** V04.81

| Product | Size | When Administered to Indicated Age Group | CPT Code |
|---|---|---|---|
| FLUZONE Pediatric | 0.25 mL prefilled syringe | Influenza virus vaccine, split virus, preservative free, when administered to children 6-35 months of age, for intramuscular use | 90655 |
| AFLURIA | 0.5 mL prefilled syringe | Influenza virus vaccine, split virus, preservative free, when administered to individuals 3 years of age and older, for intramuscular use | 90656 |
| FLUZONE | 0.5 mL single-dose vial | | |
| FLUZONE | 0.5 mL prefilled syringe | | |
| FLUVIRIN | 0.5 mL prefilled syringe | | |
| FLUZONE | 5 mL multi-dose vial | Influenza virus vaccine, split virus, when administered to children 6-35 months of age, for intramuscular use | 90657 |
| AFLURIA | 5 mL multi-dose vial | Influenza virus vaccine, split virus, when administered to individuals 3 years and older, for intramuscular use | 90658 |
| FLUVIRIN | 5 mL multi-dose vial | | |
| FLUZONE | 5 mL multi-dose vial | | |
| FLUZONE High-Dose | 0.5 mL prefilled syringe | Influenza virus vaccine, split virus, when administered to individuals 65 years of age and older, for intramuscular use | 90662 |
| FLUMIST | 0.2 mL nasal spray | Influenza virus vaccine, live, for intranasal use, when administered to individuals 2-49 years of age | 90660 |


# The PROOF is everywhere you look

## GAMUNEX is the IGIV therapy supported by robust clinical trials

- Proven efficacy in more FDA-approved indications (CIDP, PI, and ITP)* than any other liquid IGIV[1]

### Important Safety Information for GAMUNEX

Gamunex, Immune Globulin Intravenous (Human), 10% Caprylate/Chromatography Purified, is indicated for the treatment of primary humoral immunodeficiency disease (PI), idiopathic thrombocytopenic purpura (ITP), and chronic inflammatory demyelinating polyneuropathy (CIDP).

**Immune Globulin Intravenous (Human) products have been reported to be associated with renal dysfunction, acute renal failure, osmotic nephrosis and death. Patients predisposed to acute renal failure include patients with any degree of pre-existing renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs. Especially in such patients, IGIV products should be administered at the minimum concentration available and the minimum rate of infusion practicable. While these reports of renal dysfunction and acute renal failure have been associated with the use of many of the licensed IGIV products, those containing sucrose as a stabilizer accounted for a disproportionate share of the total number. Gamunex does not contain sucrose. Glycine, a natural amino acid, is used as a stabilizer.**

Gamunex is contraindicated in individuals with acute severe hypersensitivity reactions to Immune Globulin (Human). It is contraindicated in IgA deficient patients with antibodies against IgA and history of hypersensitivity.

There have been reports of noncardiogenic pulmonary edema [Transfusion-Related Lung Injury (TRALI)], hemolytic anemia, and aseptic meningitis in patients administered with IGIV.

Thrombotic events have been reported in association with IGIV. Patients at risk for thrombotic events may include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, and/or known or suspected hyperviscosity. Hyperproteinemia, increased serum viscosity, and hyponatremia may occur in patients receiving IGIV therapy.

Gamunex is made from human plasma. Because this product is made from human plasma, it may carry a risk of transmitting infectious agents, e.g., viruses, and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent.

In clinical studies, the most common adverse reactions with Gamunex were headache, fever, chills, hypertension, rash, nausea, and asthenia (in CIDP); headache, cough, injection site reaction, nausea, pharyngitis, and urticaria (in PI); and headache, vomiting, fever, nausea, back pain, and rash (in ITP). The most serious adverse reactions were pulmonary embolism (PE) in one subject with a history of PE (in CIDP), an exacerbation of autoimmune pure red cell aplasia in one subject (in PI), and myocarditis in one subject that occurred 50 days post-study drug infusion and was not considered drug related (in ITP).

*CIDP=chronic inflammatory demyelinating polyneuropathy; PI=primary immunodeficiency; ITP=idiopathic thrombocytopenic purpura.

**Reference: 1.** Data on file. Talecris Biotherapeutics, Inc.

**You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.**

**Please see adjacent page for brief summary of GAMUNEX full Prescribing Information.**

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## HIGHLIGHTS OF PRESCRIBING INFORMATION

**These highlights do not include all the information needed to use GAMUNEX®, Immune Globulin Intravenous (Human), 10% Caprylate/Chromatography Purified, safely and effectively. See full prescribing information for GAMUNEX.**

**GAMUNEX (Immune Globulin Intravenous [Human], 10% Caprylate/Chromatography Purified)** 10% Liquid Preparation

**Initial U.S. Approval: 2003**

**WARNING: ACUTE RENAL DYSFUNCTION and FAILURE**

*See full prescribing information for complete boxed warning.*

- **Renal dysfunction, acute renal failure, osmotic nephrosis, and death may be associated with Immune Globulin Intravenous (Human) (IGIV) products in predisposed patients.**
- **Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose. GAMUNEX does not contain sucrose.**
- **Administer IGIV products at the minimum concentration available and the minimum infusion rate practicable.**

## INDICATIONS AND USAGE

GAMUNEX is an immune globulin intravenous (human), 10% liquid indicated for treatment of:

- Primary Humoral Immunodeficiency (PI)
- Idiopathic Thrombocytopenic Purpura (ITP)
- Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

## CONTRAINDICATIONS

- Anaphylactic or severe systemic reactions to human immunoglobulin
- IgA deficient patients with antibodies against IgA and a history of hypersensitivity

## WARNINGS AND PRECAUTIONS

- IgA deficient patients with antibodies against IgA are at greater risk of developing severe hypersensitivity and anaphylactic reactions. Epinephrine should be available immediately to treat any acute severe hypersensitivity reactions.
- Monitor renal function, including blood urea nitrogen, serum creatinine, and urine output in patients at risk of developing acute renal failure.
- Hyperproteinemia, increased serum viscosity and hyponatremia occur in patients receiving IGIV therapy.
- Thrombotic events have occurred in patients receiving IGIV therapy. Monitor patients with known risk factors for thrombotic events; consider baseline assessment of blood viscosity for those at risk of hyperviscosity.
- Aseptic Meningitis Syndrome has been reported with GAMUNEX and other IGIV treatments, especially with high doses or rapid infusion.
- Hemolytic anemia can develop subsequent to IGIV therapy due to enhanced RBC sequestration.
- IGIV recipients should be monitored for pulmonary adverse reactions (TRALI).
- The product is made from human plasma and may contain infectious agents, e.g., viruses and, theoretically, the Creutzfeldt-Jakob disease agent.

## ADVERSE REACTIONS

- **PI** – Most common drug related adverse reactions during clinical trials were headache and cough.
- **ITP** – Most common drug related adverse reactions during clinical trials were headache, vomiting, fever, and nausea.
- **CIDP** – Most common drug related adverse reactions during clinical trials were headache and fever.

**To report SUSPECTED ADVERSE REACTIONS, contact Talecris Biotherapeutics, Inc. at 1-800-520-2807 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**

## DRUG INTERACTIONS

- The passive transfer of antibodies may interfere with the response to live viral vaccines.
- The passive transfer of antibodies may confound the results of serological testing.

## USE IN SPECIFIC POPULATIONS

- In patients over age 65 or in any patient at risk of developing renal insufficiency, do not exceed the recommended dose, and infuse GAMUNEX at the minimum infusion rate practicable.
- Pregnancy: no human or animal data. Use only if clearly needed.

Talecris BIOTHERAPEUTICS

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